supplemento 2
numero 1
anno 40
gennaio
febbraio
2016

# EPIDEMIOLOGIA & PREVENZIONE

Rivista dell'Associazione italiana di epidemiologia

e&p

AIRTUM Working Group

ITALIAN CANCER FIGURES - REPORT 2015

# THE BURDEN OF RARE CANCERS IN ITALY

I TUMORI IN ITALIA - RAPPORTO 2015

# I TUMORI RARI IN ITALIA

Associazione Italiana Registri Tumori

Centro nazionale per la prevenzione e il controllo delle malattie

EDIZIONI inferenze

Inferenze, via Ricciarelli 29, 20148 Milano. Poste Italiane spa - Sped. in abb. post. DL 353/2003 convertito in legge 27.02.04 n.46 - art.1, com.1, DCB Milano - Una copia 13,50 euro issn 1120-9763 gennaio-febbraio 2016

# EPIDEMIOLOGIA & PREVENZIONE

Rivista dell'Associazione italiana di epidemiologia

**Rivista fondata da Giulio A. Maccacaro**

**ANNO 40 (1) 2016**

**Epidemiologia & Prevenzione**
**è indicizzata in Medline, Scopus,**
**Science Citation Index Expanded,**
**Journal Citation Reports/Science Edition**

**Pubblicazione bimestrale Registrazione**
**del Tribunale di Milano**
n. 239/1977 Spedizione in AP - 45% - art. 2 comma 20b
legge 662/96 - Milano

**Iscrizione al Registro degli Operatori**
**di Comunicazione (ROC)** n. 11747

**Una copia: 13,50 euro**

**Abbonamento annuo:** informazioni e condizioni sul sito
www.epiprev.it

**Gestione abbonamenti:** ufficio abbonamenti
tel. 02 48702283, fax 02 48706089

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IVA assolta dall'editore ai sensi dell'art. 74 lettera C del DPR 26/10/1972 n.633 e successive modificazioni e integrazioni nonché ai sensi del DM 29/12/1989. Non si rilasciano quindi fatture (art. 1 c. 5 DM 29/12/1989).

Testata associata
A.N.E.S.
ASSOCIAZIONE NAZIONALE EDITORIA PERIODICA SPECIALIZZATA

**Stampa**
Arti grafiche Ancora srl - Milano

EDIZIONI inferenze

**via Ricciarelli 29, 20148 Milano**
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Versamento su conto corrente postale n. 55195440 intestato a Inferenze scarl, via Ricciarelli n. 29, 20148 Milano (segnalare la causale del versamento).
Accredito tramite c/c bancario presso:
UNIPOL BANCA Piazza Wagner n. 8, 20145 Milano, IBAN: IT53P 03127 01600 000000003681 intestato all'impresa editoriale Inferenze scarl, via Ricciarelli n. 29, 20148 Milano.

Si ringrazia la Fondazione IRCCS Istituto nazionale dei tumori di Milano che ospita la Cooperativa.

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I TUMORI IN ITALIA - RAPPORTO 2015

## I TUMORI RARI IN ITALIA

**AIRTUM Working Group**
Associazione italiana
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Centro nazionale
per la prevenzione
e il controllo delle malattie
Ministero della salute

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**ANNEX 1**
**RARECAREnet LIST OF RARE CANCERS**
LISTA DEI TUMORI RARI DI RARECAREnet

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**ACKNOWLEDGEMENTS**
**This study has the ambitious objective of offering, for the first time, a comprehensive, methodologically rigorous overview of the epidemiology of rare tumours in Italy.**
**It is the result of the joint work of research groups from the Italian National Cancer Institute of Milan (Evaluative Epidemiology Unit) and the Istituto Superiore di Sanità (Italian Epidemiology, Surveillance, and Health Promotion Centre). These groups were the first to study rare tumours from an epidemiological point of view, within Italian and European projects.**
**AIRTUM would like to thank them for contributing their experience and expertise, as we pursue the common goal of making the fullest possible use of the information collected by the Italian cancer registries.**
**The present monograph has been carried out thanks to the contribution of the "Rare Cancers in Italy: surveillance and evaluation of the access to diagnosis and treatment" project, funded by the grant for research on rare diseases (Italian Ministry of Health, Directorate general for scientific and techonologic research).**

**RINGRAZIAMENTI**
**Questo studio si pone l'obiettivo ambizioso di offrire, per la prima volta, un quadro esaustivo e metodologicamente rigoroso sull'epidemiologia dei tumori rari in Italia.**
**Il risultato è frutto della collaborazione con i gruppi di ricerca della Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (Unità di epidemiologia valutativa) e dell'Istituto Superiore di Sanità (Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute) che sono stati i primi a occuparsi, nell'ambito di progetti europei e italiani, dei tumori rari dal punto di vista epidemiologico. Ad essi va il ringraziamento di AIRTUM per aver condiviso la propria esperienza e competenza con il comune obiettivo di valorizzare le informazioni raccolte dai registri tumori italiani.**
**La presente monografia è stata realizzata anche grazie al contributo del progetto "Rare Cancers in Italy: surveillance and evaluation of the access to diagnosis and treatment" finanziato dal bando di ricerca sulle malattie rare del Ministero della salute, Direzione generale della ricerca scientifica e tecnologica.**

# FOREWORD
## PREFAZIONE

I am extremely pleased to introduce the Italian Cancer Figures Report 2015, completely devoted to the assessment of the burden of rare cancers in Italy.
This report is the latest valuable contribution to knowledge and policy development in the country by the Italian Association of Cancer Registries (AIRTUM).
The Ministry of Health, through its Centre for Prevention and Disease Control, has systematically supported AIRTUM, making careful use of the wealth of information provided by AIRTUM to orient national policies and monitor their implementation.
AIRTUM reports have been the main source of information and the benchmark for all health professionals and patient associations over the past ten years, as the share of Italian population screened by the cancer registries has increased from 23% to 51% so far, and is set to reach 70% in the next few years.
This year's report is the first in Italy to analyse rare tumours from an epidemiological perspective. It shows that one out of four diagnosed cancer cases belongs to the category of rare cancers; this proportion is similar to other European estimates (24%). This means that the affected population is more than significant and calls for highly specific care, based on cancer patterns, as well as individual needs.
Cancers defined as "rare" challenge clinical decision making, health care organisation and clinical research due to their low frequency in the population and the resulting limited expertise available. In their daily life experience, rare cancer patients and their families must overcome a wide range of obstacles, such as:

- misdiagnosis and delay in diagnosis;
- lack of scientific knowledge due to the small number of patients that may not allow for traditional clinical trial design, and limited availability of registries and tissue banks;
- difficulties in developing therapeutic tools and defining therapeutic strategies, and shortage of therapeutic products;
- low-quality healthcare due to poor, not experienced-based protocols, inappropriate referral procedures by general practitioners and misdiagnoses by inexperienced laboratories.

The most striking figure in this report relates to patient survival, which is shorter than for patients affected by more common cancers, at any evaluated period: at 1, 3, and 5 years. This is a particularly challenging figure for the National Health Service, health care professionals, and, of course and above all, patients and their families.
Italy is already committed to improving its health service delivery system in order to provide these patients with high-quality, more effective, and fairer care.
This effort will take on concrete form in a National Network for Rare Cancers which will include the most experienced cancer centres and professionals. This task is not trivial, given the current devolution and the federal structure of our national health system. This report underlines the need to overcome local interests, and provides sound, evidence-based, powerful tools to enhance scientific research and elicit new and non-traditional epidemiological, clinical, and public health analyses.
Thanks to this report we can expect an improvement in the understanding of rare tumours that will be useful not only for Italy, but also for a broader international scientific and medical audience, while supporting patient associations, strengthening their links with scientific associations, whose accountability will be key in forging a new alliance between providers and beneficiaries.
In conclusion, I would like to congratulate and thank all those who actively carried out this work and those who enthusiastically contributed to it.
To their commitment we will continue to add our own, making sure that our decisions and the related resource allocation process are based on a careful, comprehensive need assessment, so as to generate equitable care for those who might otherwise be neglected.

**Ranieri Guerra**
Head of Strategic direction for health prevention,
Ministry of Health

ITALIAN CANCER FIGURES - REPORT 2015

# THE BURDEN OF RARE CANCERS IN ITALY

I TUMORI IN ITALIA - RAPPORTO 2015

## I TUMORI RARI IN ITALIA

# INTRODUCTION
## INTRODUZIONE

This new monograph of the Italian Association of Cancer Registries (AIRTUM) deals with "rare" cancers, defined as those diagnosed in less than 6 every 100,000 citizens per year in the European population.
Rare cancers are a red-hot issue for all oncology stakeholders: patients, clinicians, the pharmaceutical industry, and policy-makers. The reason is that their rareness makes diagnosis more difficult and causes a lack of specific drugs and widespread expertise in treatment. Moreover, the continuous developments in cancer research have provided new insights into cancer biology, resulting in better identification of specific oncological entities. For example, we are now able – using specific biomarkers – to identify two or several tumours, previously considered as a single type, which differ from each other in biochemical footprint, treatment, and prognosis, as well.
This is what prompted AIRTUM to address this issue, in collaboration with the Italian National Cancer Institute of Milan, the "Istituto Superiore di Sanità", and the involvement of the Italian Association of Medical Oncology (AIOM), the Italian Federation of Volunteer-Based Cancer Organisations (FAVO), the Italian Society of Haematology (SIE), and the Italian Society of Surgical oncology (SICO).
AIRTUM's huge database proved effective in providing high-quality, reliable information even on rare cancers, with more than 330,000 cases used to compute incidence (years: 2000s) and 280,000 used to estimate survival. The study shows that about 89,000 (or 25%) of new annual cancer diagnoses in Italy are of rare cancers. The huge overall number does not solve the peculiarities of rarity: among the 198 analysed rare cancer types, more than two thirds have an incidence below 0.5 cases per 100,000 per year.
Some tumour types that are rare according to the European definition (diffuse large B-cell lymphoma, squamous cell carcinoma of larynx, multiple myeloma, hepatocellular carcinoma, and thyroid carcinoma) have an incidence in Italy that exceeds the European cut-off, introducing the need for harmonization in definition and classification to obtain reliable international comparisons.
The monograph provides an impressive amount of information on detailed types of rare tumours. To cite a few data, 5-year relative survival appears to be lower on average for rare tumours than for frequent types. The number of Italian citizens living with a rare tumour diagnosis has been estimated to be 900,000. Prevalence differs according to the different combination of incidence and survival in each of the rare tumours.
This monograph provides an invaluable amount of previously unpublished information on the epidemiology of rare tumours in Italy, both as an overall group and for each of the 198 types, which have been analysed in detail for the first time.
As is the case for all other AIRTUM reports, the data in this monograph are available to all interested stakeholders, and they focus on national peculiarities, quantifying individual burdens and outcomes, and supporting health care planners in the laying out of case-specific health care services.
Rare cancers are not only relevant today, but their relevance is expected to grow in the future, pending further discoveries and major progress in ongoing cancer research.
The quality and reliability of AIRTUM data, recently confirmed even by the Ministry of Health, support the dissemination of reliable information regarding the epidemiology of cancer in Italy, now including rare tumours.

**Steering Committee**
Italian Association of Cancer Registries (AIRTUM)

ITALIAN CANCER FIGURES - REPORT 2015

# THE BURDEN OF RARE CANCERS IN ITALY

I TUMORI IN ITALIA - RAPPORTO 2015

## I TUMORI RARI IN ITALIA

# ABSTRACT
# RIASSUNTO


## OBJECTIVES

This collaborative study, based on data collected by the network of Italian Cancer Registries (AIRTUM), describes the burden of rare cancers in Italy. Estimated number of new rare cancer cases yearly diagnosed (incidence), proportion of patients alive after diagnosis (survival), and estimated number of people still alive after a new cancer diagnosis (prevalence) are provided for about 200 different cancer entities.

## MATERIALS AND METHODS

Data herein presented were provided by AIRTUM population-based cancer registries (CRs), covering nowadays 52% of the Italian population. This monograph uses the AIRTUM database (January 2015), which includes all malignant cancer cases diagnosed between 1976 and 2010. All cases are coded according to the International Classification of Diseases for Oncology (ICD-O-3). Data underwent standard quality checks (described in the AIRTUM data management protocol) and were checked against rare-cancer specific quality indicators proposed and published by RARECARE and HAEMACARE (www.rarecarenet.eu; www.haemacare.eu).
The definition and list of rare cancers proposed by the RARECAREnet "Information Network on Rare Cancers" project were adopted: rare cancers are entities (defined as a combination of topographical and morphological codes of the ICD-O-3) having an incidence rate of less than 6 per 100,000 per year in the European population.
This monograph presents 198 rare cancers grouped in 14 major groups.
Crude incidence rates were estimated as the number of all new cancers occurring in 2000-2010 divided by the overall population at risk, for males and females (also for gender-specific tumours). The proportion of rare cancers out of the total cancers (rare and common) by site was also calculated. Incidence rates by sex and age are reported. The expected number of new cases in 2015 in Italy was estimated assuming the incidence in Italy to be the same as in the AIRTUM area.
One- and 5-year relative survival estimates of cases aged 0-99 years diagnosed between 2000 and 2008 in the AIRTUM database, and followed up to 31 December 2009, were calculated using complete cohort survival analysis.
To estimate the observed prevalence in Italy, incidence and fol-

## OBIETTIVI

*Questo studio collaborativo, basato sui dati raccolti dalla rete dei registri tumori italiani (AIRTUM, www. registri-tumori.it), descrive l'impatto dei tumori rari in Italia. Per circa 200 diversi tumori rari sono state calcolate: incidenza, sopravvivenza a 1 e 5 anni e prevalenza.*

## MATERIALI E METODI

*I dati presentati sono stati forniti dai Registri tumori di popolazione AIRTUM, che coprono oggi il 52% della popolazione italiana. Nella presente monografia sono stati analizzati i dati della Banca Dati AIRTUM (aggiornamento: gennaio 2015), che include tutti i casi di tumore maligno diagnosticati tra il 1976 e il 2010. Tutti i casi sono codificati secondo la International Classification of Diseases for Oncology (ICD-O-3) e sono stati sottoposti a controlli standard di qualità (descritti nel protocollo di gestione della Banca Dati AIRTUM) e a controlli specifici per i tumori rari proposti e pubblicati nell'ambito dei progetti RARECARE e HAEMACARE (www.rarecarenet.eu, www.haemacare.eu).*
*La definizione e l'elenco di tumori rari sono quelli proposti dal progetto RARECAREnet, Information Network on Rare Cancers: i tumori rari sono entità (definite come combinazioni di codici topografici e morfologici della ICD-O-3) con un tasso di incidenza inferiore a 6 per 100.000 per anno nella popolazione europea. In questa monografia sono stati analizzati tutti i 198 tumori rari identificati da RARECAREnet, classificati in 14 grandi gruppi. Sono stati calcolati i tassi grezzi di incidenza come numero di tutti i nuovi casi di tumore che si sono verificati nel periodo 2000-2010 divisi per la relativa popolazione a rischio, per maschi e femmine insieme (anche nel caso di tumori specifici per sesso). E' presentata anche la percentuale di tumori rari sul totale di tumori (rari e frequenti) per ogni sede, oltre ai tassi specifici per sesso ed età. E' stato stimato il numero atteso di nuovi casi diagnosticati nel 2015 in Italia, assumendo che l'incidenza nazionale sia uguale a quella osservata nelle aree coperte dai registri AIRTUM.*
*E' stata calcolata la sopravvivenza relativa (SR) a 1 e 5 anni dalla diagnosi per casi di età compresa fra 0 e 99 anni diagnosticati nel periodo 2000-2008, con follow-up aggiornato al 31 dicembre 2009, usando l'analisi di sopravvivenza completa.*
*Per stimare la prevalenza osservata in Italia sono stati selezionati i casi raccolti da 11 registri nel periodo 1992-2006 considerando*

low-up data from 11 CRs for the period 1992-2006 were used, with a prevalence index date of 1 January 2007. Observed prevalence in the general population was disentangled by time prior to the reference date (≤2 years, 2-5 years, ≤15 years). To calculate the complete prevalence proportion at 1 January 2007 in Italy, the 15-year observed prevalence was corrected by the completeness index, in order to account for those cancer survivors diagnosed before the cancer registry activity started. The completeness index by cancer and age was obtained by means of statistical regression models, using incidence and survival data available in the European RARECAREnet data.

## RESULTS

In total, 339,403 tumours were included in the incidence analysis. The annual incidence rate (IR) of all 198 rare cancers in the period 2000-2010 was 147 per 100,000 per year, corresponding to about 89,000 new diagnoses in Italy each year, accounting for 25% of all cancer.

Five cancers, rare at European level, were not rare in Italy because their IR was higher than 6 per 100,000; these tumours were: diffuse large B-cell lymphoma and squamous cell carcinoma of larynx (whose IRs in Italy were 7 per 100,000), multiple myeloma (IR: 8 per 100,000), hepatocellular carcinoma (IR: 9 per 100,000) and carcinoma of thyroid gland (IR: 14 per 100,000).

Among the remaining 193 rare cancers, more than two thirds (No. 139) had an annual IR <0.5 per 100,000, accounting for about 7,100 new cancers cases; for 25 cancer types, the IR ranged between 0.5 and 1 per 100,000, accounting for about 10,000 new diagnoses; while for 29 cancer types the IR was between 1 and 6 per 100,000, accounting for about 41,000 new cancer cases.

Among all rare cancers diagnosed in Italy, 7% were rare haematological diseases (IR: 41 per 100,000), 18% were solid rare cancers. Among the latter, the rare epithelial tumours of the digestive system were the most common (23%, IR: 26 per 100,000), followed by epithelial tumours of head and neck (17%, IR: 19) and rare cancers of the female genital system (17%, IR: 17), endocrine tumours (13% including thyroid carcinomas and less than 1% with an IR of 0.4 excluding thyroid carcinomas), sarcomas (8%, IR: 9 per 100,000), central nervous system tumours and rare epithelial tumours of the thoracic cavity (5% with an IR equal to 6 and 5 per 100,000, respectively).

The remaining (rare male genital tumours, IR: 4 per 100,000; tumours of eye, IR: 0.7 per 100,000; neuroendocrine tumours, IR: 4 per 100,000; embryonal tumours, IR: 0.4 per 100,000; rare skin tumours and malignant melanoma of mucosae, IR: 0.8 per 100,000) each constituted <4% of all solid rare cancers.

Patients with rare cancers were on average younger than those with common cancers. Essentially, all childhood cancers were rare, while after age 40 years, the common cancers (breast, prostate, colon, rectum, and lung) became increasingly more frequent.

For 254,821 rare cancers diagnosed in 2000-2008, 5-year RS was on average 55%, lower than the corresponding figures for

*come data di riferimento il 1 gennaio 2007. La prevalenza osservata nella popolazione generale è stata stratificata per durata (≤2 anni, 2-5 anni, ≤15 anni dalla diagnosi). Per calcolare la prevalenza completa al 1 gennaio 2007, la prevalenza di durata limitata a 15 anni dalla diagnosi è stata corretta utilizzando un indice di completezza che tiene conto dei soggetti che hanno affrontato la diagnosi prima dell'inizio dell'attività dei registri tumori. L'indice di completezza è stato ottenuto mediante modelli di regressione statistici applicati ai dati europei di incidenza e sopravvivenza del progetto RARECAREnet.*

## RISULTATI

*In totale, sono stati inclusi nell'analisi di incidenza 339.403 casi. Il tasso annuale di incidenza (TI) per tutti i 198 tumori rari, analizzati insieme come un unico gruppo, nel periodo 2000-2010 è risultato pari a 147 per 100.000, corrispondente a circa 89.000 nuove diagnosi in Italia ogni anno, che rappresentano il 25% di tutti i tumori.*

*Cinque tumori, rari a livello europeo, non sono risultati rari in Italia, perché il loro TI era superiore a 6 per 100.000: il linfoma diffuso a grandi cellule B e il carcinoma a cellule squamose della laringe (il cui TI in Italia era pari a 7 per 100.000), il mieloma multiplo (TI: 8 per 100.000), il carcinoma epatocellulare (TI: 9 per 100.000) e il carcinoma della tiroide (TI: 14 per 100.000).*

*Tra i restanti 193 tumori rari, più di due terzi (n. 139) avevano un TI annuo inferiore a 0,5 per 100.000, corrispondente a circa 7.100 nuovi casi; 25 entità avevano un TI tra 0,5 e 1 per 100.000, rappresentando circa 10.000 nuove diagnosi; mentre per 29 entità il TI è risultato compreso tra 1 e 6 per 100.000, circa 41.000 nuovi casi.*

*Il 7% di tutti i tumori rari diagnosticati in Italia è costituito da tumori ematologici rari (TI: 41 per 100.000) e il 18% da tumori solidi rari. Tra questi ultimi, i tumori rari epiteliali dell'apparato digerente sono i più frequenti (23%, TI: 26 per 100.000), seguiti dai tumori epiteliali del distretto testa e collo (17%, TI: 19), dai tumori rari dell'apparato genitale femminile (17%, TI: 17), dai tumori endocrini (13% includendo i carcinomi della tiroide, meno dell'1 % con TI pari a 0,4 escludendo i carcinomi della tiroide ), dai sarcomi (8%, TI: 9 per 100.000), dai tumori del sistema nervoso centrale e dai tumori epiteliali toracici rari (5% con una TI uguale a 6 e 5 per 100.000, rispettivamente).*

*I restanti tumori rari (i tumori rari genitali maschili, TI: 4 su 100.000; i tumori dell'occhio, TI: 0,7 per 100,000; i tumori neuroendocrini, TI: 4 per 100.000; i tumori embrionali, TI: 0,4 per 100,000; i tumori rari cutanei e il melanoma maligno delle mucose, TI: 0,8 per 100,000) rappresentavano complessivamente meno del 4% di tutti i tumori solidi rari.*

*I pazienti con un tumore raro sono in media più giovani di quelli con un tumore frequente. In generale, tutti i tumori infantili sono rari, mentre dopo i 40 anni, i tumori di mammella, prostata, colon retto e polmone diventano sempre più frequenti.*

*Sulla base di quanto osservato nell'analisi di sopravvivenza, basata su 254.821 casi di tumore raro diagnosticati nel periodo 2000-2008, con ultimo aggiornamento dello stato in vita al 31 dicembre 2009, la SR a 5 anni dalla diagnosi è in media del 55%, più bassa rispetto alla sopravvivenza dei pazienti con tumori frequenti*

patients with common cancers (68%). RS was lower for rare cancers than for common cancers at 1 year and continued to diverge up to 3 years, while the gap remained constant from 3 to 5 years after diagnosis. For rare and common cancers, survival decreased with increasing age. Five-year RS was similar and high for both rare and common cancers up to 54 years; it decreased with age, especially after 54 years, with the elderly (75+ years) having a 37% and 20% lower survival than those aged 55-64 years for rare and common cancers, respectively. We estimated that about 900,000 people were alive in Italy with a previous diagnosis of a rare cancer in 2010 (prevalence). The highest prevalence was observed for rare haematological diseases (278 per 100,000) and rare tumours of the female genital system (265 per 100,000).
Very low prevalence (<10 prt 100,000) was observed for rare epithelial skin cancers, for rare epithelial tumours of the digestive system and rare epithelial tumours of the thoracic cavity.

## COMMENTS

One in four cancers cases diagnosed in Italy is a rare cancer, in agreement with estimates of 24% calculated in Europe overall. In Italy, the group of all rare cancers combined, include 5 cancer types with an IR>6 per 100,000 in Italy, in particular thyroid cancer (IR: 14 per 100,000). The exclusion of thyroid carcinoma from rare cancers reduces the proportion of them in Italy in 2010 to 22%. Differences in incidence across population can be due to the different distribution of risk factors (whether environmental, lifestyle, occupational, or genetic), heterogeneous diagnostic intensity activity, as well as different diagnostic capacity; moreover heterogeneity in accuracy of registration may determine some minor differences in the account of rare cancers.
Rare cancers had worse prognosis than common cancers at 1, 3, and 5 years from diagnosis. Differences between rare and common cancers were small 1 year after diagnosis, but survival for rare cancers declined more markedly thereafter, consistent with the idea that treatments for rare cancers are less effective than those for common cancers. However, differences in stage at diagnosis could not be excluded, as 1- and 3-year RS for rare cancers was lower than the corresponding figures for common cancers. Moreover, rare cancers include many cancer entities with a bad prognosis (5-year RS <50%): cancer of head and neck, oesophagus, small intestine, ovary, brain, biliary tract, liver, pleura, multiple myeloma, acute myeloid and lymphatic leukaemia; in contrast, most common cancer cases are breast, prostate, and colorectal cancers, which have a good prognosis.
The high prevalence observed for rare haematological diseases and rare tumours of the female genital system is due to their high incidence (the majority of haematological diseases are rare and gynaecolog-

*(68%). La SR è inferiore per i tumori rari rispetto ai frequenti dopo 1 anno dalla diagnosi e continuava a divergere fino a 3 anni, il divario è costante da 3 a 5 anni. Per i tumori rari e frequenti, la sopravvivenza diminuisce con l'aumentare dell'età. La SR a 5 anni è simile, ed elevata, per i tumori rari e frequenti fino a 54 anni; diminuisce con l'età, soprattutto dopo i 54 anni, tra gli anziani (75+ anni), che presentano una SR del 37% inferiore rispetto alle persone di età compresa tra 55-64 anni.*
*Si è stimato che circa 900.000 persone fossero vive in Italia nel 2010 dopo una diagnosi di un tumore raro (prevalenza). La prevalenza più elevata è stata osservata per i tumori rari ematologici (278 per 100.000) e per i tumori rari del sistema genitale femminile (265 per 100.000). La prevalenza dei tumori rari cutanei, dei tumori epiteliali rari del tratto digerente e dei tumori epiteliali rari della cavità toracica è risultata molto bassa (<10 per 100.000).*

## DISUSSIONE

*Ogni quattro tumori diagnosticati in Italia uno è raro; questa proporzione è sovrapponibile a quella osservata in Europa (24%; www.rarecarenet.eu). In Italia l'insieme dei tumori rari comprende anche cinque patologie il cui tasso di incidenza è superiore a 6 per 100.000, con valori particolarmente elevati*

ical cancers added up to fairly high incidence rates) and relatively good prognosis.
The low prevalence of rare epithelial tumours of the digestive system was due to the low survival rates of the majority of tumours included in this group (oesophagus, stomach, small intestine, pancreas, and liver), regardless of the high incidence rate of rare epithelial cancers of these sites.
This AIRTUM study confirms that rare cancers are a major public health problem in Italy and provides quantitative estimations, for the first time in Italy, to a problem long known to exist.
This monograph provides detailed epidemiologic indicators for almost 200 rare cancers, the majority of which (72%) are very rare (IR<0.5 per 100,000). These data are of major interest for different stakeholders. Health care planners can find useful information herein to properly plan and think of how to reorganise health care services.
Researchers now have numbers to design clinical trials considering alternative study designs and statistical approaches.
Population-based cancer registries with good quality data are the best source of information to describe the rare cancer burden in a population.

**Keywords:** rare cancers, incidence, survival, prevalence, cancer registries, Italy

*per il carcinoma della tiroide (TI: 14 per 100.000). Se escludiamo il carcinoma della tiroide dall'insieme dei tumori rari, la proporzione di questi ultimi sul totale dei tumori si riduce al 22%. Le differenze di incidenza dei tumori rari in popolazioni diverse può essere dovuta alla diversa distribuzione dei fattori di rischio (ambientali, stili di vita, professionali e genetici), alla diversa intensità delle attività diagnostiche, nonché alle differenti capacità diagnostiche; inoltre, anche l'eterogeneità nella precisione della registrazione può contribuire a determinare qualche differenza nel conteggio dei tumori rari.*
*La sopravvivenza dopo 1, 3 e 5 anni dalla diagnosi è risultata inferiore per i tumori rari rispetto a quelli frequenti. Le differenze tra tumori rari e frequenti un anno dopo la diagnosi sono limitate, per poi amplificarsi, coerentemente con l'idea che i trattamenti per i tumori rari possano essere meno efficaci di quelli disponibili per i tumori frequenti. Tuttavia, non possono essere escluse differenze nella distribuzione per stadio alla diagnosi, essendo la sopravvivenza a 1 e 3 anni per tumori rari inferiore rispetto a quella osservata per i tumori frequenti. Inoltre, è necessario considerare che i tumori rari includono molti tumori con una cattiva prognosi (sopravvivenza relativa a 5 anni inferiore al 50%), quali i tumori del distretto testa e collo, dell'esofago, dell'intestino tenue, dell'ovaio, del sistema nervoso centrale, delle vie biliari, del fegato, della pleura, il mieloma multiplo, la leucemia mieloide acuta, la leucemia linfatica acuta; al contrario, tra i tumori più frequenti vi sono sedi tumorali, quali la mammella femminile, la prostata e il colon retto, caratterizzate da una buona prognosi.*
*L'alta prevalenza osservata per le malattie ematologiche rare e per i tumori rari ginecologi è dovuta all'elevata incidenza (la maggior parte delle malattie ematologiche sono rare e i tumori ginecologici hanno complessivamente tassi di incidenza abbastanza elevati) e alla loro buona prognosi.*
*La bassa prevalenza dei tumori epiteliali rari del tratto digerente è dovuta alla bassa sopravvivenza osservata per la maggior parte dei tumori delle sedi tumorali incluse in questo gruppo (esofago, stomaco, intestino tenue, pancreas e fegato), indipendentemente dal loro tasso di incidenza che, per alcune sedi, risultava comunque elevato.*
*Questo studio AIRTUM ha confermato che i tumori rari sono un rilevante problema di sanità pubblica in Italia, fornendo, per la prima volta a livello nazionale, stime quantitative di un fenomeno già noto da tempo. Questa monografia fornisce indicatori epidemiologici dettagliati per circa 200 tumori rari, la maggior parte dei quali (72%) risultano estremamente rari (TI<0,5 per 100.000). Questi dati possono essere rilevanti per diversi portatori di interesse. Politici e operatori sanitari possono trovare qui informazioni utili per pianificare e pensare a come riorganizzare i servizi di assistenza sanitaria per i tumori rari in Italia. I ricercatori hanno a disposizione i numeri per disegnare sperimentazioni cliniche, considerando anche disegni di studio alternativi e approcci statistici innovativi.*
*I registri tumori di popolazione con dati di buona qualità sono una delle principali fonti informative per descrivere l'impatto dei tumori rari in tutta la popolazione italiana.*

**Parole chiave:** tumori rari, incidenza, sopravvivenza, prevalenza, registri tumori, Italia

ITALIAN CANCER FIGURES - REPORT 2015

# THE BURDEN OF RARE CANCERS IN ITALY

I TUMORI IN ITALIA - RAPPORTO 2015

## I TUMORI RARI IN ITALIA

# MATERIALS AND METHODS
# MATERIALI E METODI

## INTRODUCTION

Until a few years ago, there was no internationally agreed definition of rarity for cancers. According to the European Parliament and Council of the European communities, rare diseases are defined as those with a prevalence of <50 per 100,000,[1] while, in line with the Orphan Drug Act, in the US rare diseases are those affecting <200,000 persons.[2] However, a published analysis of rare cancers in the US employed the definition of <15 incident cases per 100,000 per year.[3] In 2010, the EU funded RARECARE – Surveillance of rare cancers in Europe project[4] proposed a new definition of rarity for cancers and a list of rare cancers in Europe.

The objective of this Italian Network of Cancer Registries (AIRTUM) monograph is to describe the burden of rare cancers in Italy, in order to give information on rare cancers to the community at large (oncologists, general practitioners, researchers, health authorities, patients and their families).

In detail, this monograph provides estimations of incidence, survival, and prevalence of rare cancers in Italy, based on the definition and list of rare cancers proposed by RARECARE and recently (2012) updated by the RARECAREnet – Information Network on Rare Cancers project.[5]

This is the first time that such a comprehensive and detailed description of rare cancers has been provided in Italy and it was possible only thanks to the availability of AIRTUM's large database.[6]

## THE RARECARE DEFINITION OF RARE CANCERS

RARECARE defined rare cancers as those with an incidence rate (IR) of <6 per 100,000 per year in the European population. It is important to stress that rare cancers among the RARECARE list of cancers (please refer to Annex 1, see supplementary material on-line) are identified based on the above criterion, in other words, on the basis of the European population and not of a country-specific population. Thus, rare cancers are always the same in all European countries. It is also important to note that this is an incidence-based rather than prevalence-based definition, since incidence was recognised as the best indicator to define rarity for tumours.[4]

## INCIDENCE vs. PREVALENCE

Prevalence has shortcomings as a measure for rarity for tumours, although it is appropriate for non-neoplastic diseases. Many non-neoplastic diseases are chronic conditions, so prevalence, which reflects the total number of cases at any given time in a population, truly reflects the burden that a disease poses at a population level. On the contrary, tumours are sub-acute diseases in which everything tends to happen once: in the natural history of a tumour, there will be one potentially eradicating surgery, one local radiation therapy, one first chemotherapy, and each of these will take place in a definite time interval. Thus, the total amount of resources that tumours mobilise is proportional to the yearly rate of new diagnoses (incidence) and not to the total number of persons with previous cancer diagnosis (prevalence), some of whom have been cured. Incidence, which reflects the yearly number of new cases occurring in a population, might thus be a better indicator to describe the burden posed by a tumour.

Moreover, the prevalence of a disease depends on two time-dependent characteristics which are independent of one another: incidence and survival. With the prevalence threshold adopted as a definition of cancer rarity, some commonly occurring diseases for which survival is very poor, such as most cancers of the stomach (adenocarcinoma of stomach), pancreas, adenocarcinoma of lung, and squamous cell carcinoma of lung, will be defined as rare, since the proportion of the general population who are survivors is very low. By contrast, some neoplasms that occur very infrequently ("rare" in the sense of incidence) but which have very good survival, such as cancer of the testis and squamous cell carcinoma of the uterine cervix, will be defined as common on the basis of prevalence, because, although they occur infrequently, most people who develop the disease survive for long periods.

For these reasons, incidence seems to be a more useful indicator to select a threshold for rarity in the case of tumours, as opposed to non-neoplastic diseases. In addition, it is worth stressing that:

- incidence is a direct measure of the burden imposed by the need for first-line cancer treatment;
- the number of patients amenable to enter a clinical study is reflected by cancer incidence.

Any threshold for cancer rarity should be considered as merely indicative. The RARECARE rarity threshold at <6 per 100,000 per year might be considered too high. However, if the lower threshold of <3 per 100,000 per year were adopted, glial tumours, epithelial cancers of the oral cavity, epithelial cancers of gallbladder and extrahepatic biliary tract, soft tissue sarcomas, tumours of testis and paratestis, myeloproliferative neoplasms, and acute myeloid leukaemia would all be excluded. Yet these cancers are often inadequately diagnosed and treated in relation to both lack of knowledge and lack of clinical expertise, and clinical trials are rarely performed. They are all diseases that are best treated in specialised centres.

Crocetti E, Trama A, Stiller C, et al. Epidemiology of glial and non-glial brain tumours in Europe. *Eur J Cancer* 2012;48(10):1532-1542.

Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer* 2013;49(3):684-695.

## THE RARECARE LIST OF CANCERS

Usually, cancer statistics are provided for broad cancer categories, based on the anatomic site of the malignancies as defined by the International Classification of Diseases (ICD) codes. Rare tumour entities, because of their specific problems related to health care organisation and clinical management, might be more appropriately defined as a combination of topographical and morphological characteristics, as both defined by the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).[7]

Each tumour entity in the ICD-O list has a pathologic basis; however, in order to define clinically distinct diseases, the pathological entities have to be grouped. This grouping exercise, necessary to identify a list of clinically distinct entities, was undertaken in the context of the RARECARE project by an international group of experts, including oncologists, epidemiologists, pathologists, and organisations of patients.[4]

As a first step, the two large groups of epithelial and non-epithelial tumours were disentangled and, within them, broad anatomic categories were identified. Thus, the list of rare cancers starts with epithelial tumours of different sites and continues with non-epithelial tumours such as sarcomas, neuroendocrine, central nervous system, and haematological tumours (please refer to Annex 1).

The RARECARE list is organised into three tiers, as illustrated, for example, in Table 1 for epithelial tumours of nasal cavity and sinuses. The bottom tier (tier 3) on the list is the WHO name of individual cancer entities[8] and its corresponding ICD-O-3 morphology and topography codes.[7] ICD-O-3 entities are grouped into categories (tier 2) of cancers, considered similar from the point of view of clinical management and research. These categories are then further grouped into more general categories of tumours (tier 1), considered to involve the same clinical expertise and patient referral structure.

Tier 2 entities, by definition, include only specific morphologies; thus, rare cancers are identified in this tier. Not Otherwise Specified (NOS) morphology codes (NOS: 8000, 8001 for solid cancers, and 9590,9591,9760,9800,9801,9820,9860 for haematological diseases) are never assigned to tier 2, but to tier 1, which aims at identifying tumours with the same referral structure.

The choice of basing the definition of rare cancer on topography and morphology according to ICD-O-3 was made for two reasons. The first reason was to follow the existing tumour classifications. Any list of rare tumours will always be a subset of a standard list of tumours. International agencies preside over such classifications, constantly updating them. This list of rare tumours was based on the ICD-O-3 classification because this is the worldwide-recognised classification of tumours.

The second reason was data availability. Population-based cancer registry (CR) data, the only data available to calculate population-based incidence and prevalence indicators, refer to cases classified only according to ICD-O. Other, even attractive, classification criteria, such as biomarkers or gene expression, cannot be used for any quantitative description of cancer burden in a wide population.

The new RARECAREnet project on rare cancers reviewed the RARECARE list of cancers in 2012 and identified 198 rare cancers in tier 2 with a European IR (independently of the country-specific IR) <6 per 100,000 per year. The complete list of the 198 tier 2 rare cancers is provided in Annex 1 (rare cancers are identified by the R).

This monograph considers all these 198 rare cancers, including 5 cancers which have an IR that is higher than 6 per 100,000 per year in Italy: • hepatocellular carcinoma of liver (Italy 9.4 vs. EU 3.1), • squamous cell carcinoma of larynx (Italy 7.2 vs. EU 4.6), • carcinoma of thyroid gland (Italy 14.2 vs. EU 3.7), • multiple myeloma (Italy 8.4 vs. EU 5.9), • diffuse and follicular B-cell lymphoma (Italy 9.8 vs. EU 4.9). Thyroid carcinoma is not presented in the site-specific commentaries because of the peculiar characteristics of thyroid carcinoma in Italy (see paragraph «Methodological issue», pp. 20-21). The 198 rare cancers are classified, for this monograph, in 14 major groups (Table 2) considering the clinical referral pattern and the interest of clinicians. Thus, all sarcomas of soft tissue (regardless of the site of origin), bone and gastro-intestinal stromal tumours are grouped together in the sarcoma group. The rationale behind this choice was that all sarcomas should be referred to sarcoma specialists and these experts are very likely interested in having data on all different types of sarcoma. The main rare cancers of the thoracic cavity (thymoma, trachea, ma-

| TIER | TUMOUR | TOPOGRAPHY ICD-O-3 CODE | MORPHOLOGY ICD-O-3 CODE |
|---|---|---|---|
| 1 | **EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES** | C30.0, C31 | 8000, 8001, 8004, 8010, 8011, 8020-8022, 8032, 8050-8076, 8078, 8082-8084, 8123, 8144, 8560, 8980 |
| 2 | **Squamous cell carcinoma and variants of nasal cavity and sinuses** | C30.0, C31 | 8004, 8032, 8050-8076, 8078, 8083-8084, 8123, 8560, 8980 |
| 3 | Squamous cell carcinoma | C30.0, C31 | 8070 |
| 3 | Verrucous carcinoma | C30.0, C31 | 8051 |
| 3 | Squamous cell carcinoma, spindle cell | C30.0, C31 | 8004, 8032, 8074, 8980 |
| 3 | Papillary squamous cell carcinoma | C30.0, C31 | 8052 |
| 3 | Adenosquamous carcinoma | C30.0, C31 | 8560 |
| 3 | Squamous cell carcinoma, adenoid | C30.0, C31 | 8075 |
| 3 | Basaloid squamous cell carcinoma | C30.0, C31 | 8083 |
| 2 | **Lymphoepithelial carcinoma of nasal cavity and sinuses** | C30.0, C31 | 8082 |
| 2 | **Undifferentiated carcinoma of nasal cavity and sinuses** | C30.0, C31 | 8020-8022 |
| 2 | **Intestinal type adenocarcinoma of nasal cavity and sinuses** | C30.0, C31 | 8144 |

**Table 1.** The hierarchical three-tier structure of the RARECARE list of cancers illustrated for epithelial tumours of nasal cavity and sinuses.

| MAJOR GROUPS | RARE TUMOURS |
|---|---|
| Epithelial tumours of head and neck | Epithelial tumours of nasal cavity and sinuses, nasopharynx, hypopharynx and larynx, oropharynx, oral cavity and lip, middle ear, major salivary glands and salivary gland type tumours |
| Tumours of the eye | Epithelial tumours of eye and adnexa, malignant melanoma of uvea |
| Rare epithelial tumours of the digestive system and mesothelioma of peritoneum | Rare epithelial tumours of stomach, colon, rectum, pancreas, epithelial tumours of oesophagus, small intestine, anal canal, liver and intrahepatic bile tract, gallbladder, and extrahepatic biliary tract, and mesothelioma of peritoneum |
| Rare epithelial tumours of the thoracic cavity and mesothelioma of pleura and pericardium | Epithelial tumours of trachea, thymus, rare epithelial tumours lung, and mesothelioma of pleura and pericardium |
| Rare tumours of the female genital system | Rare epithelial tumours of breast, and corpus uteri, epithelial tumours of cervix uteri, ovary and fallopian tube, vulva and vagina, trophoblastic tumours of placenta, non epithelial tumours of ovary and epithelial tumours of males breast |
| Rare epithelial tumours of the urinary system | Epithelial tumours of renal pelvis and ureter, and urethra; rare epithelial tumours of kidney and bladder |
| Rare tumours of the male genital system | Epithelial tumours of penis, testicular and paratesticular cancers, extragonadal germ cells tumours, rare epithelial tumours of prostate, and mesothelioma of tunica vaginalis |
| Rare skin tumours and malignant melanoma of mucosa (extracutaneaous melanoma) | Rare skin tumours (adnexal carcinoma of skin) and malignant melanoma of mucosa (extracutaneous melanoma) |
| Embryonal tumours | Neuroblastoma and ganglioneuroblastoma, nephroblastoma, retinoblastoma, hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma, olfactory neuroblastoma, odontogenic malignant tumours |
| Sarcomas | Soft tissue sarcomas, bone sarcomas, gastrointestinal stromal tumours, Kaposi sarcoma |
| Neuroendocrine tumours | Neuroendocrine tumours of lung, gastroenteropancreatic tract, skin, thyroid, of other sites, pheochromocytoma, paraganglioma |
| Tumours of the Central Nervous System (CNS) | Central Nervous System tumours and embryonal tumours of CNS |
| Tumours of the endocrine organs | Carcinoma of pituitary gland, parathyroid gland, and adrenal cortex |
| Rare haematological diseases | Rare lymphoid diseases, acute myeloid leukemia and related precursor neoplasms, myeloproliferative neoplasms, myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases, hystiocytic and dendritic cell neoplasms |

**Table 2.** List of the 14 major groups of rare cancers included in this AIRTUM monograph.

lignant pleural mesothelioma, and rare histotypes of lung) are placed together in the group of rare epithelial thoracic cavity tumours (including pleural mesothelioma) because all these tumours should be referred to experts of lung and thoracic cavity cancers. With the same rationale, cancers of the nasal cavity and sinuses, nasopharynx, major salivary glands and salivary gland type tumours, hypopharynx, larynx, oropharynx, oral cavity, and lip are grouped together as head and neck cancers because they should all be referred to head and neck cancer experts. The same rationale was applied to the other rare cancers arising in the major sites of the body: digestive system, female genital system, urological tract, male genital system, central nervous system, eye, skin. In addition to these sites, 4 other groups included are neuroendocrine tumours regardless of their site of origin, all endocrine tumours (carcinoma of thyroid excluded), all embryonal tumours, and all rare haematological diseases.

## MATERIALS AND METHODS

Epidemiology of rare cancers presented in this monograph is based on incidence, survival, and prevalence estimates. On the basis of national or local data, mortality rates for each RARECAREnet considered cancer entity cannot be computed. Besides, the available mortality rates by major cancer site pose some limits, as in the case of uterine cancers: the poor specification of the subsites in official death statistics makes it impossible to disentangle mortality between cervix and corpus uteri; this is confirmed by a high proportion of deaths attributed to not otherwise specified uterine cancer.[9]

### The AIRTUM database

This monograph is based on the AIRTUM database updated to January 2015. The AIRTUM[6] at present includes 40 general population-based CRs and 5 specialised CRs.

Since 2005, AIRTUM has had a central database, which stores data from all accredited CRs. Accreditation indicates a CR meets the quality standards set by AIRTUM,[10] which verifies data quality and completeness and uses data for collaborative studies on cancer epidemiology in Italy.[11-14]

All cases in the AIRTUM database are coded according to the third edition of the ICD-O.[7] Data are double checked (by the Registry and by the centralised database) with the DEPedits program. In addition, other checks are carried out based on software developed by AIRTUM, CheckAIRTUM, that compares data from a specified registry to the weighted average of the other registries of the database.[6]

### Quality checks

The following data quality indicators, usually considered in international population-based survival studies like EUROCARE and RARECARE, were calculated for incident malignant cancers collected between 2000 and 2010, by CR:

1. proportion of cases known from death certificate only (DCO);
2. proportion of microscopically verified (MV) cases;
3. proportion of cases with survival time of zero days (date of diagnosis coincident with date of life status ascertainment);
4. proportion of cases diagnosed incidentally at autopsy;
5. proportion of Not Otherwise Specified (NOS) cases.

| AREA<br>MAJOR GROUPS | MALIGNANT CASES DIAGNOSED BETWEEN 2000 AND 2010 | NOS[$] | DCO | AUTOPSY ONLY CASES | CASES WITH ZERO SURVIVAL TIME | MICROSCOPICALLY CONFIRMED CASES | LOST TO FOLLOW-UP CASES |
|---|---|---|---|---|---|---|---|
| | No. | % | % | % | % | % | % |
| **AIRTUM POOL** | | | | | | | |
| Epithelial tumours of head and neck | 43 163 | | 0.3 | 0.2 | 0.2 | 97.1 | 0.8 |
| Tumours of the eye | 1 530 | | 0.6 | 0.2 | 0.2 | 58.9 | 0.7 |
| Digestive system tumours | 358 109 | | 1.4 | 0.6 | 0.2 | 78.7 | 0.6 |
| Rare epithelial tumours of the digestive system | 57 891 | | 0.7 | 1.2 | 0.2 | 73.5 | 0.6 |
| Thoracic cavity tumours | 157 478 | | 1.6 | 1.0 | 0.2 | 74.4 | 0.5 |
| Rare epithelial tumours of the thoracic cavity | 12 027 | | 0.1 | 2.8 | 0.2 | 97.4 | 0.5 |
| Female genital system tumours | 246 903 | | 0.6 | 0.1 | 0.2 | 95.5 | 1.0 |
| Rare tumours of the female genital system | 41 141 | | 0.1 | 0.2 | 0.2 | 99.3 | 1.0 |
| Urinary system tumours | 104 116 | | 0.6 | 0.4 | 0.2 | 89.0 | 0.9 |
| Rare epithelial tumours of the urinary system | 6 394 | | 0.2 | 0.5 | 0.2 | 94.5 | 0.6 |
| Male genital system tumours | 152 102 | | 0.8 | 0.3 | 0.2 | 92.3 | 0.8 |
| Rare tumours of the male genital system | 9 049 | | 0.1 | 0.1 | 0.3 | 95.4 | 1.8 |
| Tumours of the Central Nervous System | 13 071 | | 0.0 | 0.5 | 0.2 | 91.2 | 1.0 |
| Haematological diseases | 123 307 | | 0.8 | 0.5 | 0.3 | 93.1 | 0.9 |
| Rare haematological diseases | 91 094 | | 0.4 | 0.5 | 0.3 | 94.4 | 0.9 |
| Skin tumours^ | 33 823 | | 0.1 | 0.0 | 0.3 | 97.5 | 5.9 |
| Rare skin tumours and malignant melanoma of mucosa | 1 699 | | 0.0 | 0.0 | 0.5 | 99.5 | 1.5 |
| Embryonal tumours | 859 | | 0.1 | 0.0 | 0.5 | 93.2 | 0.9 |
| Sarcomas | 20 019 | | 0.0 | 0.4 | 0.3 | 98.6 | 1.4 |
| Neuroendocrine tumours | 9 196 | | 0.0 | 0.5 | 0.3 | 99.6 | 0.8 |
| Tumours of the endocrine organs* | 32 268 | | 0.2 | 0.2 | 0.3 | 95.4 | 1.2 |
| **NORTH-WEST** | | | | | | | |
| All malignant cancers^ | 445 918 | 14.7 | 1.1 | 0.1 | 0.3 | 85.7 | 1.0 |
| Rare cancers | 111 744 | – | 0.3 | 0.0 | 0.4 | 92.1 | 1.3 |
| **NORTH-EAST** | | | | | | | |
| All malignant cancer^ | 470 760 | 13.4 | 0.8 | 1.1 | 0.1 | 87.3 | 0.2 |
| Rare cancers | 116 808 | – | 0.1 | 0.0 | 0.1 | 93.5 | 2.0 |
| **CENTRE** | | | | | | | |
| All malignant cancer^ | 125 671 | 14.9 | 0.7 | 0.0 | 0.1 | 85.1 | 1.6 |
| Rare cancers | 31 005 | – | 0.3 | 0.2 | 0.2 | 90.0 | 0.8 |
| **SOUTH** | | | | | | | |
| All malignant cancer^ | 282 706 | 19.2 | 2.1 | 0.0 | 0.3 | 82.5 | 0.9 |
| Rare cancers | 79 846 | – | 0.9 | 0.5 | 0.0 | 91.1 | 0.0 |
| **AIRTUM POOL** | | | | | | | |
| All malignant cancer^ | 1 325 055 | 15.2 | 1.2 | 0.4 | 0.2 | 85.5 | 0.8 |
| Rare cancers | 339 403 | – | 0.9 | 0.0 | 0.0 | 92.1 | 0.6 |

[$] **NOS**: ICD-O-3 morphological code: 8000,8001,9800,9590,9820,9760,9860,9800,9801 / * including carcinomas of thyroid gland / ^ excluding non melanoma skin cancer

**Table 3.** Number of cases diagnosed in 2000-2010 and data quality indicators for the 14 major groups of rare cancers and corresponding common cancers (when the group included also common cancers), and for all malignant tumours vs. all rare cancers, by geographic area and in the overall AIRTUM Pool. Quality indicators include proportion of not otherwise specified (NOS) morphologies (8000,8001 for solid cancers, and 9590, 9591, 9760, 9800, 9801, 9820, 9860 for haematological diseases), death certificate only (DCO) cases, autopsy only cases, cases with zero survival time, microscopically confirmed cases, and lost to follow-up cases (follow-up time <5 years). Pool of 39 general CR of the AIRTUM database.

All standard indicators of data quality for Italian CRs are satisfactory according to international standards.[15]

The new and most relevant indicator to evaluate the accuracy of diagnosis for rare cancers, with respect to the other routinely applied indicators, is the proportion of cases with a NOS category (ICD-O-3 8000-8001 for solid cancers, and ICD-O-3 9590-9591, 9760, 9800-9801, 9820, 9860 for haematological diseases). For rare cancers, the most likely quality problem is lack of specificity of morphology codes, which make it impossible to assign such cases to a specific (rare) cancer entity, resulting in underestimation of the true incidence and prevalence of such entities. Unspecified morphology can be due to genuine difficulty in assigning a specific morphological category or because inadequate documentation was supplied to the CR when the case was registered. The latter problem is registration bias and results in incidence and prevalence underestimation. To assess the extent of registration bias at European level, RARECARE reviewed the original data (mainly pathologic reports) of a selected sample (about 18,000 cases) of eight rare cancers (for details see RARECARE web site).[5] Briefly, the great majority of NOS morphology cases were confirmed as NOS. The few NOS cases that changed to a more specific diagnosis generally increased the incidence of the more common cancer forms. For example, 11% of epithelial oral cavity cancers were reclassified from NOS to more specific diagnoses: 8% were reclassified as squamous

cell carcinoma (more common) and only 3% as adenocarcinoma (rarer). This finding suggests that the problem with poorly specified morphology cases is mainly one of difficulty in reaching a precise diagnosis, not registration bias. However, it raises an important topic for collaboration with pathologists and CRs.

Table 3 shows quality indicators for the 14 major groups of rare cancers included in this monograph, compared, when possible, to common cancers, and the quality indicators for all tumours in the AIRTUM pool and by geographic area. The overall proportion of NOS was 15%, with a higher proportion in the CRs of the South of Italy. Overall, the proportion of DCO cases was 1.2%, with, again, a slightly higher proportion in the CRs of the South of Italy. The proportion of cases discovered at autopsy was 0.4% in total. A high proportion of cases (86% overall) was MV. Follow-up was complete for most CRs, with follow-up censored before 5 years for only 1% of cases overall. These results indicate a high quality dataset.

NOS cases were also analysed within each of the 14 major groups of cancers presented in this monograph. As expected, grouping with major problems were those of the digestive system (mainly liver and pancreas), thoracic cavity, and CNS. NOS cases for these groups were 21%, 29%, and 38%. The difficult access to these sites led to a proportion of MV cases lower than the one observed in other sites. For example, the proportion of MV cases was 58% for tumours of the pancreas and 74% for tumours of the liver. Incidence and prevalence indicators of rare cancers of lung, liver, and pancreas, and specific histotypes of the CNS might therefore be underestimated. Rare cancers always had a higher proportion of MV cases compared to the common counterpart, except in the digestive system. This is due to the fact that rare cancers of the digestive system include all cancers of liver and intrahepatic bile tract and of gallbladder and extrahepatic biliary tract, for which the proportion of MV cases was very low (70% and 58%, respectively), therefore the NOS was high. This influenced the overall proportion of NOS cases for rare digestive system cancers, making it higher than that for common cancers of the digestive system, including cancers of more accessible sites such as stomach and colon.

### Cancer registry selection

In order to guarantee homogeneity, all indicators were computed on the same database, therefore only general population-based CRs were considered. Thus, we did not consider in the analyses 3 specialised (Palermo-breast cancer; Modena-colorectal cancers; Liguria-mesothelioma) CRs, and 2 other CRs which collect data on childhood and adolescent cancers only (Piemonte, Marche).

Three CRs (Biella, Napoli, Ragusa) extended their area of registration in recent years: different areas of the same CR are therefore analysed separately in incidence and survival analyses.

To provide estimates of epidemiological indicators, the following inclusion criteria for AIRTUM CRs were applied:

- availability of at least three years of incidence between 2000 and 2010;
- complete follow-up for at least one year after the last year of incidence (i.e. at 31st December 2009) for cases diagnosed between 2000 and 2008 in survival analysis;
- proportion of NOS cases <20%.

All AIRTUM accredited CRs had a proportion of NOS cases

| MACROAREA/ REGION | RESIDENT POPULATION (ITALY 2013) | RESIDENTS IN AREAS COVERED BY CANCER REGISTRIES INCLUDED IN THE PRESENT MONOGRAPH (ITALY 2013) | | CANCER REGISTRIES |
|---|---|---|---|---|
| | No. | No. | % | No. |
| Piemonte | 4 374 052 | 1 229 824 | 28 | 2 |
| Valle d'Aosta | 127 844 | 0 | 0 | 0 |
| Lombardia | 9 794 525 | 8 307 271 | 85 | 10 |
| Liguria | 1 565 127 | 851 283 | 54 | 1 |
| **NORTH-WEST** | 15 861 548 | 10 388 378 | 65 | 13 |
| Trentino-Alto Adige | 1 039 934 | 1 039 934 | 100 | 2 |
| Veneto | 4 881 756 | 2 346 610 | 48 | 1 |
| Friuli Venezia Giulia | 1 221 860 | 1 221 860 | 100 | 1 |
| Emilia-Romagna | 4 377 487 | 3 500 936 | 80 | 6 |
| **NORTH-EAST** | 11 521 037 | 8 109 340 | 70 | 10 |
| Toscana | 3 692 828 | 1 235 646 | 33 | 1 |
| Umbria | 886 239 | 886 239 | 100 | 1 |
| Marche | 1 545 155 | 0 | 0 | 0 |
| Lazio | 5 557 276 | 552 090 | 10 | 1 |
| **CENTRE** | 11 681 498 | 2 673 975 | 23 | 3 |
| Abruzzo | 1 312 507 | 0 | 0 | 0 |
| Molise | 313 341 | 0 | 0 | 0 |
| Campania | 5 769 750 | 2 262 522 | 39 | 2 |
| Puglia | 4 050 803 | 1 776 450 | 44 | 3 |
| Basilicata | 576 194 | 0 | 0 | 0 |
| Calabria | 1 958 238 | 228 126 | 12 | 1 |
| Sicilia | 4 999 932 | 4 381 032 | 88 | 5 |
| Sardegna | 1 640 379 | 688 066 | 42 | 2 |
| **SOUTH AND ISLANDS** | 20 621 144 | 9 336 196 | 45 | 14 |
| **ITALY** | 59 685 227 | 30 507 889 | 52 | 39 |

▲ **Figure 1.** Italian geographical areas covered by the general cancer registries included in the present monograph.

◀ **Table 4.** Distribution of the Italian resident population by region, macroarea, and overall. Number (No.) and proportion (%) of the resident population covered by the cancer registries included in this monograph and number of general cancer registries by region, macroarea, and overall. Italy, 2013. (**Source**: ISTAT).[16]

<20%, thus none of the CRs were excluded because of data quality problem. The CR of Macerata was excluded from all analyses because it did not fulfil the first inclusion criterion (it did not have at least 3 years of incidence between 2000 and 2010). General CRs included in this monograph cover more than 30 million people, 52% of the Italian population at 2013 (Table 4 and Figure 1).
In the framework of the RARECARE and RARECAREnet projects, all participating Italian AIRTUM CRs were considered to estimate the burden on rare cancers in Europe because they completely fulfilled the quality criteria and the sensitivity analyses performed.[5]
In order to reduce the uncertainty due to the casual variability of sparse data and the resulting imprecision of the estimates, we considered three different pools of AIRTUM CRs for the different analyses (Table 5); in detail:

- 39 CRs with at least three years of available incidence data on patients registered between 2000 and 2010, for the incidence analysis;
- 37 CRs with cases diagnosed between 2000 and 2008, and followed up to 31st December 2009 or after, for the survival analysis;
- 11 CRs which provided incidence and follow-up data for the period 1992-2006 with a prevalence index date of 1st January 2007 for the prevalence analysis.

Table 5 shows data availability by year of incidence and CRs included in the analyses.

### Epidemiological indicators

The epidemiological indicators are estimated considering multiple tumours. The inclusion of multiple tumours in the analyses implies that each single patient may be counted several times. We considered 1,325,055 malignant cancer cases collected by 39 Italian CRs during the 2000-2010 period and included in the AIRTUM database as of January 2015.
For neuronal and mixed neuronal-glial tumours none of the indicators are provided, since they are mainly benign or borderline tumours and thus not available in the AIRTUM database. In addition, incidence of a few entities, including gastrointestinal stromal tumours and several haematological malignancies, is underestimated because the specific ICD-O codes were introduced with the ICD-O-3 in 2000, thus during the study period.
As some rare cancers are extremely rare, estimates stratified by geographic area could not be calculated.
All estimates were computed using SeerStat, version 8.1.2.[17]

### Incidence

Crude IRs of rare cancers were calculated as the number of new cancers occurring in 2000-2010 divided by the population at risk (male and female also for gender-specific rare cancers) over the same period, expressed as person-years. In total, 339,403 rare tumours were included in the incidence analysis from 39 CRs. The proportion of rare cancers out of the total cancers (rare and common) by site is also calculated considering rare and common cancers of each specific cancer site. Crude incidence was obtained for rare tumours overall, by sex, and by age class (0-54, 55-64, 65+; 0-4, 5-14, 15+ for embryonal cancers). The normal approximation is used with the standard errors to obtain 95% confidence intervals (95%CI) for incidence rates. Sex- and age-specific incidence rate for 25 rare cancers with less than 15 observed cases between 2000

| MACROAREA CANCER REGISTRY/ GEOGRAPHICAL AREA | | AVAILABLE INCIDENCE YEARS | INCIDENCE | SURVIVAL | PREVALENCE (OBS) |
|---|---|---|---|---|---|
| | | | PERIOD OF DIAGNOSIS | | |
| | | | 2000-2010 | 2000-2008 follow-up at 31st Dec 2009 | 1992-2006 prevalence date at 1st Jan 2007 |
| | | | CRs INCLUDED No. YEARS INCLUDED | | |
| **NORTH-WEST** | | | | | |
| Bergamo | | 2007-2009 | ✓ (3 yrs) | ✓ | |
| Biella | Biella | 1995-2009 | ✓ (9 yrs) | ✓ | |
| | Vercelli | 2007-2009 | ✓ (3 yrs) | ✓ | |
| Brescia | | 1999-2006 | ✓ (7 yrs) | ✓ | |
| Como | | 2003-2009 | ✓ (7 yrs) | ✓ | |
| Cremona | | 2005-2009 | ✓ (5 yrs) | ✓ | |
| Genova | | 1986-2007 | ✓ (8 yrs) | ✓ | ✓ |
| Mantova | | 1999-2010 | ✓ (11 yrs) | ✓ | |
| Milano (municipality) | | 1999-2007 | ✓ (8 yrs) | ✓ | |
| Milano 1-2 | | 2007-2009 | ✓ (3 yrs) | ✓ | |
| Monza e Brianza | | 2007-2009 | ✓ (3 yrs) | ✓ | |
| Sondrio | | 1998-2010 | ✓ (11 yrs) | ✓ | |
| Torino | | 1985-2010 | ✓ (11 yrs) | ✓ | ✓ |
| Varese | | 1976-2010 | ✓ (11 yrs) | ✓ | ✓ |
| **NORTH-EAST** | | | | | |
| Alto Adige | | 1995-2007 | ✓ (8 yrs) | ✓ | |
| Ferrara | | 1991-2009 | ✓ (10 yrs) | ✓ | ✓ |
| Friuli Venezia Giulia | | 1995-2009 | ✓ (10 yrs) | ✓ | |
| Modena | | 1988-2010 | ✓ (11 yrs) | ✓ | ✓ |
| Parma | | 1978-2011 | ✓ (11 yrs) | ✓ | ✓ |
| Piacenza | | 2006-2010 | ✓ (5 yrs) | ✓ | |
| Reggio Emilia | | 1996-2010 | ✓ (11 yrs) | ✓ | |
| Romagna | | 1986-2009 | ✓ (10 yrs) | ✓ | ✓ |
| Trento | | 1995-2006 | ✓ (7 yrs) | ✓ | |
| Veneto | | 1987-2007 | ✓ (8 yrs) | ✓ | ✓ |
| **CENTRE** | | | | | |
| Firenze-Prato | | 1985-2005 | ✓ (6 yrs) | | |
| Latina | | 1990-2010 | ✓ (11 yrs) | ✓ | ✓ |
| Umbria | | 1994-2009 | ✓ (10 yrs) | ✓ | |
| **SOUTH AND ISLANDS** | | | | | |
| Barletta | | 2006-2008 | ✓ (3 yrs) | ✓ | |
| Catania-Messina | | 2003-2008 | ✓ (6 yrs) | ✓ | |
| Catanzaro | | 2003-2007 | ✓ (5 yrs) | ✓ | |
| Lecce | | 2003-2007 | ✓ (5 yrs) | | |
| Napoli | ex ASL 4 | 1996-2010 | ✓ (11 yrs) | ✓ | |
| | ASL 3 Sud | 2008-2010 | ✓ (3 yrs) | ✓ | |
| Nuoro | | 2003-2008 | ✓ (6 yrs) | ✓ | |
| Palermo | | 2003-2010 | ✓ (8 yrs) | ✓ | |
| Ragusa | Ragusa | 1981-2009 | ✓ (10 yrs) | ✓ | ✓ |
| | Caltanissetta | 2007-2010 | ✓ (4 yrs) | ✓ | |
| Salerno | | 1996-2009 | ✓ (10 yrs) | ✓ | |
| Sassari | | 1992-2009 | ✓ (10 yrs) | ✓ | ✓ |
| Siracusa | | 1999-2009 | ✓ (10 yrs) | ✓ | |
| Taranto | | 2006-2008 | ✓ (3 yrs) | ✓ | |
| Trapani | | 2002-2007 | ✓ (6 yrs) | ✓ | |
| **AIRTUM POOL** | | **1976-2010** | **39** | **37** | **11** |

**Table 5.** Available incidence years by general cancer registries (CRs) considered in this monograph ordered by macroarea. CRs included in incidence analysis with number of incident years considered. Cancer registries included in survival and observed prevalence analyses. AIRTUM database at January 2015.

and 2010 were considered as not estimable (NE). The expected number of new cases in 2015 was estimated assuming incidence in Italy to be the same as that in the AIRTUM sample, and multiplying the age- and sex-specific incidence rate by the corresponding Italian population in 2015 provided by ISTAT.[16]

### Survival

Survival analysis was performed for 254,821 rare tumours. One- and 5-year relative survival (RS) estimates[18] in Italy were obtained considering the pool of 37 AIRTUM CRs with cases diagnosed between 2000 and 2008, and followed up to 31st December 2009 or after. Relative survival is defined as the ratio of observed survival to the expected survival in the general population of the same age and sex and it is used to correct for deaths from causes other than the cancer under investigation. RS was calculated for patients aged 0-99. Since all patients are included (not only those followed up for 5 years) we used a *complete* analysis, which is a modification of traditional cohort approach, in which more recently diagnosed patients are also included, even if they could not possibly have completed the entire follow-up interval of interest.[19] Cancers diagnosed only on the basis of DCO, or diagnosed incidentally at autopsy or with survival time of zero days (421 tumours, 0.2%), were excluded from the analysis. Ninety-five% CI are computed through logarithmic transformation, so that the lower bound is always positive and the upper bound can exceed 100%. Whenever it happens, the upper bound is put as equal to 100%. RS for 42 rare cancers with less than 30 observed cases in the period of diagnosis 2000-2008 was considered as not estimable.

A sensitivity analysis of survival was performed restricting the analysis to 29 CRs with cases diagnosed between 2000 and 2010, and follow-up available to 31st December 2011 (data not shown). This analysis was performed to verify whether the use of more updated data would have had an impact on the survival estimates provided. In the sensitivity analysis, 11 CRs were excluded. The analysis performed on this restricted pool (29 CRs) shows percentage differences higher than 10% only for 18 rare cancers among the 198 considered ones in 1-year RS and for 42 rare cancer entities in 5-year RS. However, when considering only 29 CRs the number of analysed cases becomes smaller and the uncertainty in the estimates increases; therefore, considering the rarity of the phenomena and the narrow changes between the two analyses, we decided to present results for the 37 CR pool.

### Observed and complete prevalence

To estimate the observed prevalence in Italy – the proportion of cancer patients in a population diagnosed at age x within a given time period (L) and who are still alive at a certain reference date – incidence and follow-up data from 11 CRs for the period 1992-2006 were used, with a prevalence index date of 1st January 2007. Observed prevalence in the general population (male and female also for gender-specific rare cancers) disentangled by time prior to the reference date (<2 years, 2-5 years, <15 years) was calculated using the counting method.[20-22] When including multiple tumours, a patient will not contribute more than one tumour diagnosis to a single prevalence estimate.

The life status of cases lost to follow-up or censored before the prevalence index date was estimated from the survival probability between the censoring and the index date, derived from a subset of cancer patients matched by age and cancer.

The objective of the present monograph is to produce reliable prevalence estimations for all the 198 rare cancers. In order to achieve this objective, a standard methodology, applicable to all these rare cancers, had to be defined. The complete prevalence proportion at 1st January 2007 was estimated overall in Italy, correcting the 15-year observed prevalence by the completeness index,[23-26] to account for those cancer survivors diagnosed before the cancer registry activity started. The completeness indices estimation requires a long stable time series of incidence and survival indicators; the Italian cancer registry database, even though it is continuously increasing, could not guarantee such information for all the 198 analysed rare cancers. Moreover, sparse data did not allow to consider the geographical variability (stratifying the estimates by geographic area) of the prevalence estimates as in the previous AIRTUM monograph on prevalence for common cancers.[14]

To allow more robust estimation, the completeness indices by cancer site and age (0-4, […], 75-99 years), were obtained by means of statistical regression models using incidence and survival data available in the European CRs participating to the RARECARE[4,27] and RARECAREnet projects.

The assumptions are:

- homogeneity of time trends in incidence and survival between Italy and Europe;
- homogeneity of prevalence proportions of rare cancers among geographic areas in Italy.

For cancers with no observed cases within 2, 2-5, or 15 years in the past, prior to 1st January 2007, the observed prevalence was considered as not estimable. If the 15-year observed prevalence is not estimable (NE), then the complete prevalence has to be considered not estimable. This is the case for 13 rare cancers.

Finally, the number of prevalent cases at 1st January 2010 in Italy was calculated assuming the same prevalence proportion as in the AIRTUM sample and applying the obtained complete prevalence proportion by age (0-4, […], 75-99 years) to the corresponding Italian population at 2010 provided by ISTAT.[16]

For the purpose of including as much as possible cancer registries in the prevalence analysis, the reference date is 1st January 2007. Different and more recent reference dates would have determined a restriction of the analysed POOL.

The uncertainty that characterise rare cancers made impossible the projection of prevalence estimates to 2015, therefore only the number of prevalent cases at 1st January 2010 in Italy was calculated.

### Methodological issues

The methodological decisions, taken because of the rarity of the majority of the cancers analysed, could have led to prevalence estimates slightly different from those published by the AIRTUM monograph on prevalence for common cancers.[14]

For prevalence, the rationale of using the same methodology for all rare cancers made necessary the assumption of homogeneity between some European and Italian epidemiological indicators.

These assumptions are reasonable for the majority of the analysed rare cancers; nevertheless for diseases with markedly increasing incidence time trends and/or significant differences among geographic areas, some caution in result interpretation should be borne in mind. This

is the case for testicular and paratesticular cancers, rare epithelial tumours of hypopharynx and larynx, carcinoma of the thyroid gland. For cancers of testis and paratestis the estimated number of prevalent cases reported in the present monograph is about 45,000, slightly higher than the national prevalence estimates for testis previously published by AIRTUM[14] (about 38,000). As the incidence rates are higher at younger ages and the prognosis very good, the estimation of prevalent cases is mainly influenced by incidence. In Italy, incidence is lower in the South compared to the Centre-North, therefore the assumption of homogeneity in incidence may have determined an overestimation of prevalence.
We estimated about 53,000 persons to be alive at 1st January 2010 with a previous diagnosis of squamous cell carcinoma with variants of larynx (the majority of larynx cancer), slightly higher than the national prevalence estimates previously published by AIRTUM[14] (about 50,000). These differences may be associated with a difference in time trend among males and females,[28] assumed to be homogeneous for the above-mentioned reasons.
Thyroid cancer is a common cancer in Italy, with an IR higher than 6 per 100,000 per year during the analysed period, affected by a markedly increasing incidence over time in both sexes, with significant differences across areas:[28] the assumptions for rarity are therefore violated. As a consequence, the methodology developed for estimation of epidemiological indicators for rare cancers is not applicable and carcinoma of the thyroid gland was excluded from the specific commentary on endocrine tumours.

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# THE BURDEN OF RARE CANCERS IN ITALY

## L'IMPATTO DEI TUMORI RARI IN ITALIA

For years, most resources and attention have been directed to common cancers such as breast, colon, rectum, lung, and prostate, which still affect and kill many people every year. In reality, there are also many types of rare cancers which, taken together, account for a relatively high proportion of newly diagnosed cancers.

Rare cancers are those cancers with an incidence rate lower than 6 per 100,000 per year in the EU population.[1] Their low frequency, and the consequent limited medical expertise on the matter, create specific problems in clinical decision making, clinical research, and health care organisation. In addition, patients and their families are confronted with a wide range of difficulties arising directly from the rarity of the pathologies. Such difficulties include:

- wrong diagnosis leading to inaccurate treatments;
- delays in the period between the onset of the first symptoms and the diagnosis;[2-4]
- insufficient scientific knowledge: the small number of patients undermines the possibility to organise clinical trials and registries and tissue banks are few. This results in difficulties in developing therapeutic tools and defining the therapeutic strategy, as well as in shortage of therapeutic products;[2-4]
- lack of appropriate quality healthcare: lack of appropriate medical expertise for the management of rare cancers, poor referral rates from general practitioners, and pathologic misdiagnosis.[2-4]

The overall burden of rare cancers on society has not been adequately estimated. The "Surveillance of rare cancers in Europe" (RARECARE) project estimated that rare cancers represent 22% of all new cancer diagnoses in Europe;[1] however, country-specific estimates of rare cancer burden are still lacking.

This paper presents the burden of rare cancers in Italy, combining all 198 rare cancers in one group named "rare cancers". The descriptive epidemiology of each of the 198 rare cancers is presented in the specific data sheets of this monograph. It is the first time that such a detailed description is given for this comprehensive list of rare cancers in Italy.

The estimates of incidence, prevalence, and survival of rare cancers in Italy are based on the pool of the AIRTUM cancer registries (CRs) in 2000-2010, covering more than 30 million people, 51% of the 2013 Italian population (more information on the definition and the list of rare cancers, as well as on methods, are provided in the «Materials and methods» chapter, pp. 14-21).

### INCIDENCE

AIRTUM estimated that about 360,000 persons were diagnosed with new cancers in Italy in 2011.[6] The annual incidence rate (IR) of all 198 rare cancers in the period 2000-2010 was 147 per 100,000, corresponding to about 89,000 new diagnoses annually or 25% of all cancer diagnoses.

Five cancers, rare at European level, were not rare in Italy because their IR was higher than 6 per 100,000. These tumours were: • diffuse large B-cell lymphoma and squamous cell carcinoma of larynx, whose IRs in Italy were 7 per 100,000; • multiple myeloma (IR: 8 per 100,000); • hepatocellular carcinoma (IR: 9 per 100,000); • carcinoma of thyroid gland (IR: 14 per 100,000).

Figure 1a shows the proportion of rare cancers according to IR. Figure 1b shows the estimated number of new rare cancer diagnoses in Italy in 2010, again according to IR. The 5 cancers that are "not rare" in Italy are excluded from Figure 1.

Seventy two percent of rare cancers (No. 139/193) had an annual IR of <0.5 per 100,000 (Figure 1a). However, this plethora of rare cancers accounted for only 7,119 cases in Italy (Figure 1b). Thirteen percent of rare cancers (No. 25/193) with IR 0.5-0.9 per 100,000, accounted for 10,000 new diagnoses in Italy in 2010. On the opposite extreme, 2% of rare cancers (including only 3 rare cancers out of the 193) with an IR of 4-5 per 100,000 accounted for 8,000 new diagnoses in 2010 in Italy. This distribution of rare cancers by IR is similar to the one observed in Europe.[1]

It is noteworthy that 19% of Italians with a rare cancer (17,138/89,000) have one of the particularly rare forms that affect <1 per 100,000 (Figure 1b) and this is important, because low incidence is a major obstacle to conducting clinical trials to develop effective treatments. The proportion of Europeans with a particularly rare form of rare cancer was 30%.[1]

Five cancers that are rare in Europe were common in Italy. These 5 cancers affected around 30,000 Italians (data not shown), thus rarity-specific critical issues were not relevant in Italy for these 5 cancers, unlike in Europe.

Among all rare cancers, 7% were rare haematological diseases, 18% were solid rare cancers. Figure 2 describes the distribution of the 13 groups of solid rare cancers presented in this monograph (for detailed definition of the grouping, please refer to «Materials and methods», pp.14-21 ), among all rare solid tumours. Rare epithelial tumours of the digestive system were the most common (23%), followed by epithelial tumours of head and neck and rare tumours of the female genital system (17%), tumours of the endocrine organs (13% including thyroid carcinoma), sarcomas (8%), central nervous system tumours, and rare epithelial tumours of the thoracic cavity (5%). The remaining (rare male genital tumours, tumours of eye, neuroendocrine tumours, embryonal tumours, rare skin tumours, malignant melanoma of mucosa) each comprised <4% of all solid rare cancers (Figure 2).

Figure 3 shows age-specific IRs for rare and common cancers. Considering 3 major age-groups, IR of rare cancers was 15 per 100,000 in children (0-14 years), 45 per 100,000 in adolescents and young adults (15-39 years) and 245 per 100,000 in adults (40+ years). The

Figure 1A

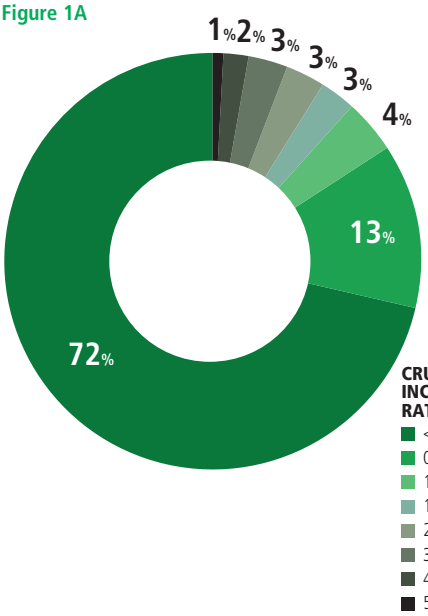


Figure 1B

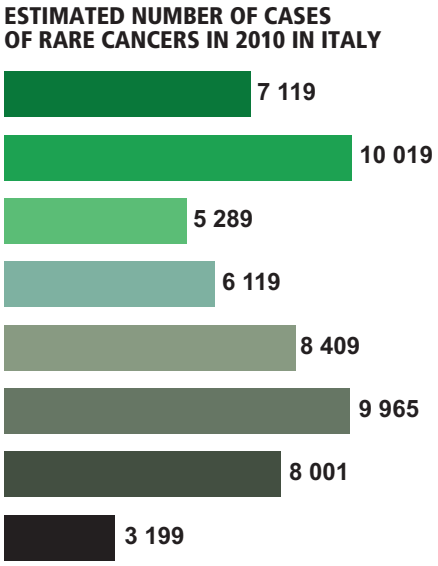


**Figure 1.** Proportion of rare cancers (**A**) and estimated number of new cases of rare cancers (**B**) in Italy in 2010 by crude incidence rate. Crude incidence rate for 193 out of the 198 rare cancers of the RARECAREnet list grouped together and obtained from the Pool of 39 AIRTUM cancer registries in 2000-2010. The 5 cancers that are not rare in Italy are excluded.

Figure 2

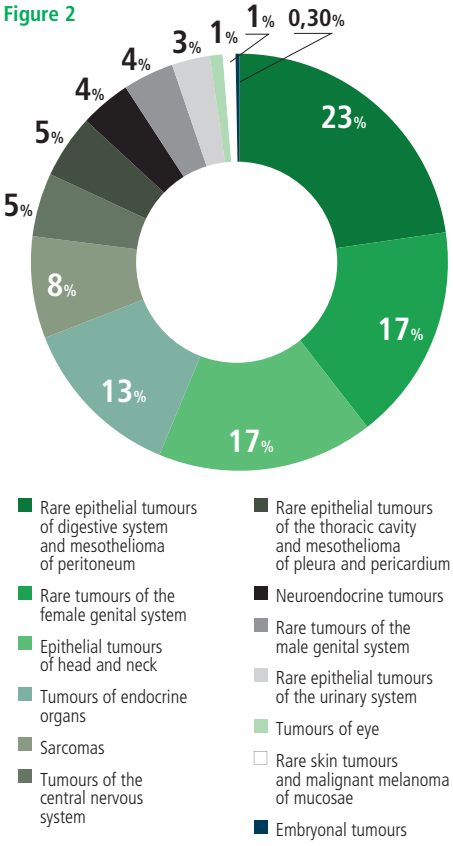


**Figure 2.** Distribution of the 13 groups of rare solid cancers presented in this monograph among all solid rare cancers. AIRTUM Pool of 39 cancer registries (period of diagnosis 2000-2010).

corresponding figures for common cancers were 0.3 per 100,000, 26 per 100,000 and 608 per 100,000 (data not shown). Essentially, all childhood cancers were rare and, from age 40 on, the common cancers (breast, prostate, colon, rectum, and lung) became increasingly prominent.

Table 1 shows incidence, 5-year relative survival (RS) and prevalence of rare and common cancers for 7 out of the 14 groups of rare cancers presented in this monograph. The objective is to present differences between rare and common cancers, thus only the 7 groups with common and rare cancers are included. This is the only table with estimates on common cancers. In the rare-cancer-specific data sheets, common cancers are not presented. Rare cancers constituted 74% of incident haematological malignancies, 17% of incident female genital system cancers, 16% of incident digestive system cancers, 8% of incident respiratory cancers. Rare cancers were ≤6% of incident cancers at other sites.

Table 2 describes the number of expected cases in Italy and by Italian region in 2010 of all 198 rare cancers and of 2 groups of rare cancers representative of very low and very high IR (within the cut-off of rarity of <6 per 100,000): embryonal tumours (IR of 0.4 per 100,000) and neuroendocrine tumours (IR of 4.15 per 100,000). For embryonal tumours the number of new expected cases ranged from 1 in Valle D'Aosta and Molise to 39 in Lombardia, with most of the other regions having less than 20 cases per year. For neuroendocrine tumours the number of new expected cases was relevant in regions with a large population, such as Lombardia, Lazio, Campania, and Sicilia. However, for many of the other regions the number of new cases was still lower than 100 per year. With these numbers of rare cancers per region, the identification of centres of

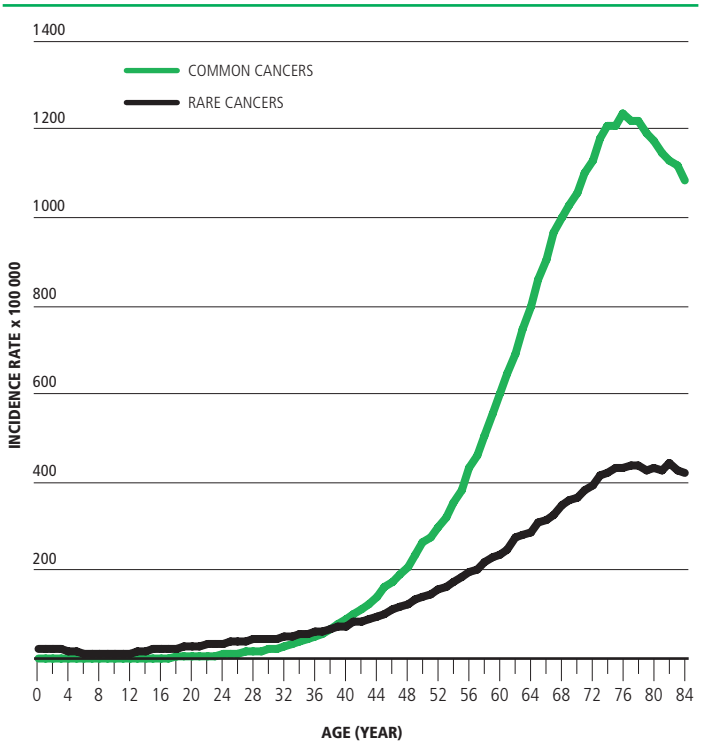


**Figure 3.** Age-specific incidence rates for rare and common cancers (solid + haematological tumours) of the RARECAREnet list in Italy, period of diagnosis 2000-2010. AIRTUM Pool of 39 cancer registries.

| GROUPS OF CANCER | | INCIDENCE RATE (x100 000) | 95%CI | 5-YEAR RS (%) | 95%CI | COMPLETE PREVALENCE PROPORTION (x100 000) | 95%CI |
|---|---|---|---|---|---|---|---|
| EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM | rare | 26 | 25.9-26.3 | 20 | 19.2-20.1 | 74 | 72.4-76.3 |
| | common | 135 | 134.9-135.9 | 51 | 50.8-51.4 | 735 | 728.8-741.8 |
| EPITHELIAL TUMOURS OF THE THORACIC CAVITY | rare | 5 | 5.3-5.5 | 17 | 15.4-17.6 | 17 | 16.3-18.3 |
| | common | 66 | 65.3-65.9 | 17 | 16.8-17.5 | 112 | 109.4-114.3 |
| TUMOURS OF THE FEMALE GENITAL SYSTEM | rare | 19 | 18.4-18.7 | 65 | 64.6-65.9 | 265 | 259.5-269.6 |
| | common | 93 | 92.4-93.2 | 88 | 87.9-88.4 | 1150 | 1135.9-1164.3 |
| EPITHELIAL TUMOURS OF THE URINARY SYSTEM | rare | 3 | 2.8-3.0 | 54 | 52.3-55.9 | 23 | 21.7-24.1 |
| | common | 44 | 43.8-44.3 | 73 | 72.6-73.6 | 402 | 389.8-413.2 |
| TUMOURS OF THE MALE GENITAL SYSTEM | rare | 4 | 4.0-4.2 | 90 | 88.9-90.7 | 89 | 84.8-92.7 |
| | common | 65 | 64.2-64.8 | 94 | 93.2-94.0 | 567 | 561.2-572.8 |
| SKIN TUMOURS^ | rare | 1 | 0.7-0.8 | 75 | 71.4-79.1 | 8 | 6.8-8.2 |
| | common | 14 | 14.3-14.7 | 85 | 84.1-85.4 | 238 | 234.0-242.6 |
| HAEMATOLOGIAL DISEASES | rare | 41 | 40.8-41.4 | 55 | 54.3-55.2 | 278 | 271.1-284.5 |
| | common | 15 | 14.4-14.7 | 71 | 70.4-72.4 | 82 | 79.4-83.8 |

**Table 1.** Crude incidence rate, 5-year relative survival (RS) and complete prevalence for rare and common cancers of the RARECAREnet list for 7 out of the 14 groups of rare cancers presented in this monograph (only groups with common cancers are included). AIRTUM Pool.* 95%CI: 95% confidence intervals.

* Incidence rate obtained from 39 AIRTUM cancer registries, period of diagnosis 2000-2010; 5-year relative survival calculated on the basis of 37 AIRTUM cancer registries, period of diagnosis 2000-2008 and follow-up till 31st December 2009; complete prevalence, obtained correcting the 15-year observed prevalence (incidence and survival data from a pool of 11 AIRTUM cancer registries, period of diagnosis 1992-2006, prevalence index date: 1st January 2007).
^ excluding non melanoma skin cancer

| REGION | POPULATION AT 1ST JANUARY 2010 | ESTIMATED NEW CASES OF RARE CANCER (ITALY 2010) RATE (x100 000 PER YEAR) | | |
|---|---|---|---|---|
| | | 198 rare cancers of the RARECAREnet list grouped together (IR: 147 per 100 000) | embryonal tumours (IR: 0.4 per 100 000) | neuroendocrine tumours (IR: 4.15 per 100 000) |
| VALLE D'AOSTA | 127 866 | 188 | 1 | 5 |
| MOLISE | 320 229 | 471 | 1 | 13 |
| BASILICATA | 588 879 | 867 | 2 | 24 |
| UMBRIA | 900 790 | 1 326 | 4 | 37 |
| TRENTINO-ALTO ADIGE | 1 028 260 | 1 514 | 4 | 43 |
| FRIULI VENEZIA GIULIA | 1 234 079 | 1 816 | 5 | 51 |
| ABRUZZO | 1 338 898 | 1 971 | 5 | 56 |
| MARCHE | 1 559 542 | 2 296 | 6 | 65 |
| LIGURIA | 1 615 986 | 2 379 | 6 | 67 |
| SARDEGNA | 1 672 404 | 2 462 | 7 | 69 |
| CALABRIA | 2 009 330 | 2 958 | 8 | 83 |
| TOSCANA | 3 730 130 | 5 490 | 15 | 155 |
| PUGLIA | 4 084 035 | 6 011 | 16 | 169 |
| PIEMONTE | 4 395 569 | 6 470 | 18 | 182 |
| EMILIA-ROMAGNA | 4 446 230 | 6 544 | 18 | 185 |
| VENETO | 4 912 438 | 7 231 | 20 | 204 |
| SICILIA | 5 042 992 | 7 423 | 20 | 209 |
| CAMPANIA | 5 681 868 | 8 363 | 23 | 236 |
| LAZIO | 5 824 662 | 8 573 | 23 | 242 |
| LOMBARDIA | 9 826 141 | 14 463 | 39 | 408 |
| ITALY | 60 340 328 | 88 816 | 241 | 2 504 |

Source of population data: http://demo.istat.it/pop2010/index1.html

**Table 2.** Estimated new cases of rare cancers, obtained applying the crude incidence rate (IR) (AIRTUM Pool of 39 cancer registries, period of diagnosis 2000-2010) to the Italian population in 2010. Estimated new cases for 2 groups of rare cancers (embryonal tumours and neuroendocrine tumours) obtained applying the incidence rate of each group (0.4 and 4.15 per 100,000) to the Italian population in 2010. These 2 groups of rare cancers are representative of rare cancers with very low IR and relatively high IR.

expertise dedicated to specific groups of rare cancers at regional level does not seem feasible. The number of cases per region (especially for very rare cancers such as embryonal tumours) does not make it possible to reach adequate expertise to treat such tumours regionally. A national (inter-regional) organisation would seem more appropriate for rare cancers.

## SURVIVAL

For patients with rare cancers diagnosed in 2000-2008, 5-year RS was 55%; the corresponding figure for patients with common cancers was 68% (Figure 4) (p<0.001). Rare cancers had a worse prognosis than common cancers in many sites but not in the thoracic cavity (Table 1). Relative survival was lower for rare cancers at 1 year and continued to diverge up to 3 years, while the gap remained constant from 3 to 5 years after diagnosis (Figure 4)(p<0.001).
Figure 5 shows 5-year RS for rare and common cancers by age class. For patients 0-54 years – most of whose cancers were rare – survival did not differ between common and rare cancers. The survival disadvantage of having a rare cancer increased from -16% at 55-64 years to -23% at 75+ years.

## PREVALENCE

We estimated that about 900,000 persons were alive in Italy in 2010 with a previous diagnosis of a rare cancer.
Table 1 shows incidence, 5-year RS, and prevalence of rare and common cancers for 7 out of the 14 groups of rare cancers presented in this monograph. The prevalence of a disease depends on two time-dependent characteristics which are independent of one another: incidence and survival. Thus, looking at incidence and survival data, it is possible to interpret the prevalence. This is important for the definition of rare cancer (please refer to the box *Incidence vs. prevalence* in the «Material and methods» chapter, p. 14).
Within the groups of cancers of Table 1, the highest prevalence was observed for rare haematological diseases and rare tumours of the female genital system. The high prevalence of these two groups of rare tumours is explained by their high IR (41 per 100,000 and 19

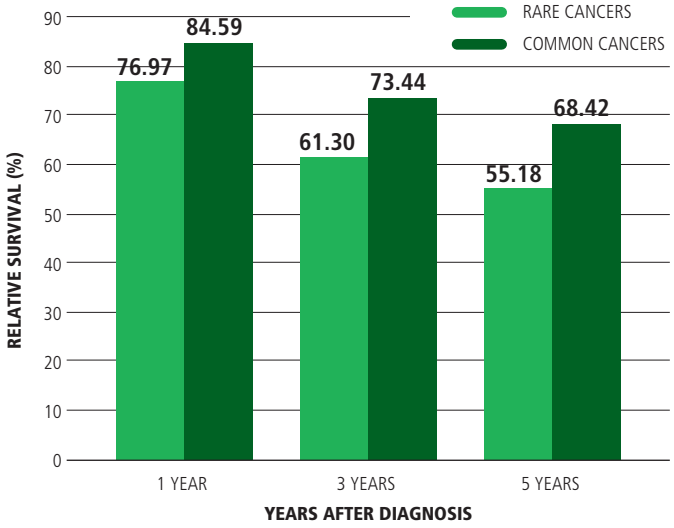


**Figure 4.** Relative survival (%) for rare and common cancers of the RARECAREnet list in Italy by time since diagnosis (1, 3, and 5 years). Cases diagnosed in 2000-2008, and followed up to 31st December 2009. AIRTUM Pool of 37 cancer registries.

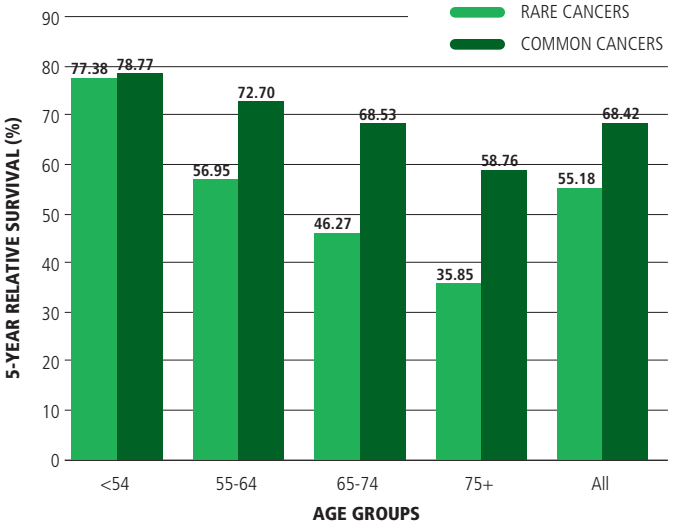


**Figure 5.** Five-year relative survival (%) for rare and common cancers of the RARECAREnet list in Italy by age group. Cases diagnosed in 2000-2008, and followed up to 31st December 2009. AIRTUM Pool of 37 cancer registries.

per 100,000, respectively) and their intermediate 5-year RS (55% and 65%, respectively).

Very low prevalence (<10 per 100,000) was observed for rare epithelial skin cancers, which had a very low IR (<1 per 100,000) and a relatively high 5-year RS (75%). In this case, the incidence contributes to the low prevalence of these tumours.

The low prevalence of rare epithelial tumours of the digestive system was due to the low survival rates of the majority of tumours included in this group (oesophagus, stomach, small intestine, pancreas, and liver), regardless of the high IR of the rare epithelial cancers of these sites.

Rare epithelial tumours of the thoracic cavity had a relatively low incidence and survival. This group included very rare cancers with a very poor prognosis, such as mesothelioma of pleura, trachea, and rare histotypes of lung.

## DISCUSSION

### Proportion of rare cancers in Italy

Our estimates indicate that 25% of all cancers diagnosed in Italy in 2010 were rare, similar to the estimates reported in Europe (24%, see www.rarecarenet.eu). In Italy, the higher proportion of rare cancers is due to the fact that the group of all rare cancers combined includes 5 cancers that are rare according to the EU rate, but common in Italy: diffuse large B-cell lymphoma, squamous cell carcinoma of larynx, multiple myeloma, hepatocellular carcinoma, and carcinoma of thyroid gland. The latter is the one which contributes most to the high proportion of rare cancers in Italy. Thus, without thyroid carcinoma the proportion of rare cancers in Italy in 2010 would be 22%.

Differences in incidence across populations can be due to the different distribution of risk factors (environmental, lifestyle, occupational, and genetic), to heterogeneous intensity in diagnostic activity, as well as to different diagnostic capacity. Nevertheless, differences in IR may also be due to the heterogeneity in the proportion of microscopically confirmed cases in different populations and, more importantly, to the different capacity of pathologists of identifying the accurate histotype. In addition, CRs might not always be able to retrieve the detailed pathological diagnosis. This is important for rare cancers because they are defined on the basis of morphology and topography, which require a detailed pathological diagnosis (for more information on the list of rare cancers, please refer to «Materials and methods», pp. 14-21).

Among the cancers that are rare on the basis of the European IR and not the Italian one, thyroid cancers show an incidence peak in the middle age in Italy (45-49 years in women and 65-69 in men)[7] and are 3-fold more frequent in females than in males. The female predominance of thyroid cancer remains largely unexplained. Considered rare until a few years ago, thyroid cancers have shown a marked increase in incidence worldwide, with a different pace across countries. This increased incidence seems mainly due to small papillary tumours that show an excellent prognosis, which could explain the stable mortality. The topic is still being discussed, especially with regard to how much of the observed increase in incidence is explained by the increased use of ultrasound in the last decades, opportunistic screening of thyroid disease, and enhanced health care access, which have led to an overdiagnosis of small and indolent tumours.[7-12] A greater access of women to health service and diagnostic procedures in childbearing age could contribute to the higher incidence of thyroid cancer in females. In Italy, the incidence of thyroid carcinoma increased sharply up to mid 2000 (+11.4% per year among men and +17.5% among women) and plateaued in recent years.[7] The increasing trend can explain the high incidence rate of thyroid cancers observed in Italy.

Over 70% of cases of primary liver cancers are attributable to known risk factors, primarily related to the prevalence of hepatitis C (HCV). In Italy, HCV prevalence explains the observed high IR and the already reported regional differences in incidence, with an atypical South-North gradient.[13,14] Although infection with hepatitis B virus (HBV) is related to the onset of the disease, its role is expected to drop as a result of vaccination campaigns in infants born from 1978 onwards. In areas of Northern Italy, about one third of tumours of the liver are also attributable to the abuse of alcohol.[7]

Alcohol and tobacco are the two most important risk factors for cancer of the head and neck, in particular for cancers of the oral cavity, oropharynx, hypopharynx, and larynx.[15-18] At least 75% of cancers of the head and neck are caused by tobacco and alcohol.[19] People who use both tobacco and alcohol are at increased risk of developing these cancers than people who use just one of the two.[19-21] In Italy these neoplasms during 2007-2011 were, in both males and females, more common in Northern and Southern regions than in those of the Centre, reflecting the distribution of the well-known risk factors. Temporal trends of head and neck tumours are associated with the prevalence of one of the main risk factors (cigarette smoking). Thus, a decrease in head and neck incidence was observed among men, whereas an increase in incidence was reported among women, although it was not statistically significant.[22]
To conclude, the high prevalence of known risk factors such as alcohol consumption and smoking, the prevalence of HCV, and diagnostic pressure seems to contribute to explain the high incidence rates of laryngeal, thyroid, and liver cancers which are rare at European level but not so rare in Italy.

### Survival of rare cancers

Rare cancers had worse RS than common cancers at 1, 3, and 5 years from diagnosis. For patients with rare cancers diagnosed in 2000-2009, 1-, 3-, and 5-year RS was 77%, 61%, and 55%, respectively; the corresponding figures for patients with common cancers were 85%, 73%, and 68% (Figure 4). Differences between rare and common cancers were small 1 year after diagnosis, but survival for rare cancers declined more markedly thereafter, consistent with the idea that treatments for rare cancers are less effective than those for common cancers. However, the difference between 1- and 3-year RS for rare cancers was high and higher than that for common cancers, suggesting that even stage at diagnosis could be a contributing factor in the poorer RS for rare cancers.
Rare cancers include many cancer entities with a bad prognosis (5-year RS<50%): cancers of head and neck, oesophagus, small intestine, ovary, brain, biliary tract, liver, pleura, multiple myeloma, acute myeloid and lymphatic leukemia.[23] In contrast, most common cancer cases are breast, prostate, and colorectal cancers, which have a good prognosis (5-year survival, 81%, 77%, and 54%, respectively).[23]
It is unclear why survival for rare cancers is low, especially in adults. Possibilities include factors inherent in the diseases, and inadequacies of care or treatment, including delayed diagnosis, lack of effective therapies, or lack of evidence-based treatment guidelines.
Even though, overall, rare cancers seem to have a worse prognosis than common cancers, it is worth stressing that rare cancers even include cancers with a good prognosis. Five-year RS was highest (≥90%) for testicular cancers, which were the most common tumours among rare male genital cancers. In the group of rare cancers, all 198 rare cancers are considered, including thyroid carcinoma, for which no specific commentary and data are provided because of methodological issues (please refer to «Materials and methods», pp.14-21). Survival was relatively high for tumours of the eye, rare skin tumours, and embryonal tumours. Survival was poor for rare epithelial tumours of the thoracic cavity and digestive system, and for central nervous system tumours. The other major groups of rare cancers had survival ranging from 50% to 65%. Finally, despite these results, examples of success do exist in rare cancer treatment. In the world of adult oncology, the astonishing success of Glivec in 2 rare cancers – chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumour (GIST) – moved the field of molecularly targeted therapies into high gear and controlled these two killer diseases.
Regarding differences of survival by age group, it is important to note that most cancers in children and young adults were rare (Figure 3) and usually of embryonal or haematological types, for which effective treatments are available. In older patients, most of the rare cancers were rare epithelial forms, for which therapies are not as effective as those for rare paediatric cancers. In addition, advances in treatment as a result of clinical trials have markedly improved prognoses for many childhood cancers over the last 30-40 years.[24] Perhaps this lesson can be applied to rare cancers in adults.

### Challenges of rare cancers: what should be done?

Rare cancers represent 25% of all new cancers diagnosed in Italy each year; most rare cancers are very rare (for 72% of them, the incidence rate is <0.5 per 100,000).
Rare cancer patients and their families are confronted with a wide range of difficulties specifically caused by the rarity of these diseases. These difficulties are hard to overcome, but some suggestions can be made even with the currently limited but growing knowledge and means:

- both in Italy and across Europe, establish centres of expertise for rare cancers as well as networks of these centres in order to achieve the required organisational structure and expertise. This is also necessary in order to recruit the number of patients needed to carry out clinical trials, to develop alternative study designs and methodological approaches. It will also help in improving the accuracy and standardisation of staging procedures and treatment for rare cancers;[2]
- develop a multidisciplinary clinical approach;
- spread knowledge and good clinical practice guidelines on rare cancers;
- increase awareness about rare cancers amongst general practitioners and pathologists;[2]
- disseminate information tailored to the needs of patients and all concerned stakeholders;
- support patient associations to build the capacity of patient groups;
- continue to encourage initiatives to put rare cancers on the map.

The European Commission is responding to the problems of rare cancers in several ways, including the implementation of Directive 2011/24/EU of the European Parliament and the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. This Directive is meant to grant European patients the right to access safe, good-quality treatment across European borders. Amongst its provisions, article 12 refers to the notion of European Reference Networks (ERNs) for rare and complex diseases, including rare cancers, calling for strong collaboration between Member States.[25]
In Italy, the "Rete Tumori Rari" (Italian rare cancer network)[26] was first established in 1997 to provide diagnosis and care for sarcomas with the aim of covering rare adult solid cancers. Due to the main clinical interest of the coordinating group at the Fondazione IRCCS, Istituto Nazionale Tumori (Italian National Cancer Insti-

tute, Milan), sarcomas were the first and main subject of this Network. In the last 15 years, the network has grown to include 100 centres of expertise and is currently working on enlarging its scope to additional rare solid cancers. However, it is based on the voluntary collaboration of participating centres. Formalising the "Rete Tumori Rari" is an urgent measure, which should include the identification of centres of expertise for rare cancers in Italy. This will help to ensure adequate care to all Italians diagnosed with a rare cancer and to guarantee the participation of Italy in the upcoming European Reference Networks.

## CONCLUDING REMARKS

For the first time in Italy, the present monograph has provided figures for a problem long known to exist. The data retrieved from AIRTUM confirm that rare cancers are a major public health problem in Italy. The monograph also provides epidemiologic indicators for 198 rare cancers, the majority of which (72%) are very rare. Thanks to the present monograph, health care planners have all the data of expected incident and prevalent cases to properly plan and reorganise health care services. Researchers can now better plan clinical trials, considering alternative study designs and statistical approaches. These data also show that CRs can be a source of information even to build external control groups in clinical trials.
National and regional health technology assessment agencies have important data for their assessment.
Clinicians have data on incidence and prognosis of cancer entities that had never been provided before, such as neuroendocrine tumours and soft tissue sarcomas, as well as detailed morphologies rarely reported in the classic statistics.
Patients have their cancers officially recognised and measured, thus no longer hidden by the common cancers.
We believe that this monograph is a major step forward in the description of the burden of rare cancers in Italy and should provide an opportunity to work on the quality of rare cancer data, strengthening collaboration with oncologists, pathologists, patients' associations, and the Rete tumori rari.

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# A GUIDE TO THE CANCER-SPECIFIC DATA SHEETS

# GUIDA ALLA LETTURA DELLE SCHEDE SPECIFICHE PER TUMORE

## HOW TO READ THE CANCER-SPECIFIC DATA SHEETS

This guide is for laymen. For more detailed information please refer to the «Material and methods» chapter (pp. 14-21).

This monograph includes 14 data sheets. Every sheet shows data of a major group of rare tumours identified by combining rare cancers of broad anatomic sites sharing the same clinical referral pattern and expertise.

In this guide the **Rare epithelial tumours of the thoracic cavity** group is used as an example to clarify how rare cancers were identified and described in each group.

## HOW THE RARE CANCER GROUPS WERE IDENTIFIED

The rare cancers included in each of the 14 groups come from the RARECARE list of cancers (see Annex 1, supplementary material on-line). Briefly, the RARECARE list of cancers has a hierarchal structure:

- **tier 2** includes several specific cancer histotypes (identified by the ICD-O-3 morphology and topography codes) considered to require similar clinical management and research;
- **tier 1** includes the tier 2 entities plus the Not Otherwise Specified (NOS) morphologies. Tier 1 includes cancers considered to involve the same clinical expertise and patient referral structure.

In this AIRTUM monograph, tier 1 is written in green uppercase, tier 2 entities are written in black below the tier 1 they belong to, and are never in all caps.

In the RARECARE list, a tier 1 can be common or rare, but in this monograph only data on *rare* cancers are presented, therefore:

- **if a tier 1 is common** (incidence >6 per 100,000 at EU level), such as epithelial tumours of lung, the common tier 2 entities of this tier and the NOS histotype are excluded from the tier 1 definition (e.g., for the lung: squamous cell carcinoma, adenocarcinoma, and poorly differentiated endocrine carcinoma are excluded from tier 1 together with the NOS histotypes; see the example below). As its common cancers and the NOS morphologies are excluded, the tier 1 is labelled as **RARE** EPITHELIAL TUMOURS OF LUNG (to clarify that only the rare histotypes are included);
- **if a tier 1 is rare** (incidence rate <6 per 100,000 at EU level), such as epithelial tumours of trachea, all the corresponding tier 2 entities as well as the NOS histotypes are included in the tier 1 definition. The label will not include the "*rare*" specification because all the included cancers are rare.

**EPITHELIAL TUMOURS OF TRACHEA**
**Tier 1** includes all the corresponding tier 2 entities, as well as the NOS histotypes. It is not necessary to add the "rare" specification to the label.

**EPITHELIAL TUMOURS OF LUNG**
**Tier 1** includes only the rare corresponding tier 2 entities, while common tier 2 entities and NOS morphologies are excluded. The label includes the "rare" specification.

## AN EXAMPLE

## RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY

| MAJOR GROUP | RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY | TOPOGRAPHY ICD-O-3 CODE | MORPHOLOGY ICD-O-3 CODE |
|---|---|---|---|
| TIER 1 | EPITHELIAL TUMOURS OF TRACHEA | C33.9 | 8000-8001, 8004, 8010-8011, 8012, 8020-8022, 8031-8032, 8033, 8050-8076, 8078, 8082-8084, 8140-8141, 8143- 8144, 8147, 8190, 8200-8201, 8210-8211, 8221, 8230-8231, 8255, 8260-8263, 8290, 8310, 8315, 8320, 8323, 8333, 8380-8384, 8430, 8440-8441, 8470, 8480-8482, 8490, 8504, 8510, 8512, 8514, 8525, 8542, 8550-8551, 8560, 8562-8576, 8980, 8982 |
| Tier 2 | Squamous cell carcinoma with variants of trachea | C33.9 | 8004, 8020-8022, 8031-8032, 8050-8076, 8078, 8082-8084, 8560, 8980 |
| Tier 2 | Adenocarcinoma with variants of trachea | C33.9 | 8140-8141, 8143, 8144, 8147, 8190, 8201, 8210-8211, 8221, 8230, 8231, 8255, 8260-8263, 8290, 8310, 8315, 8320, 8323, 8333, 8380-8384, 8440-8441, 8470, 8480-8482, 8490, 8504, 8510, 8512, 8514, 8525, 8542, 8550-8551, 8562-8576 |
| Tier 2 | Salivary gland type tumours of trachea | C33.9 | 8200, 8430, 8982 |
| TIER 1 | RARE EPITHELIAL TUMOURS OF LUNG | C34.0-34.9 | 8560, 8012, 8014, 8034, 8071, 8072, 8074, 8123, 8200, 8430, 8982, 8004, 8022, 8030-8033, 8074, 8972, 8980 |
| COMMON | ~~Squamous cell carcinoma with variants of lung~~ | C34.0-34.9 | |
| COMMON | ~~Adenocarcinoma with variants of lung~~ | C34.0-34.9 | |
| Tier 2 | Adenosquamous carcinoma of lung | C34.0-34.9 | 8560 |
| Tier 2 | Large cell carcinoma of lung | C34.0-34.9 | 8012, 8014, 8034, 8071-8072, 8123 |
| COMMON | ~~Poorly differentiated endocrine carcinoma of lung~~ | C34.0-34.9 | |
| Tier 2 | Salivary gland type tumours of lung | C34.0-34.9 | 8200, 8430, 8982 |
| Tier 2 | Sarcomatoid carcinoma of lung | C34.0-34.9 | 8004, 8022, 8030-8033, 8074, 8972, 8980 |
| TIER 1 | EPITHELIAL TUMOURS OF THYMUS | C37.9 | 8000-8001,8003, 8010-8011, 8012, 8020-8022, 8032, 8033, 8050-8076, 8078, 8082-8084, 8123, 8140-8141, 8143-8144, 8147, 8190, 8200-8201, 8210-8211, 8221, 8230-8231, 8255, 8260-8263, 8290, 8310, 8315, 8320, 8323, 8333, 8380-8384, 8430, 8440-8441, 8480-8482, 8490, 8504, 8510, 8512, 8514, 8525, 8542, 8550-8551, 8560... |

# A GUIDE TO THE CANCER-SPECIFIC DATA SHEETS

## AN EXAMPLE
## RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY

**INCIDENCE (OF THE MAJOR GROUP)**
Estimated number of Italians (M+F) diagnosed with a rare epithelial tumour of the thoracic cavity in 2015.

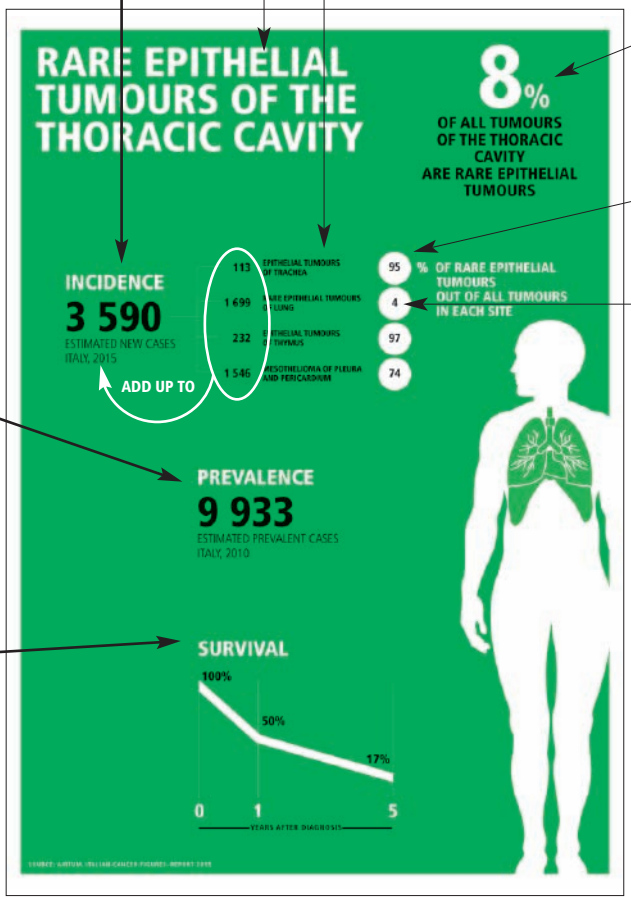
**PREVALENCE (OF THE MAJOR GROUP)**
Estimated number of Italians (M+F) diagnosed with a rare epithelial tumour of the thoracic cavity who were alive in 2010 (date of the last reliable estimate), regardless of time since diagnosis.

**SURVIVAL (OF THE MAJOR GROUP)**
Proportion of Italians (M+F) still alive 1 and 5 years after receiving a diagnosis of a rare epithelial tumour of the thoracic cavity. These figures refer to diagnoses delivered in the period 2000-2008 and are calculated net of deaths from other causes.

**Are these actually registered cases? No, these are estimated cases. The AIRTUM Network covers 52% of the Italian population, which is why we have to use statistics to estimate the number of cases at the national level.**

MAJOR GROUP

TIER 1




Percentage of rare epithelial tumours of the thoracic cavity out of all tumours (common+rare) of the thoracic cavity.

In the white circle: percentage of rare epithelial tumours out of all tumours (common+rare) of a tier 1.

**FOR EXAMPLE:**
the 1,699 rare epithelial tumours expected in Italy in 2015 represent only 4% of all the tumours of the lung (common+rare) which are diagnosed in the country in the same period.

**Note:** this percentage was calculated on the AIRTUM pool cases observed in 2000-2010, see incidence table next page.

**GLOSSARIO E GUIDA IN ITALIANO SONO DISPONIBILI ON-LINE.**

**GLOSSARY AVAILABLE ON-LINE**

# A GUIDE TO THE CANCER-SPECIFIC DATA SHEETS

## AN EXAMPLE
## RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY

The **CRUDE INCIDENCE RATE** is the ratio between the number of new cases arising in a specific population and the total number of subjects (males and females) at risk during the same period. Usually it is expressed as annual rate per 100,000 subjects.

* **E.g., large cell carcinoma of the lung: Crude rate = 1.84 per 100,000/year means that in the areas covered by AIRTUM less than 2 persons out of 100,000 develop this kind of cancer.**

**Note:** even in the case of gender-specific tumours – such as male and female genital tumours – the denominator of the ratio is the resident M+F population.

The **CONFIDENCE INTERVAL (CI)** is the measure of the uncertainty of the figures we present. The larger the interval, the more uncertain the figures. When you read the value of an indicator we suggest you also look at the CI in which the value is included.

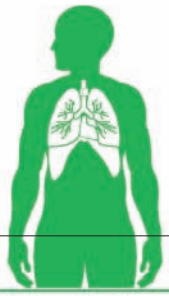
* **E.g., incidence rate 1.84, CI:1.78-1.89. This CI is narrow, showing reliability of the provided estimation.**

**Note:** confidence intervals equal to 0.00-0.00 mean that both lower and upper boundaries are smaller than 0.01 (e.g., 0.001-0.004), therefore when they are rounded to two decimal places they become 0.00.

The **CRUDE INCIDENCE RATE** was calculated for populations divided into gender groups (M-F) and age groups.

**AGE GROUPS** are wider than usual because of the rarity of the tumours and are the same for all the major groups of tumours except for embryonal tumours, where special attention was paid to children and young people.

**Note:** the sex- and age-specific rates for cancers with less than 15 observed cases between 2000 and 2010 were considered not estimable (NE).



# INCIDENCE

**RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY** | **5.42** | **5.33-5.52** | **13 027** | **8%** | **8.57** | **8.39-8.74** | **2.48** | **2.39-2.57** | **0.87** | **0.82-0.92** | **10.14** | **9.77-10.53** | **18.08** | **17.69-18.49** | **3 590** |
| EPITHELIAL TUMOURS OF TRACHEA | 0.17 | 0.15-0.19 | 374 | 95% | 0.27 | 0.24-0.30 | 0.07 | 0.06-0.09 | 0.03 | 0.02-0.04 | 0.33 | 0.27-0.41 | 0.55 | 0.48-0.62 | 113 |
| Squamous cell carcinoma with variants of trachea | 0.08 | 0.07-0.09 | 175 | | 0.14 | 0.11-0.16 | 0.03 | 0.02-0.04 | 0.01 | 0.01-0.02 | 0.16 | 0.12-0.22 | 0.26 | 0.21-0.31 | 53 |
| Adenocarcinoma with variants of trachea | 0.03 | 0.02-0.04 | 64 | | 0.05 | 0.04-0.06 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.08 | 0.05-0.12 | 0.08 | 0.06-0.11 | 19 |
| Salivary gland type tumours of trachea | 0.01 | 0.01-0.02 | 26 | | 0.01 | 0.01-0.02 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.02 | 0.01-0.04 | 0.03 | 0.02-0.05 | 8 |
| RARE EPITHELIAL TUMOURS OF LUNG | 2.58 | 2.51-2.65 | 5 722 | 4% | 4.37 | 4.24-4.49 | 0.91 | 0.85-0.96 | 0.40 | 0.36-0.43 | 4.97 | 4.71-5.25 | 8.57 | 8.30-8.85 | 1 699 |
| Adenosquamous carcinoma of lung | 0.41 | 0.38-0.44 | 909 | | 0.66 | 0.61-0.71 | 0.18 | 0.15-0.20 | 0.06 | 0.05-0.08 | 0.76 | 0.66-0.87 | 1.39 | 1.28-1.50 | 268 |
| Large cell carcinoma of lung | *1.84 | *1.78-1.89 | 4 071 | | 3.18 | 3.07-3.29 | 0.58 | 0.54-0.62 | 0.26 | 0.23-0.28 | 3.53 | 3.31-3.76 | 6.20 | 5.97-6.43 | 1 213 |
| Salivary gland type tumours of lung | 0.06 | 0.05-0.07 | 140 | | 0.09 | 0.07-0.11 | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | 0.12 | 0.09-0.17 | 0.15 | 0.11-0.19 | 41 |
| Sarcomatoid carcinoma of lung | 0.27 | 0.25-0.29 | 602 | | 0.44 | 0.40-0.48 | 0.11 | 0.09-0.13 | 0.05 | 0.04-0.06 | 0.56 | 0.48-0.66 | 0.85 | 0.76-0.94 | 177 |
| EPITHELIAL TUMOURS OF THYMUS | 0.36 | 0.34-0.39 | 804 | 97% | 0.41 | 0.38-0.45 | 0.32 | 0.28-0.35 | 0.18 | 0.16-0.20 | 0.73 | 0.64-0.84 | 0.75 | 0.67-0.84 | 232 |
| Malignant thymoma | 0.28 | 0.25-0.30 | 612 | | 0.31 | 0.28-0.35 | 0.24 | 0.21-0.27 | 0.15 | 0.13-0.17 | 0.56 | 0.47-0.65 | 0.54 | 0.47-0.61 | 175 |

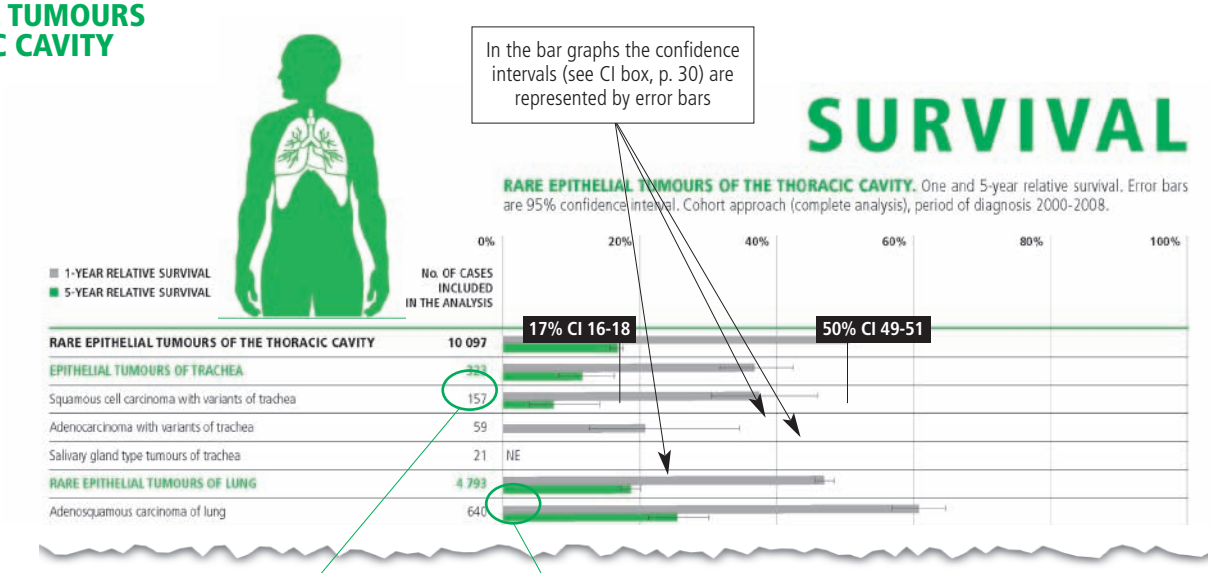
**Note:**
for **RARE EPITHELIAL TUMOURS OF LUNG** the sum of the observed cases of tier 2 entities (5,722) is exactly the same as the number of observed cases of the corresponding tier 1 (5,722) because tier 1 includes only rare tier 2 entities and exclude common tier 2 entities and NOS morphologies.

For **EPITHELIAL TUMOURS OF TRACHEA** the sum (265) of the observed cases of tier 2 entities is different from the number of observed cases of the corresponding tier 1 (374) because tier 1 includes NOS histotypes. NOS histotypes are never included in tier 2 because tier 2 entities include rare cancers which, by definition, are identified by detailed morphologies.

**Note:**
the absolute numbers reported in these two columns are not directly comparable because the ones in the **OBSERVED CASES** column are actually registered in the area covered by the CRs, while the others are estimated cases for the whole Italian territory; the former refer to a period of 11 years, while the latter are cases expected in one year only.

# A GUIDE TO THE CANCER-SPECIFIC DATA SHEETS

## AN EXAMPLE
## RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY



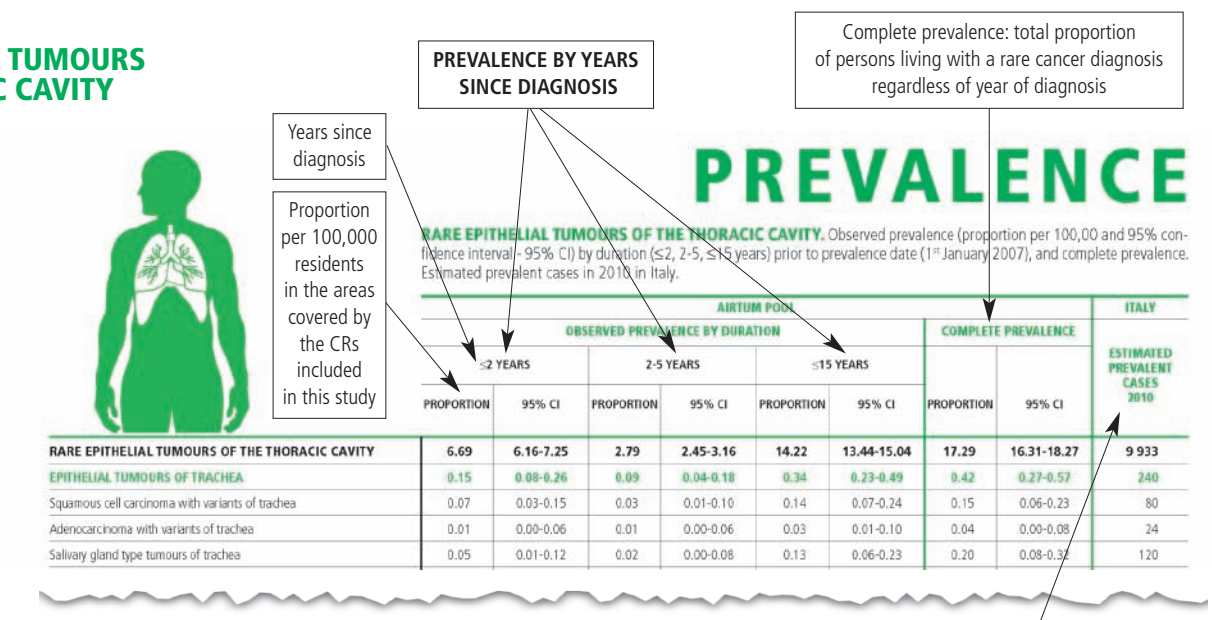

### HOW TO READ THIS GRAPH (AN EXAMPLE)

For **RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY** (major group) we read: in the period 2000-2008 more than ten thousand rare epithelial tumours of the thoracic cavity were registered. One year after diagnosis **50%** of the patients were still alive; only **17%** were alive 5 years after diagnosis.

**NOTE:** CIs of tier 1 and 2 entities are wider than CIs of the major group because the smaller the number of analysed cases, the larger the uncertainty affecting the estimates.

In this monograph survival estimates were computed only if the number of cases was sufficient to produce reliable indicators, with interpretable CIs. That is the reason why relative survival was not computed when 30 or fewer cases were observed in the AIRTUM pool during 2000-2008. In this case the indicator is marked as not estimable (**NE** in the graph) and we suggest readers consult European survival data (www.rarecarenet.eu).

## AN EXAMPLE
## RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY




### HOW TO READ THIS TABLE (AN EXAMPLE)

For **RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY** (major group) we read: slightly less than seven (6.69) persons out of every 100,000 residents (M+F) were alive in 2007 after receiving, in the previous **2 years**, a diagnosis of a rare epithelial tumour of the thoracic cavity. Slightly less than three (2.79) were alive in 2007 after **2-5 years** since diagnosis and fourteen (14.2) were alive in 2007 after being diagnosed in the previous **15 years**. In the **complete prevalence** column, we read how many people diagnosed with a rare epithelial tumour of the thoracic cavity out of 100,000 residents in the area covered by AIRTUM were alive in 2007, regardless of time since diagnosis.

ITALIAN CANCER FIGURES - REPORT 2015

# THE BURDEN OF RARE CANCERS IN ITALY

I TUMORI IN ITALIA - RAPPORTO 2015

## I TUMORI RARI IN ITALIA

# EPITHELIAL TUMOURS OF HEAD AND NECK

**93%**
**OF HEAD AND NECK TUMOURS ARE RARE EPITHELIAL TUMOURS**

## INCIDENCE

**12 984**
ESTIMATED NEW CASES
ITALY, 2015

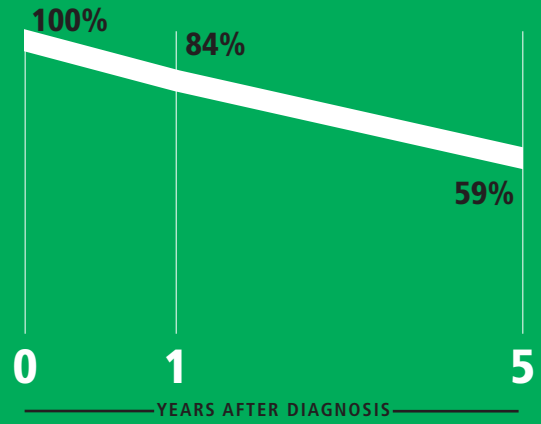
| | | |
|---|---|---|
| 338 | EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES | 62 |
| 574 | EPITHELIAL TUMOURS OF NASOPHARYNX | 96 |
| 1 180 | EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY GLAND TYPE TUMOURS | 8 |
| 5 466 | EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX | 91 |
| 1 915 | EPITHELIAL TUMOURS OF OROPHARYNX | 96 |
| 3 492 | EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP | 95 |
| 19 | EPITHELIAL TUMOURS OF MIDDLE EAR | 97 |

**%** OF RARE EPITHELIAL TUMOURS OUT OF ALL TUMOURS IN EACH SITE

## PREVALENCE

**116 200**
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# INCIDENCE

**EPITHELIAL TUMOURS OF HEAD AND NECK.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

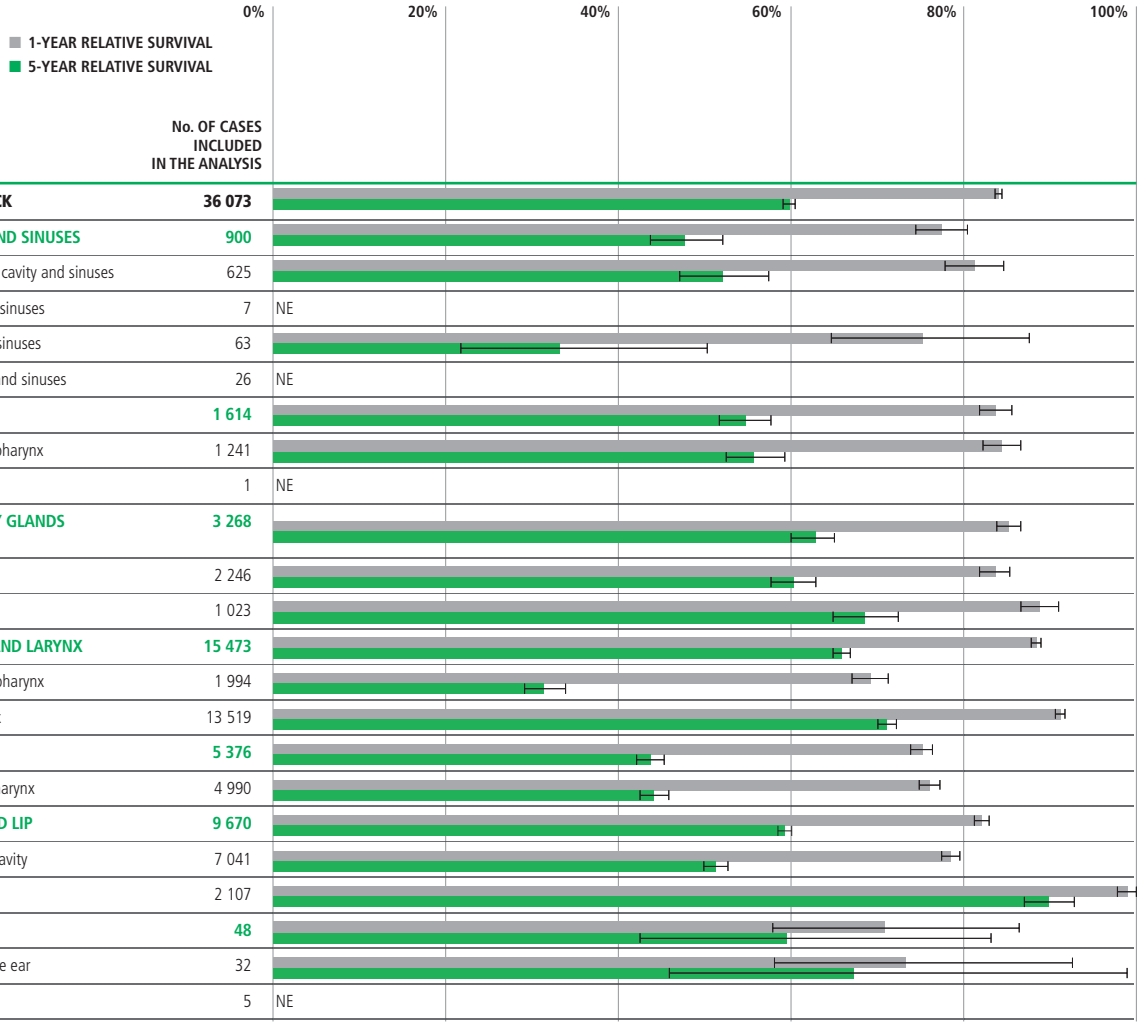
| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE EPITHELIAL CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **EPITHELIAL TUMOURS OF HEAD AND NECK** | **19.46** | **19.28-19.65** | **43 163** | **93%** | **31.20** | **30.87-31.54** | **8.47** | **8.30-8.64** | **5.57** | **5.45-5.69** | **42.36** | **41.59-43.14** | **52.83** | **52.15-53.52** | **12 984** |
| **EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES** | **0.50** | **0.47-0.53** | **1 114** | **62%** | **0.67** | **0.63-0.73** | **0.34** | **0.31-0.38** | **0.14** | **0.12-0.16** | **0.86** | **0.75-0.98** | **1.54** | **1.42-1.66** | **338** |
| Squamous cell carcinoma with variants of nasal cavity and sinuses | 0.34 | 0.31-0.36 | 749 | | 0.45 | 0.41-0.49 | 0.23 | 0.20-0.26 | 0.08 | 0.07-0.10 | 0.57 | 0.49-0.67 | 1.07 | 0.97-1.17 | 227 |
| Lymphoepithelial carcinoma of nasal cavity and sinuses | <0.01 | 0.00-0.01 | 7 | | NE | – | NE | – | NE | – | NE | – | NE | – | 2 |
| Undifferentiated carcinoma of nasal cavity and sinuses | 0.04 | 0.03-0.04 | 80 | | 0.05 | 0.04-0.07 | 0.02 | 0.01-0.03 | 0.02 | 0.01-0.03 | 0.08 | 0.05-0.12 | 0.07 | 0.05-0.10 | 24 |
| Intestinal type adenocarcinoma of nasal cavity and sinuses | 0.02 | 0.02-0.03 | 47 | | 0.04 | 0.03-0.05 | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.01 | 0.04 | 0.02-0.07 | 0.06 | 0.04-0.09 | 14 |
| **EPITHELIAL TUMOURS OF NASOPHARYNX** | **0.88** | **0.85-0.92** | **1 961** | **96%** | **1.34** | **1.27-1.41** | **0.46** | **0.42-0.50** | **0.59** | **0.55-0.63** | **1.72** | **1.57-1.89** | **1.38** | **1.28-1.50** | **574** |
| Squamous cell carcinoma with variants of nasopharynx | 0.67 | 0.64-0.71 | 1 489 | | 1.03 | 0.97-1.09 | 0.34 | 0.30-0.37 | 0.45 | 0.42-0.49 | 1.35 | 1.22-1.50 | 1.00 | 0.91-1.09 | 435 |
| Papillary adenocarcinoma of nasopharynx | <0.01 | 0.00-0.00 | 1 | | NE | – | NE | – | NE | – | NE | – | NE | – | 0* |
| **EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY GLAND TYPE TUMOURS** | **1.77** | **1.71-1.82** | **3 921** | **8%** | **2.09** | **2.00-2.18** | **1.47** | **1.40-1.54** | **0.66** | **0.62-0.70** | **2.71** | **2.52-2.91** | **4.99** | **4.78-5.20** | **1 180** |
| Epithelial tumours of major salivary glands | 1.23 | 1.18-1.28 | 2 726 | | 1.43 | 1.36-1.50 | 1.04 | 0.98-1.10 | 0.44 | 0.40-0.47 | 1.78 | 1.62-1.94 | 3.60 | 3.43-3.78 | 829 |
| Salivary gland type tumours of head and neck | 0.54 | 0.51-0.57 | 1 195 | | 0.66 | 0.61-0.71 | 0.43 | 0.39-0.46 | 0.22 | 0.20-0.24 | 0.93 | 0.82-1.05 | 1.39 | 1.28-1.50 | 351 |
| **EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX** | **8.21** | **8.09-8.33** | **18 205** | **91%** | **15.28** | **15.05-15.52** | **1.58** | **1.51-1.66** | **1.81** | **1.74-1.88** | **19.98** | **19.45-20.52** | **22.82** | **22.38-23.27** | **5 466** |
| Squamous cell carcinoma with variants of hypopharynx | 1.04 | 0.99-1.08 | 2 296 | | 1.87 | 1.79-1.95 | 0.25 | 0.22-0.28 | 0.34 | 0.31-0.37 | 2.81 | 2.61-3.02 | 2.33 | 2.19-2.48 | 686 |
| Squamous cell carcinoma with variants of larynx | 7.17 | 7.06-7.29 | 15 909 | | 13.41 | 13.19-13.63 | 1.33 | 1.27-1.40 | 1.47 | 1.41-1.54 | 17.17 | 16.68-17.67 | 20.49 | 20.07-20.92 | 4 780 |
| **EPITHELIAL TUMOURS OF OROPHARYNX** | **2.89** | **2.82-2.96** | **6 410** | **96%** | **4.71** | **4.58-4.84** | **1.19** | **1.13-1.25** | **1.01** | **0.96-1.07** | **7.61** | **7.28-7.94** | **6.40** | **6.16-6.64** | **1 915** |
| Squamous cell carcinoma with variants of oropharynx | 2.67 | 2.60-2.74 | 5 914 | | 4.35 | 4.23-4.48 | 1.09 | 1.03-1.15 | 0.95 | 0.90-1.00 | 7.10 | 6.79-7.43 | 5.81 | 5.59-6.04 | 1 762 |
| **EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP** | **5.18** | **5.09-5.28** | **11 492** | **95%** | **7.08** | **6.92-7.24** | **3.41** | **3.30-3.52** | **1.37** | **1.31-1.43** | **9.45** | **9.09-9.82** | **15.60** | **15.24-15.98** | **3 492** |
| Squamous cell carcinoma with variants of oral cavity | 3.76 | 3.68-3.84 | 8 330 | | 4.88 | 4.75-5.02 | 2.70 | 2.61-2.80 | 1.16 | 1.10-1.21 | 7.57 | 7.25-7.91 | 10.29 | 9.99-10.60 | 2 499 |
| Squamous cell carcinoma with variants of lip | 1.10 | 1.06-1.14 | 2 437 | | 1.77 | 1.69-1.85 | 0.47 | 0.43-0.51 | 0.12 | 0.10-0.14 | 1.38 | 1.25-1.53 | 4.28 | 4.08-4.47 | 765 |
| **EPITHELIAL TUMOURS OF MIDDLE EAR** | **0.03** | **0.02-0.03** | **60** | **97%** | **0.03** | **0.02-0.05** | **0.02** | **0.01-0.03** | **<0.01** | **0.00-0.01** | **0.04** | **0.02-0.07** | **0.10** | **0.07-0.13** | **19** |
| Squamous cell carcinoma with variants of middle ear | 0.02 | 0.01-0.03 | 41 | | 0.02 | 0.02-0.04 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.03 | 0.01-0.05 | 0.07 | 0.05-0.10 | 13 |
| Adenocarcinoma with variants of middle ear | <0.01 | 0.00-0.01 | 5 | | NE | – | NE | – | NE | – | NE | – | NE | – | 1 |

**NE:** not estimable because 15 or less incident cases were observed

*One case every 3 years is expected

# SURVIVAL

**EPITHELIAL TUMOURS OF HEAD AND NECK.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **EPITHELIAL TUMOURS OF HEAD AND NECK** | **36 073** |
| **EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES** | **900** |
| Squamous cell carcinoma with variants of nasal cavity and sinuses | 625 |
| Lymphoepithelial carcinoma of nasal cavity and sinuses | 7 |
| Undifferentiated carcinoma of nasal cavity and sinuses | 63 |
| Intestinal type adenocarcinoma of nasal cavity and sinuses | 26 |
| **EPITHELIAL TUMOURS OF NASOPHARYNX** | **1 614** |
| Squamous cell carcinoma with variants of nasopharynx | 1 241 |
| Papillary adenocarcinoma of nasopharynx | 1 |
| **EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY GLAND TYPE TUMOURS** | **3 268** |
| Epithelial tumours of major salivary glands | 2 246 |
| Salivary gland type tumours of head and neck | 1 023 |
| **EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX** | **15 473** |
| Squamous cell carcinoma with variants of hypopharynx | 1 994 |
| Squamous cell carcinoma with variants of larynx | 13 519 |
| **EPITHELIAL TUMOURS OF OROPHARYNX** | **5 376** |
| Squamous cell carcinoma with variants of oropharynx | 4 990 |
| **EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP** | **9 670** |
| Squamous cell carcinoma with variants of oral cavity | 7 041 |
| Squamous cell carcinoma with variants of lip | 2 107 |
| **EPITHELIAL TUMOURS OF MIDDLE EAR** | **48** |
| Squamous cell carcinoma with variants of middle ear | 32 |
| Adenocarcinoma with variants of middle ear | 5 |

| | |
|---|---|
| NE | |
| NE | |
| NE | |
| NE | |

**NE:** not estimable because 30 or less incident cases were observed

# PREVALENCE

**EPITHELIAL TUMOURS OF HEAD AND NECK.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **EPITHELIAL TUMOURS OF HEAD AND NECK** | **34.22** | **33.00-35.47** | **37.10** | **35.83-38.40** | **144.25** | **141.73-146.79** | **200.86** | **197.23-204.50** | **116 200** |
| **EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES** | **0.75** | **0.58-0.95** | **0.75** | **0.58-0.95** | **2.74** | **2.40-3.11** | **3.71** | **3.23-4.18** | **2 129** |
| Squamous cell carcinoma with variants of nasal cavity and sinuses | 0.53 | 0.39-0.71 | 0.63 | 0.48-0.82 | 2.17 | 1.88-2.51 | 2.97 | 2.54-3.40 | 1 706 |
| Lymphoepithelial carcinoma of nasal cavity and sinuses | 0.01 | 0.00-0.06 | NE | – | 0.01 | 0.00-0.06 | NE | – | NE |
| Undifferentiated carcinoma of nasal cavity and sinuses | 0.07 | 0.03-0.15 | 0.03 | 0.01-0.10 | 0.14 | 0.07-0.24 | 0.20 | 0.08-0.32 | 110 |
| Intestinal type adenocarcinoma of nasal cavity and sinuses | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.06 | 0.05 | 0.01-0.12 | 0.09 | 0.00-0.17 | 48 |
| **EPITHELIAL TUMOURS OF NASOPHARYNX** | **1.30** | **1.07-1.56** | **1.31** | **1.08-1.58** | **4.78** | **4.34-5.27** | **6.69** | **6.04-7.34** | **3 903** |
| Squamous cell carcinoma with variants of nasopharynx | 1.01 | 0.81-1.25 | 1.12 | 0.91-1.36 | 3.71 | 3.32-4.14 | 4.90 | 4.36-5.44 | 2 866 |
| Papillary adenocarcinoma of nasopharynx | NE | – | NE | – | NE | – | NE | – | NE |
| **EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY GLAND TYPE TUMOURS** | **3.29** | **2.92-3.69** | **3.57** | **3.18-3.99** | **13.69** | **12.92-14.49** | **21.44** | **20.21-22.67** | **12 466** |
| Epithelial tumours of major salivary glands | 2.18 | 1.88-2.52 | 2.24 | 1.93-2.57 | 8.85 | 8.24-9.50 | 14.54 | 13.49-15.59 | 8 464 |
| Salivary gland type tumours of head and neck | 1.10 | 0.89-1.35 | 1.33 | 1.10-1.60 | 4.84 | 4.39-5.32 | 7.19 | 6.49-7.90 | 4 184 |
| **EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX** | **14.88** | **14.08-15.71** | **17.23** | **16.37-18.13** | **70.43** | **68.68-72.22** | **98.31** | **95.74-100.89** | **56 626** |
| Squamous cell carcinoma with variants of hypopharynx | 1.49 | 1.25-1.77 | 1.00 | 0.80-1.24 | 4.31 | 3.89-4.77 | 5.15 | 4.62-5.68 | 2 964 |
| Squamous cell carcinoma with variants of larynx | 13.39 | 12.63-14.18 | 16.24 | 15.41-17.11 | 66.18 | 64.48-67.91 | 93.16 | 90.65-95.68 | 53 662 |
| **EPITHELIAL TUMOURS OF OROPHARYNX** | **4.60** | **4.16-5.08** | **4.33** | **3.90-4.79** | **15.68** | **14.86-16.54** | **19.10** | **18.06-20.15** | **11 070** |
| Squamous cell carcinoma with variants of oropharynx | 4.34 | 3.91-4.80 | 4.18 | 3.76-4.63 | 14.95 | 14.15-15.78 | 18.19 | 17.17-19.21 | 10 543 |
| **EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP** | **9.47** | **8.83-10.14** | **9.96** | **9.30-10.64** | **38.09** | **36.80-39.41** | **51.34** | **49.52-53.15** | **29 842** |
| Squamous cell carcinoma with variants of oral cavity | 6.83 | 6.29-7.40 | 6.68 | 6.15-7.24 | 24.45 | 23.43-25.51 | 31.15 | 29.78-32.52 | 18 075 |
| Squamous cell carcinoma with variants of lip | 2.30 | 1.99-2.64 | 2.98 | 2.63-3.37 | 12.15 | 11.43-12.91 | 16.66 | 15.65-17.68 | 9 726 |
| **EPITHELIAL TUMOURS OF MIDDLE EAR** | **0.05** | **0.01-0.12** | **0.05** | **0.01-0.12** | **0.17** | **0.10-0.28** | **0.28** | **0.14-0.42** | **163** |
| Squamous cell carcinoma with variants of middle ear | 0.03 | 0.01-0.10 | 0.01 | 0.00-0.06 | 0.07 | 0.03-0.15 | 0.12 | 0.02-0.21 | 69 |
| Adenocarcinoma with variants of middle ear | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.06 | 0.06 | 0.02-0.13 | 0.07 | 0.01-0.13 | 40 |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

According to the RARECARE project,[1] this group includes cancers originating from body sites that are very close to each other. Given the heterogeneous types of tissues and organs included in the head and neck, aetiology and pathogenesis are extremely different. However, head and neck cancers, as defined here, include only epithelial cancers originating from the oral cavity, nasal cavity and sinuses, nasopharynx, salivary glands, pharynx, and larynx (these two latter are sometimes grouped with trachea and lung cancers in other publications). This is because the list of rare cancers proposed by the RARECARE project[1] separates epithelial and non-epithelial tumours in addition to combining topographies and morphologies to define a specific tumour. Thus, non-epithelial tumours, such as sarcomas, neuroendocrine tumours, and lymphomas of the head and neck, are not included and will be described in the sarcoma, neuroendocrine tumours, and lymphoma grouping.
The definition of rare cancer is based on the incidence of a specific tumour in the European population. According to the European RARECAREnet database (www.rarecarenet.eu), all head and neck cancers have an incidence that is lower than 6 per 100,000 and are rare. Thus, even though in Italy some head and neck cancer types (such as larynx cancers) have an incidence >6 per 100,000, they are considered rare cancers because the definition is based on the European and not on the country-specific incidence rate.

Epithelial head and neck tumours comprise the following:
- **epithelial tumours of nasal cavity and sinuses** (squamous cell carcinomas, lymphoepithelial carcinoma, undifferentiated carcinoma, intestinal type adenocarcinoma);
- **epithelial tumours of nasopharynx** (squamous cell carcinomas, papillary adenocarcinoma);
- **epithelial tumours of major salivary glands and salivary gland type tumours** (epithelial tumours of major salivary glands, salivary gland type tumours of head and neck);
- **epithelial tumours of hypopharynx** (squamous cell carcinomas);
- **epithelial tumours of larynx** (squamous cell carcinomas);
- **epithelial tumours of oropharynx** (squamous cell carcinomas);
- **epithelial tumours of oral cavity and lip** (squamous cell carcinomas);
- **epithelial tumours of middle ear** (squamous cell carcinomas, adenocarcinomas).

## WHAT DO WE KNOW ABOUT THESE CANCERS?

Head and neck squamous cell carcinoma is the 6th most prevalent type of cancer worldwide and arises in the mucosa of the upper aerodigestive tract.[2] Incidence shows large variations across Europe and between sexes.[1] In Italy, incidence is higher in the Northern regions and the risk is much higher in men than women. These differences reflect differences in the diffusion of the main risk factors: smoking, alcohol, viruses (Human Papilloma virus – HPV, Epstein-Barr virus – EBV) and occupational exposures. Smoking and alcohol consumption are strong risk factors for larynx and oro-hypopharynx cancers,[3] intestinal-type carcinomas of the nasal cavity and ethmoid cancers have a high attributable fraction due to occupational exposure to wood, leather, dusts, and formaldehyde.[4] Nasopharynx carcinomas are related to EBV infection, while oropharynx carcinomas are related to HPV type 16 infection.[4] Even though most of the known risk factors are more frequent in males than in females, incidence is much higher in males than expected based on the prevalence of the listed risk factors.[4]
Prognosis is very different depending on disease site, and in some cases aetiology (HPV-related cancers have better prognosis if appropriately treated).[1]
Primary treatment varies with the anatomic site and stage of disease. For most early cancers, surgical resection is the cornerstone of treatment. However, for certain anatomic sites such as tonsils, base of tongue and floor of the mouth, as well as for all locally advanced cancers, radiotherapy is used, either alone or combined with surgery. Chemotherapy may be used in addition to radiotherapy. Nasopharynx carcinoma is sensitive to both radiation therapy and chemotherapy. The responsiveness of nasopharyngeal carcinoma to both radiotherapy and chemotherapy distinguishes it from other head and neck cancers, which are typically insensitive to chemotherapy.[5]
Because tumours of different localisations are managed differently, epidemiological data reflecting clinically relevant tumour grouping are essential.

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

The majority of cases of head and neck cancers in Italy (incidence table, p. 34) arise from the larynx (37%), followed by the oral cavity (19%), oropharynx (15%), salivary glands (6%), lip (6%), hypopharynx (5%), nasopharynx (5%), salivary gland type tumours of head and neck (3%), nasal cavity and sinuses (3%), and finally by the very rare cancers of the middle ear (0.1%). For all sites, males have a higher risk than females: from 10-fold for larynx to 1.4-fold for salivary glands. The incidence rate (IR) increases with age for all cancer sites, with the exception of the nasopharynx, where the age-specific IR shows a plateau from intermediate age upward (data not shown). In children, head and neck cancers are extremely rare and are mostly epithelial tumours of the major salivary glands, squamous cell carcinoma of nasopharynx and oral cavity (data not shown). These results are similar to those observed in Europe in the RARECAREnet database (www.rarecarenet.eu), with the exception of tumours of nasopharynx and larynx which have a higher incidence in Italy than in Europe. This is most likely due to the different distribution of the previously listed risk factors.

### Survival

Five-year overall relative survival (RS) is 59%. Five-year RS ranges from 31% for squamous cell carcinoma of the hypopharynx to 89% for squamous cell carcinoma of the lip. Between these extremes, 5-year RS for squamous cell carcinoma of the larynx is 71%, for salivary gland type tumours it is 68%, and for squamous cell carcinoma of the middle ear it is 67% (based on 32 cases only). Squamous cell carcinomas of all other sites have similar 5-year RS (about 50%). Undifferentiated carcinoma of the nasal cavity and sinuses has a 5-year RS of 33%, based on 63 cases (survival figure, p. 35). Differences in survival among sites reflect the availability of effective surgical and radiotherapy treatments, responsiveness of the major histotypes to chemotherapy, and stage at diagnosis: some cancers give symptoms at a very early stage (oropharynx) and others remain asymptomatic until advanced stage (nasopharynx).[4] Five-year RS rates are similar to those observed in Europe in the

RARECAREnet database, with the exception of 5-year RS of larynx cancer, which in Europe is slightly lower than in Italy (61% vs. 71%, respectively). Five-year RS rates in Europe differ between geographic areas and countries, ranging (excluding larynx cancer) from 46.5% in Northern Europe to 28% in Eastern Europe,[6] probably reflecting different mix of head and neck sites and aetiologies, as well as different access to adequate treatment.

### Prevalence

Around 116,000 persons were estimated to be living with a diagnosis of head and neck epithelial tumours in 2010. About 32,000 cases had survived more than 15 years after diagnosis.

Squamous cell carcinoma with variants of larynx are the most frequent (46% of all prevalent cases), followed by squamous cell carcinoma with variants of oral cavity (16%), squamous cell carcinoma with variants of oropharynx (10%), squamous cell carcinoma with variants of lip (8%), epithelial tumours of major salivary glands (7%), salivary gland type tumours of head and neck (4%), epithelial tumours of nasopharynx (3%), squamous cell carcinoma with variants of hypopharynx (3%), epithelial tumours of nasal cavity and sinuses (2%), and finally epithelial tumours of middle ear (0.1%).

These results may be different from previous AIRTUM-published figures of incidence and prevalence, due to different selections of topographical and morphological codes. For Head and Neck group, this monograph includes only epithelial cancers (which account for most cancers of head and neck) and salivary gland types of head and neck cancer are not included within each site but in a distinct group, «salivary gland type tumours of head and neck». Because of this, incidence and prevalence estimates will be slightly lower for most head and neck sites. In addition, for larynx, oropharynx, and oral cavity, prevalence estimates are slightly higher compared to AIRTUM published data on prevalence because the methodology used to calculate complete prevalence is different (for more details, see «Materials and Methods», pp. 14-21).

## REFERENCES

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# TUMOURS OF THE EYE

**100%**
**OF EYE TUMOURS ARE RARE**

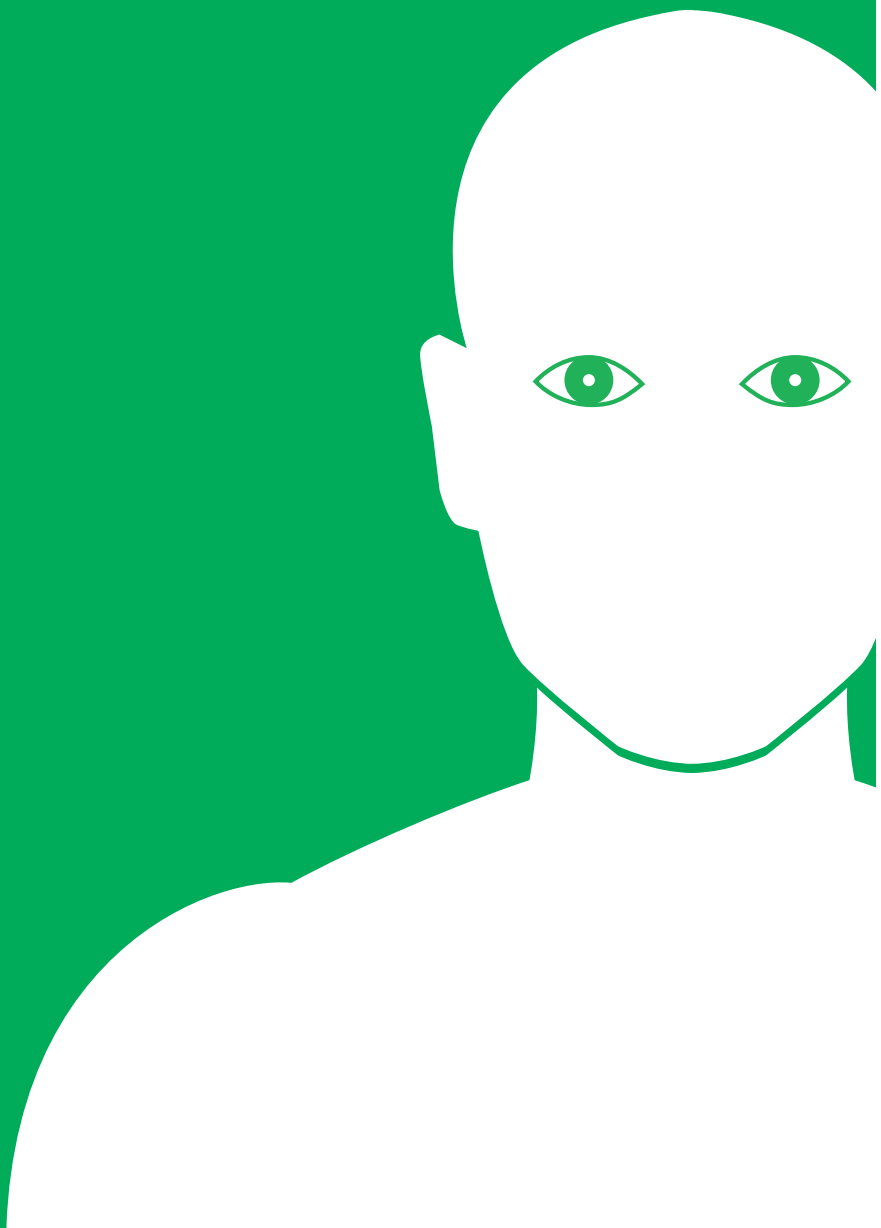
## INCIDENCE

**451**
ESTIMATED NEW CASES
ITALY, 2015

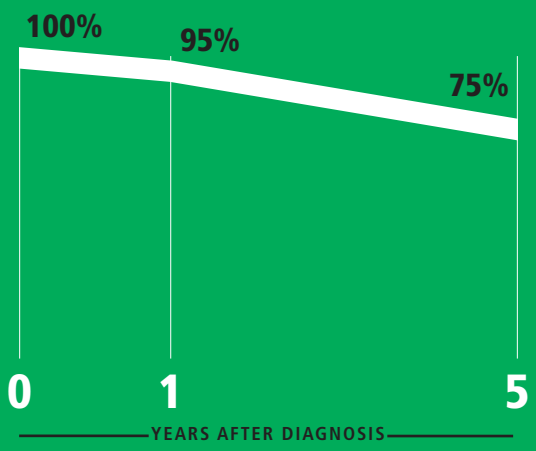
- **41** EPITHELIAL TUMOURS OF EYE AND ADNEXA
- **410** MALIGNANT MELANOMA OF UVEA

## PREVALENCE

**5 869**
ESTIMATED PREVALENT CASES
ITALY, 2010

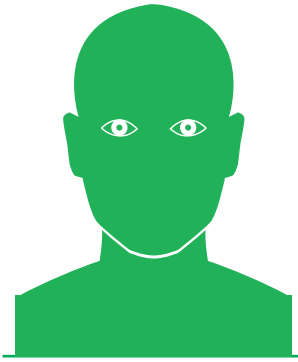


## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# INCIDENCE



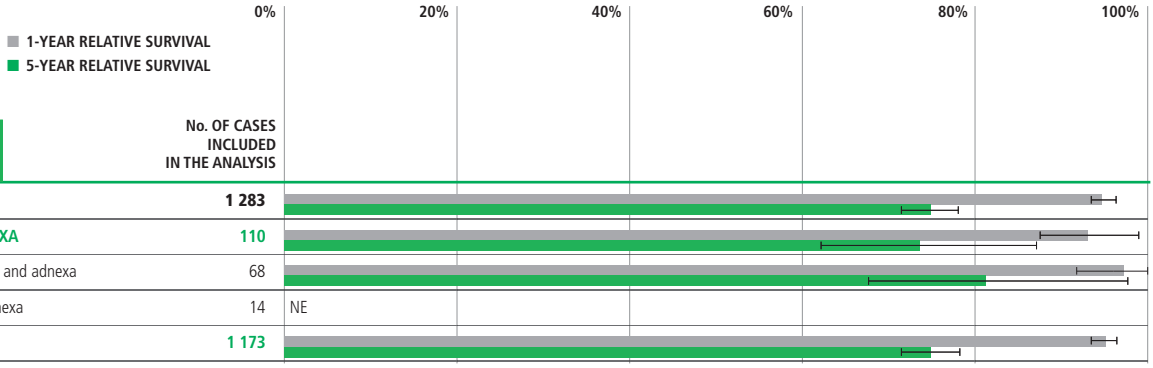
**TUMOURS OF THE EYE.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **TUMOURS OF THE EYE** | **0.69** | **0.66-0.73** | **1 530** | **100%** | **0.70** | **0.65-0.75** | **0.68** | **0.64-0.73** | **0.26** | **0.23-0.28** | **1.21** | **1.08-1.35** | **1.85** | **1.72-1.98** | **451** |
| EPITHELIAL TUMOURS OF EYE AND ADNEXA | 0.06 | 0.05-0.07 | 133 | NA | 0.09 | 0.07-0.11 | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | 0.07 | 0.04-0.11 | 0.17 | 0.13-0.21 | 41 |
| Squamous cell carcinoma with variants of eye and adnexa | 0.03 | 0.03-0.04 | 77 | NA | 0.05 | 0.04-0.07 | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | 0.05 | 0.03-0.08 | 0.11 | 0.08-0.14 | 24 |
| Adenocarcinoma with variants of eye and adnexa | <0.01 | 0.00-0.01 | 18 | NA | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.03 | 0.02 | 0.01-0.04 | 5 |
| MALIGNANT MELANOMA OF UVEA | 0.63 | 0.60-0.66 | 1 397 | NA | 0.61 | 0.56-0.66 | 0.65 | 0.60-0.70 | 0.23 | 0.21-0.26 | 1.14 | 1.02-1.28 | 1.68 | 1.56-1.80 | 410 |

**NA:** not applicable

# SURVIVAL

**TUMOURS OF THE EYE.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.

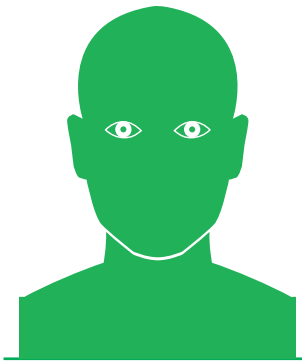



| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **TUMOURS OF THE EYE** | **1 283** |
| EPITHELIAL TUMOURS OF EYE AND ADNEXA | 110 |
| Squamous cell carcinoma with variants of eye and adnexa | 68 |
| Adenocarcinoma with variants of eye and adnexa | 14 |
| MALIGNANT MELANOMA OF UVEA | 1 173 |

Adenocarcinoma with variants of eye and adnexa: NE

**NE:** not estimable because 30 or less incident cases were observed

# PREVALENCE



**TUMOURS OF THE EYE.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **TUMOURS OF THE EYE** | **1.57** | **1.32-1.86** | **1.89** | **1.62-2.21** | **6.89** | **6.35-7.47** | **10.11** | **9.28-10.93** | **5 869** |
| EPITHELIAL TUMOURS OF EYE AND ADNEXA | 0.15 | 0.08-0.26 | 0.09 | 0.04-0.18 | 0.52 | 0.38-0.69 | 0.78 | 0.55-1.01 | 454 |
| Squamous cell carcinoma with variants of eye and adnexa | 0.10 | 0.05-0.20 | 0.06 | 0.02-0.13 | 0.38 | 0.26-0.53 | 0.48 | 0.31-0.64 | 271 |
| Adenocarcinoma with variants of eye and adnexa | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.06 | 0.05 | 0.01-0.12 | 0.06 | 0.00-0.13 | 39 |
| MALIGNANT MELANOMA OF UVEA | 1.42 | 1.18-1.70 | 1.80 | 1.53-2.11 | 6.37 | 5.86-6.93 | 9.33 | 8.54-10.12 | 5 415 |

This group of tumours includes the major cancers occurring in the eye:

- **epithelial tumours and adnexa**;
- **uveal melanoma**.

Both are extremely rare, with annual incidence rates (IR) <0.5 per 100,000year.[1] These exceptional cancers have already been described in previous papers based on two large datasets, the EUROCARE study and the RARECARE project.[2-4] These two large population-based studies used data from almost 100 cancer registries, thus providing solid measures of incidence, survival, and prevalence for these very rare cancers in Europe.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**Uveal melanoma** is an adult intraocular tumour, arising from melanocytes in the uvea. **Adnexal skin tumours** are extremely diverse group of neoplasms, arising from cutaneous appendages, particularly the sebaceous, apocrine, and eccrine glands. Because of their rarity, even the basic descriptive epidemiology of these tumour types is sparse.[4]

**Uveal melanoma** is the most common ocular tumour. A very large study based on data published in *Cancer Incidence In 5 Continents*, Volumes VI-VIII covering a long period of registration (1983 to 1997) showed the highest IR in Northern Europe and Australia and the lowest rates among Asian, Hispanic, and black populations, consistent with other observations of lower rates in pigmented race and a positive association with fair skin.[5] One of the largest European studies[2] confirmed the results of the previous paper, but added that IR increased with age and reached a plateau after 75 years. A few hypotheses were provided for this levelling off in older age: susceptible individuals develop cancer due to environmental exposure in adulthood and the pattern is due to a 1- to 2-decade biological lag between the beginning of the exposure and the clinical onset of uveal melanoma; the internal environment of the eye is less stimulating for malignant cells after age 70; or tumour ascertainment is lower for elderly people.

Epidemiological studies have demonstrated that individual exposure to UV radiation is related to the risk of these cancers.[6] Lesions were reported to occur more often on the left than the right side of the face, and the left side is expected to receive more UV radiation through the driver's side window.[7] Individuals treated with ionizing radiation as children or adolescents may be at particularly high risk. From the early 1920s to the late 1950s, ionizing radiation was commonly used to treat acne or other inflammatory and benign conditions of the head and neck in the US.[8]

Organ transplant recipients who are immunosuppressed have a greatly increased risk of cutaneous appendageal tumours compared with apparently immunocompetent individuals. In addition, their tumours are more likely to be malignant and of sebaceous origin.[9]

The International Agency for Research on Cancer (IARC) has classified welding with sufficient evidence and solar radiation with limited evidence as risk factors for epithelial tumours of the eye. Occupational exposure to ultraviolet radiation has been described to increase uveal melanoma in workers exposed during outdoor occupational activities and welders.[10]

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

In 2015, we estimate 451 **tumours of the eye**, most of them are **uveal melanoma** (No. 410). The crude annual (IRs) per 100,000 are 0.1 for epithelial tumours of the eye and adnexa, and 0.6 for uveal melanoma. Slightly more than 50% of cases are over 65 years of age.

Incidence increases with age: in people over 65 years old, IRs are 0.2 and 1.7 for epithelial tumour and melanoma, respectively. The occurrence of uveal melanoma shows an increase from 1.7 in cases in the 65-69 age group, up to 1.9 in cases aged 75-79, then incidence decreases to 1.2 (data not shown).

No difference between genders is relevant statistically. From the SEER program database in the US11 and the RARECARE database in Europe[4] the same IRs were reported for uveal melanoma for the periods 1973-2008 and 1995-2002, respectively. The age-adjusted incidence trend remained unchanged in the US from 1973 to 2008.[11] Cutaneous appendageal carcinoma IRs were reported to increase in the US, especially for sebaceous carcinoma. The authors attributed the increase in trends to improved recognition and classification, and did not exclude factors such as UV exposure and immunosuppression.[12]

### Survival

Based on about 1,300 cases, survival analysis shows good 5-year relative survival for both epithelial tumours of the eye and uveal melanoma. Relative survival at 1 and 5 years is 93% and 95%, and 74% and 75%, respectively. Squamous cell carcinoma is characterised by the best prognosis: 82% at 5 years (based on 68 cases).

Treatments of uveal melanoma have changed with the progressive introduction of conservative management for smaller tumours during the 1980s.[11,13] With this therapeutic shift, 5-year RS is reported to be stable both in the US and in Europe.[11,13]

The Collaborative Ocular Melanoma Study (COMS) demonstrated that metastatic disease survival rate and overall survival was not significantly different between those treated with enucleation and radiotherapy (brachytherapy). Treatment of epithelial tumours of the eye and uveal melanoma is concentrated in high-volume and specialized hospitals.[4] Patients for which treatments are not available should enter clinical trials. In consideration of the rarity of the disease, international cooperation for research should be arranged.[1]

### Prevalence

Around 6,000 persons were estimated to be living with a diagnosis of epithelial tumours of the eye and uveal melanoma in Italy in 2010. The majority of these persons (>90%) have a previous diagnosis of uveal melanomas. Our prevalence estimates of uveal melanoma differ from those published in the AIRTUM prevalence monograph,[14] because of the different sites and morphology definition. Here we included ICD-O-3 topographies C69.3-C69.4 and morphologies M8000, M8001, M8720-M8780; the AIRTUM prevalence monograph included ICD-10 C69 + ICD-O-3 morphologies M8720-M8790.[14]

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# RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM

**16%**
**OF DIGESTIVE SYSTEM TUMOURS ARE RARE EPITHELIAL TUMOURS**

## INCIDENCE

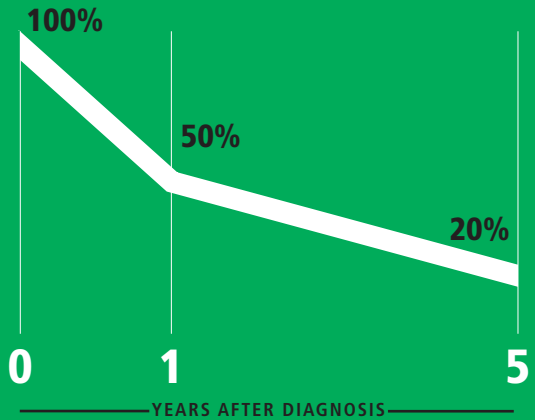
**17 532**
ESTIMATED NEW CASES
ITALY, 2015

| | | % OF RARE EPITHELIAL TUMOURS OUT OF ALL TUMOURS IN EACH SITE |
|---|---|---|
| 2 262 | EPITHELIAL TUMOURS OF OESOPHAGUS | 81 |
| 271 | RARE EPITHELIAL TUMOURS OF STOMACH | 1 |
| 696 | EPITHELIAL TUMOURS OF SMALL INTESTINE | 56 |
| 87 | RARE EPITHELIAL TUMOURS OF COLON | <1 |
| 97 | RARE EPITHELIAL TUMOURS OF RECTUM | 1 |
| 1 143 | EPITHELIAL TUMOURS OF ANAL CANAL | 97 |
| 71 | RARE EPITHELIAL TUMOURS OF PANCREAS | 1 |
| 7 291 | EPITHELIAL TUMOURS OF LIVER AND INTRAHEPATIC BILE TRACT | 53 |
| 5 483 | EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT | 99 |
| 132 | MESOTHELIOMA OF PERITONEUM | |

## PREVALENCE

**43 452**
ESTIMATED PREVALENT CASES
ITALY, 2010

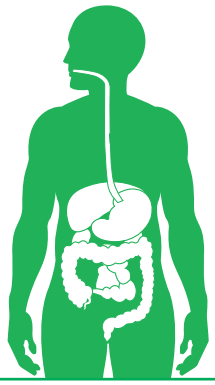
## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM

# INCIDENCE



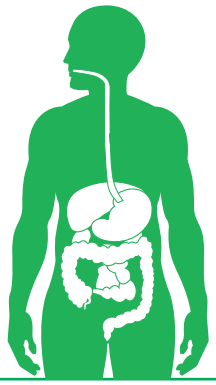
**RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE EPITHELIAL CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM** | **26.11** | **25.89-26.32** | **57 891** | **16%** | **32.11** | **31.78-32.45** | **20.48** | **20.22-20.74** | **3.74** | **3.64-3.83** | **40.15** | **39.40-40.91** | **93.99** | **93.08-94.90** | **17 532** |
| **EPITHELIAL TUMOURS OF OESOPHAGUS** | **3.38** | **3.30-3.45** | **7 488** | **81%** | **5.35** | **5.21-5.49** | **1.53** | **1.46-1.60** | **0.63** | **0.59-0.67** | **6.90** | **6.60-7.22** | **10.59** | **10.29-10.90** | **2 262** |
| Squamous cell carcinoma with variants of oesophagus | 2.44 | 2.37-2.50 | 5 405 | | 3.74 | 3.63-3.86 | 1.21 | 1.15-1.28 | 0.47 | 0.43-0.50 | 5.43 | 5.15-5.71 | 7.33 | 7.07-7.58 | 1 619 |
| Adenocarcinoma with variants of oesophagus | 0.90 | 0.86-0.94 | 1 993 | | 1.54 | 1.47-1.62 | 0.30 | 0.26-0.33 | 0.15 | 0.13-0.17 | 1.41 | 1.27-1.55 | 3.14 | 2.97-3.31 | 616 |
| Salivary gland type tumours of oesophagus | <0.01 | 0.00-0.00 | 4 | | NE | – | NE | – | NE | – | NE | – | NE | – | 2 |
| Undifferentiated carcinoma of oesophagus | 0.04 | 0.03-0.05 | 86 | | 0.06 | 0.04-0.07 | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | 0.07 | 0.04-0.11 | 0.13 | 0.10-0.17 | 27 |
| **RARE EPITHELIAL TUMOURS OF STOMACH** | **0.40** | **0.37-0.42** | **879** | **1%** | **0.50** | **0.46-0.54** | **0.30** | **0.27-0.33** | **0.06** | **0.05-0.07** | **0.62** | **0.53-0.72** | **1.42** | **1.31-1.53** | **271** |
| Squamous cell carcinoma with variants of stomach | 0.09 | 0.08-0.11 | 204 | | 0.14 | 0.12-0.17 | 0.04 | 0.03-0.06 | 0.01 | 0.01-0.02 | 0.18 | 0.14-0.24 | 0.31 | 0.26-0.37 | 62 |
| Salivary gland type tumours of stomach | <0.01 | 0.00-0.00 | 2 | | NE | – | NE | – | NE | – | NE | – | NE | – | 1 |
| Undifferentiated carcinoma of stomach | 0.30 | 0.28-0.33 | 673 | | 0.35 | 0.32-0.39 | 0.26 | 0.23-0.29 | 0.05 | 0.04-0.06 | 0.43 | 0.36-0.51 | 1.11 | 1.01-1.21 | 208 |
| **EPITHELIAL TUMOURS OF SMALL INTESTINE** | **1.02** | **0.98-1.06** | **2 261** | **56%** | **1.15** | **1.09-1.22** | **0.90** | **0.84-0.95** | **0.20** | **0.18-0.22** | **1.40** | **1.26-1.55** | **3.60** | **3.42-3.78** | **696** |
| Adenocarcinoma with variants of small intestine | 0.78 | 0.74-0.81 | 1 722 | | 0.91 | 0.85-0.97 | 0.65 | 0.61-0.70 | 0.16 | 0.14-0.19 | 1.19 | 1.06-1.32 | 2.62 | 2.47-2.77 | 521 |
| Squamous cell carcinoma with variants of small intestine | <0.01 | 0.01-0.01 | 21 | | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.00 | <0.01 | 0.00-0.03 | 0.04 | 0.02-0.06 | 6 |
| **RARE EPITHELIAL TUMOURS OF COLON** | **0.13** | **0.12-0.15** | **293** | **0.2%** | **0.11** | **0.09-0.13** | **0.15** | **0.13-0.17** | **0.05** | **0.04-0.06** | **0.18** | **0.14-0.24** | **0.38** | **0.32-0.44** | **87** |
| Squamous cell carcinoma with variants of colon | 0.03 | 0.03-0.04 | 74 | | 0.02 | 0.01-0.03 | 0.04 | 0.03-0.06 | 0.01 | 0.01-0.02 | 0.06 | 0.03-0.09 | 0.10 | 0.07-0.13 | 23 |
| Fibromixoma and low grade mucinous adenocarcinoma of the appendix | 0.10 | 0.09-0.11 | 219 | | 0.09 | 0.07-0.11 | 0.11 | 0.09-0.13 | 0.04 | 0.03-0.05 | 0.13 | 0.09-0.18 | 0.28 | 0.23-0.33 | 65 |
| **RARE EPITHELIAL TUMOURS OF RECTUM** | **0.14** | **0.13-0.16** | **318** | **1%** | **0.08** | **0.06-0.10** | **0.20** | **0.18-0.23** | **0.05** | **0.04-0.06** | **0.20** | **0.15-0.26** | **0.43** | **0.37-0.50** | **97** |
| Squamous cell carcinoma with variants of rectum | 0.14 | 0.13-0.16 | 318 | | 0.08 | 0.06-0.10 | 0.20 | 0.18-0.23 | 0.05 | 0.04-0.06 | 0.20 | 0.15-0.26 | 0.43 | 0.37-0.50 | 97 |
| **EPITHELIAL TUMOURS OF ANAL CANAL** | **1.69** | **1.64-1.75** | **3 750** | **97%** | **1.40** | **1.33-1.47** | **1.97** | **1.89-2.05** | **0.47** | **0.43-0.50** | **2.53** | **2.35-2.73** | **5.36** | **5.15-5.58** | **1 143** |
| Squamous cell carcinoma with variants of anal canal | 0.92 | 0.88-0.96 | 2 042 | | 0.56 | 0.52-0.61 | 1.26 | 1.19-1.32 | 0.34 | 0.31-0.37 | 1.52 | 1.38-1.68 | 2.52 | 2.38-2.68 | 611 |
| Adenocarcinoma with variants of anal canal | 0.60 | 0.57-0.64 | 1 338 | | 0.71 | 0.66-0.77 | 0.50 | 0.46-0.54 | 0.10 | 0.08-0.12 | 0.85 | 0.74-0.96 | 2.18 | 2.04-2.32 | 411 |
| Paget's disease of anal canal | <0.01 | 0.00-0.01 | 8 | | NE | – | NE | – | NE | – | NE | – | NE | – | 2 |
| **RARE EPITHELIAL TUMOURS OF PANCREAS** | **0.11** | **0.10-0.12** | **241** | **1%** | **0.12** | **0.10-0.14** | **0.10** | **0.08-0.12** | **0.04** | **0.03-0.05** | **0.17** | **0.12-0.22** | **0.32** | **0.27-0.38** | **71** |
| Squamous cell carcinoma with variants of pancreas | 0.02 | 0.01-0.02 | 39 | | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.03 | 0.01-0.05 | 0.05 | 0.03-0.08 | 12 |
| Acinar cell carcinoma of pancreas | 0.04 | 0.03-0.05 | 94 | | 0.06 | 0.05-0.08 | 0.02 | 0.02-0.04 | 0.01 | 0.01-0.02 | 0.08 | 0.05-0.13 | 0.12 | 0.09-0.16 | 28 |
| Mucinous cystadenocarcinoma of pancreas | 0.03 | 0.02-0.03 | 56 | | 0.02 | 0.01-0.03 | 0.03 | 0.02-0.04 | <0.01 | 0.00-0.01 | 0.03 | 0.01-0.06 | 0.08 | 0.06-0.11 | 16 |
| Intraductal papillary mucinous carcinoma invasive of pancreas | 0.02 | 0.01-0.02 | 34 | | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.03 | 0.01-0.05 | 0.05 | 0.03-0.08 | 10 |
| Solid pseudopapillary carcinoma of pancreas | <0.01 | 0.00-0.01 | 13 | | NE | – | NE | – | NE | – | NE | – | NE | – | 4 |
| Serous cystadenocarcinoma of pancreas | <0.01 | 0.00-0.00 | 3 | | NE | – | NE | – | NE | – | NE | – | NE | – | 1 |
| Carcinoma with osteoclast-like giant cells of pancreas | <0.01 | 0.00-0.00 | 2 | | NE | – | NE | – | NE | – | NE | – | NE | – | 1 |
| **EPITHELIAL TUMOURS OF LIVER AND INTRAHEPATIC BILE TRACT** | **11.05** | **10.91-11.19** | **24 497** | **53%** | **16.32** | **16.08-16.57** | **6.10** | **5.96-6.25** | **1.53** | **1.47-1.59** | **18.62** | **18.11-19.14** | **38.93** | **38.35-39.52** | **7 291** |
| Hepatocellular carcinoma of liver and IBT | 9.37 | 9.25-9.50 | 20 784 | | 14.22 | 14.00-14.45 | 4.83 | 4.70-4.96 | 1.22 | 1.17-1.28 | 15.63 | 15.17-16.11 | 33.39 | 32.85-33.94 | 6 195 |
| Hepatocellular carcinoma, fibrolamellar of liver and IBT | 0.09 | 0.07-0.10 | 189 | | 0.13 | 0.11-0.16 | 0.04 | 0.03-0.06 | 0.01 | 0.01-0.02 | 0.13 | 0.09-0.18 | 0.30 | 0.26-0.36 | 55 |
| Cholangiocarcinoma of IBT | 0.90 | 0.86-0.94 | 2 003 | | 1.09 | 1.03-1.16 | 0.73 | 0.68-0.78 | 0.18 | 0.16-0.20 | 1.65 | 1.50-1.81 | 2.91 | 2.76-3.08 | 593 |
| Adenocarcinoma with variants of liver and IBT | 0.65 | 0.61-0.68 | 1 432 | | 0.83 | 0.77-0.88 | 0.48 | 0.44-0.52 | 0.11 | 0.09-0.13 | 1.14 | 1.02-1.28 | 2.17 | 2.04-2.32 | 422 |
| Undifferentiated carcinoma of liver and IBT | 0.02 | 0.01-0.02 | 40 | | 0.02 | 0.02-0.03 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.04 | 0.02-0.07 | 0.06 | 0.04-0.09 | 12 |
| Squamous cell carcinoma with variants of liver and IBT | 0.02 | 0.01-0.02 | 36 | | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.00 | 0.02 | 0.01-0.04 | 0.07 | 0.04-0.09 | 11 |
| Bile duct cystadenocarcinoma of IBT | <0.01 | 0.00-0.01 | 13 | | NE | – | NE | – | NE | – | NE | – | NE | – | 4 |
| **EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT** | **7.99** | **7.87-8.11** | **17 715** | **99%** | **6.84** | **6.68-7.00** | **9.07** | **8.89-9.24** | **0.66** | **0.62-0.70** | **9.15** | **8.79-9.52** | **32.37** | **31.84-32.91** | **5 483** |
| Adenocarcinoma with variants of gallbladder | 2.03 | 1.97-2.09 | 4 498 | | 1.31 | 1.24-1.38 | 2.71 | 2.61-2.80 | 0.20 | 0.18-0.23 | 3.14 | 2.93-3.36 | 7.59 | 7.34-7.85 | 1 328 |
| Adenocarcinoma with variants of EBT | 2.24 | 2.17-2.30 | 4 960 | | 2.54 | 2.44-2.64 | 1.95 | 1.87-2.04 | 0.31 | 0.28-0.34 | 3.67 | 3.44-3.90 | 7.94 | 7.68-8.21 | 1 479 |
| Squamous cell carcinoma of gallbladder and EBT | 0.04 | 0.03-0.05 | 84 | | 0.02 | 0.02-0.04 | 0.05 | 0.04-0.07 | <0.01 | 0.00-0.01 | 0.06 | 0.04-0.10 | 0.14 | 0.11-0.18 | 25 |
| **MESOTHELIOMA OF PERITONEUM** | **0.20** | **0.18-0.22** | **449** | **NA** | **0.25** | **0.22-0.28** | **0.16** | **0.14-0.18** | **0.06** | **0.05-0.07** | **0.38** | **0.31-0.46** | **0.59** | **0.52-0.66** | **132** |

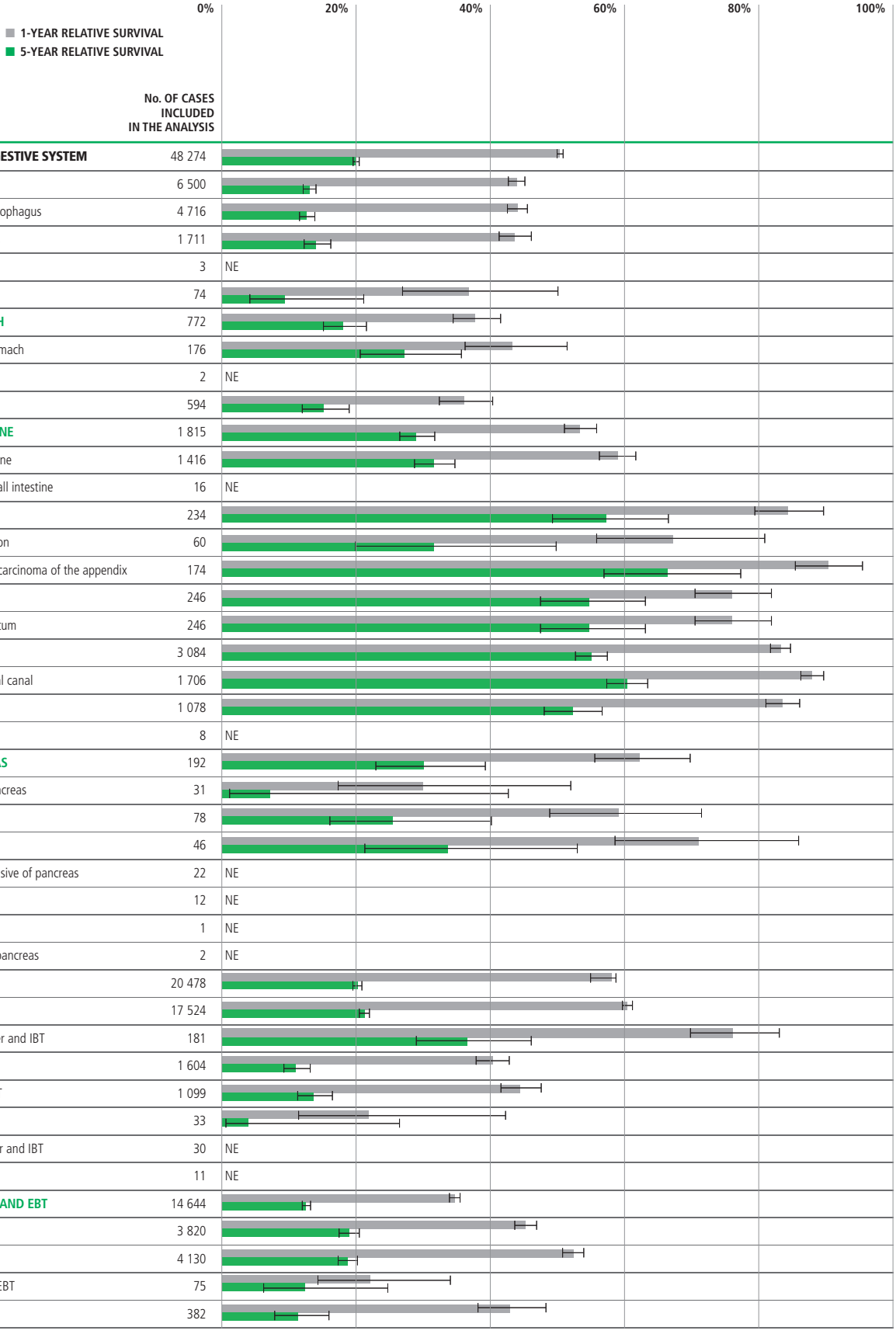
**NE:** not estimable because 15 or less incident cases were observed **IBT:** intrahepatic bile tract **EBT:** extrahepatic bile tract **NA:** not applicable

# RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM

# SURVIVAL



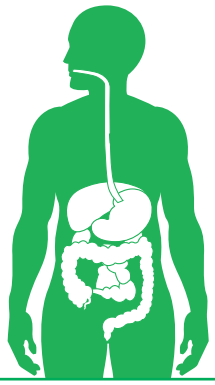
**RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM** | 48 274 |
| **EPITHELIAL TUMOURS OF OESOPHAGUS** | 6 500 |
| Squamous cell carcinoma with variants of oesophagus | 4 716 |
| Adenocarcinoma with variants of oesophagus | 1 711 |
| Salivary gland type tumours of oesophagus | 3 |
| Undifferentiated carcinoma of oesophagus | 74 |
| **RARE EPITHELIAL TUMOURS OF STOMACH** | 772 |
| Squamous cell carcinoma with variants of stomach | 176 |
| Salivary gland type tumours of stomach | 2 |
| Undifferentiated carcinoma of stomach | 594 |
| **EPITHELIAL TUMOURS OF SMALL INTESTINE** | 1 815 |
| Adenocarcinoma with variants of small intestine | 1 416 |
| Squamous cell carcinoma with variants of small intestine | 16 |
| **RARE EPITHELIAL TUMOURS OF COLON** | 234 |
| Squamous cell carcinoma with variants of colon | 60 |
| Fibromixoma and low grade mucinous adenocarcinoma of the appendix | 174 |
| **RARE EPITHELIAL TUMOURS OF RECTUM** | 246 |
| Squamous cell carcinoma with variants of rectum | 246 |
| **EPITHELIAL TUMOURS OF ANAL CANAL** | 3 084 |
| Squamous cell carcinoma with variants of anal canal | 1 706 |
| Adenocarcinoma with variants of anal canal | 1 078 |
| Paget's disease of anal canal | 8 |
| **RARE EPITHELIAL TUMOURS OF PANCREAS** | 192 |
| Squamous cell carcinoma with variants of pancreas | 31 |
| Acinar cell carcinoma of pancreas | 78 |
| Mucinous cystadenocarcinoma of pancreas | 46 |
| Intraductal papillary mucinous carcinoma invasive of pancreas | 22 |
| Solid pseudopapillary carcinoma of pancreas | 12 |
| Serous cystadenocarcinoma of pancreas | 1 |
| Carcinoma with osteoclast-like giant cells of pancreas | 2 |
| **EPITHELIAL TUMOURS OF LIVER AND IBT** | 20 478 |
| Hepatocellular carcinoma of liver and IBT | 17 524 |
| Hepatocellular carcinoma, fibrolamellar of liver and IBT | 181 |
| Cholangiocarcinoma of IBT | 1 604 |
| Adenocarcinoma with variants of liver and IBT | 1 099 |
| Undifferentiated carcinoma of liver and IBT | 33 |
| Squamous cell carcinoma with variants of liver and IBT | 30 |
| Bile duct cystadenocarcinoma of IBT | 11 |
| **EPITHELIAL TUMOURS OF GALLBLADDER AND EBT** | 14 644 |
| Adenocarcinoma with variants of gallbladder | 3 820 |
| Adenocarcinoma with variants of EBT | 4 130 |
| Squamous cell carcinoma of gallbladder and EBT | 75 |
| **MESOTHELIOMA OF PERITONEUM** | 382 |

**NE:** not estimable because 30 or less incident cases were observed **IBT:** intrahepatic bile tract **EBT:** extrahepatic bile tract

# PREVALENCE



**RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | ESTIMATED PREVALENT CASES 2010 |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | |
| **RARE EPITHELIAL TUMOURS OF THE DIGESTIVE SYSTEM** | **28.41** | **27.3-29.55** | **17.74** | **16.87-18.65** | **65.73** | **64.04-67.46** | **74.38** | **71.54-75.42** | **43 452** |
| **EPITHELIAL TUMOURS OF OESOPHAGUS** | **3.69** | **3.30-4.12** | **1.69** | **1.43-1.98** | **7.72** | **7.15-8.33** | **8.70** | **8.04-9.36** | **5 013** |
| Squamous cell carcinoma with variants of oesophagus | 2.63 | 2.30-3.00 | 1.16 | 0.94-1.41 | 5.54 | 5.05-6.06 | 6.31 | 5.74-6.87 | 3 629 |
| Adenocarcinoma with variants of oesophagus | 1.03 | 0.83-1.26 | 0.48 | 0.35-0.65 | 2.09 | 1.80-2.42 | 2.28 | 1.95-2.61 | 1 319 |
| Salivary gland type tumours of oesophagus | NE | – | NE | – | NE | – | NE | – | NE |
| Undifferentiated carcinoma of oesophagus | 0.03 | 0.01-0.10 | 0.05 | 0.01-0.12 | 0.09 | 0.04-0.18 | 0.11 | 0.03-0.19 | 65 |
| **RARE EPITHELIAL TUMOURS OF STOMACH** | **0.21** | **0.13-0.33** | **0.17** | **0.09-0.28** | **0.82** | **0.64-1.03** | **0.96** | **0.73-1.18** | **556** |
| Squamous cell carcinoma with variants of stomach | 0.05 | 0.01-0.12 | 0.09 | 0.04-0.18 | 0.34 | 0.23-0.48 | 0.36 | 0.23-0.49 | 207 |
| Salivary gland type tumours of stomach | NE | – | NE | – | NE | – | NE | – | NE |
| Undifferentiated carcinoma of stomach | 0.17 | 0.09-0.28 | 0.07 | 0.03-0.16 | 0.48 | 0.35-0.65 | 0.59 | 0.41-0.78 | 349 |
| **EPITHELIAL TUMOURS OF SMALL INTESTINE** | **1.02** | **0.82-1.26** | **0.87** | **0.69-1.09** | **3.16** | **2.80-3.56** | **4.35** | **3.83-4.88** | **2 517** |
| Adenocarcinoma with variants of small intestine | 0.86 | 0.68-1.08 | 0.79 | 0.61-1.00 | 2.79 | 2.45-3.16 | 3.77 | 3.29-4.26 | 2 187 |
| Squamous cell carcinoma with variants of small intestine | 0.01 | 0.00-0.06 | NE | – | 0.02 | 0.00-0.08 | 0.04 | 0.00-0.10 | 23 |
| **RARE EPITHELIAL TUMOURS OF COLON** | **0.24** | **0.15-0.37** | **0.25** | **0.16-0.38** | **0.83** | **0.65-1.04** | **0.92** | **0.71-1.14** | **589** |
| Squamous cell carcinoma with variants of colon | 0.02 | 0.00-0.08 | 0.02 | 0.00-0.08 | 0.08 | 0.03-0.17 | 0.10 | 0.03-0.17 | 58 |
| Fibromixoma and low grade mucinous adenocarcinoma of the appendix | 0.22 | 0.13-0.34 | 0.23 | 0.14-0.35 | 0.75 | 0.58-0.95 | 0.83 | 0.62-1.03 | 531 |
| **RARE EPITHELIAL TUMOURS OF RECTUM** | **0.23** | **0.14-0.36** | **0.18** | **0.11-0.30** | **0.80** | **0.62-1.01** | **1.10** | **0.83-1.37** | **651** |
| Squamous cell carcinoma with variants of rectum | 0.23 | 0.14-0.36 | 0.18 | 0.11-0.30 | 0.80 | 0.62-1.01 | 1.10 | 0.83-1.37 | 651 |
| **EPITHELIAL TUMOURS OF ANAL CANAL** | **3.01** | **2.66-3.40** | **2.79** | **2.45-3.16** | **10.11** | **9.45-10.80** | **13.24** | **12.36-14.13** | **7 735** |
| Squamous cell carcinoma with variants of anal canal | 1.85 | 1.58-2.16 | 1.92 | 1.64-2.23 | 6.57 | 6.04-7.13 | 9.18 | 8.41-9.94 | 5 397 |
| Adenocarcinoma with variants of anal canal | 1.05 | 0.84-1.28 | 0.76 | 0.58-0.96 | 3.05 | 2.69-3.44 | 3.81 | 3.35-4.28 | 2 196 |
| Paget's disease of anal canal | NE | – | 0.01 | 0.00-0.06 | 0.05 | 0.01-0.12 | 0.06 | 0.00-0.11 | 34 |
| **RARE EPITHELIAL TUMOURS OF PANCREAS** | **0.14** | **0.07-0.24** | **0.15** | **0.08-0.26** | **0.40** | **0.28-0.56** | **0.57** | **0.37-0.76** | **329** |
| Squamous cell carcinoma with variants of pancreas | NE | – | 0.01 | 0.00-0.06 | 0.05 | 0.01-0.12 | 0.08 | 0.00-0.16 | 45 |
| Acinar cell carcinoma of pancreas | 0.06 | 0.02-0.13 | 0.09 | 0.04-0.18 | 0.17 | 0.10-0.28 | 0.24 | 0.11-0.36 | 138 |
| Mucinous cystadenocarcinoma of pancreas | 0.02 | 0.00-0.08 | 0.04 | 0.01-0.10 | 0.11 | 0.06-0.21 | 0.17 | 0.06-0.27 | 97 |
| Intraductal papillary mucinous carcinoma invasive of pancreas | 0.05 | 0.01-0.12 | 0.01 | 0.00-0.06 | 0.06 | 0.02-0.13 | 0.07 | 0.01-0.14 | 42 |
| Solid pseudopapillary carcinoma of pancreas | 0.01 | 0.00-0.06 | NE | – | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.03 | 7 |
| Serous cystadenocarcinoma of pancreas | NE | – | NE | – | NE | – | NE | – | NE |
| Carcinoma with osteoclast-like giant cells of pancreas | NE | – | NE | – | NE | – | NE | – | NE |
| **EPITHELIAL TUMOURS OF LIVER AND INTRAHEPATIC BILE TRACT** | **13.32** | **12.56-14.10** | **8.09** | **7.57-8.78** | **27.12** | **26.04-28.24** | **27.97** | **26.68-28.94** | **16 092** |
| Hepatocellular carcinoma of liver and IBT | 11.86 | 11.15-12.61 | 7.46 | 7.08-8.25 | 24.82 | 23.78-25.89 | 25.55 | 24.47-26.63 | 14 690 |
| Hepatocellular carcinoma, fibrolamellar of liver and IBT | 0.03 | 0.01-0.10 | 0.08 | 0.05-0.20 | 0.14 | 0.07-0.24 | 0.18 | 0.07-0.28 | 103 |
| Cholangiocarcinoma of IBT | 0.98 | 0.79-1.22 | 0.33 | 0.20-0.45 | 1.55 | 1.30-1.83 | 1.60 | 1.33-1.87 | 922 |
| Adenocarcinoma with variants of liver and IBT | 0.43 | 0.31-0.60 | 0.21 | 0.03-0.16 | 0.59 | 0.44-0.77 | 0.61 | 0.44-0.77 | 347 |
| Undifferentiated carcinoma of liver and IBT | NE | – | NE | – | NE | – | NE | – | NE |
| Squamous cell carcinoma with variants of liver and IBT | NE | – | 0.02 | 0.00-0.08 | 0.02 | 0.00-0.08 | 0.03 | 0.00-0.08 | 19 |
| Bile duct cystadenocarcinoma of IBT | NE | – | NE | – | 0.01 | 0.00-0.06 | 0.02 | 0.00-0.05 | 11 |
| **EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT** | **6.40** | **5.88-6.95** | **3.48** | **3.00-3.79** | **14.46** | **13.68-15.29** | **16.65** | **15.73-17.57** | **9 669** |
| Adenocarcinoma with variants of gallbladder | 1.98 | 1.69-2.30 | 1.43 | 1.14-1.64 | 5.64 | 5.15-6.16 | 6.52 | 5.94-7.10 | 3 792 |
| Adenocarcinoma with variants of EBT | 2.55 | 2.23-2.91 | 1.60 | 1.37-1.92 | 5.98 | 5.47-6.51 | 6.76 | 6.18-7.34 | 3 887 |
| Squamous cell carcinoma of gallbladder and EBT | 0.03 | 0.01-0.10 | NE | – | 0.05 | 0.01-0.12 | 0.05 | 0.00-0.10 | 29 |
| **MESOTHELIOMA OF PERITONEUM** | **0.16** | **0.09-0.27** | **0.11** | **0.07-0.23** | **0.38** | **0.26-0.54** | **0.52** | **0.34-0.70** | **300** |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

**IBT:** intrahepatic bile tract **EBT:** extrahepatic bile tract

This group includes epithelial tumours of:
- **oesophagus** (squamous cell carcinoma, adenocarcinoma, salivary gland type, undifferentiated carcinoma);
- **stomach** (squamous cell carcinoma, salivary gland type, undifferentiated carcinoma);
- **small intestine** (adenocarcinoma and squamous cell carcinoma);
- **colon** (squamous cell carcinoma, fibromyxoma and low grade mucinous adenocarcinoma of appendix);
- **rectum** (squamous cell carcinoma);
- **anal canal** (squamous cell carcinoma, adenocarcinoma, Paget's disease);
- **liver and intrahepatic bile duct** (hepatocellular carcinoma, fibrolamellar hepatocellular carcinoma, cholangiocarcinoma, adenocarcinoma, undifferentiated carcinoma, squamous cell carcinoma, bile duct cystoadenocarcinoma);
- **gallbladder and extrahepatic biliary tract** (adenocarcinoma, squamous cell carcinoma);
- **pancreas** (squamous cell carcinoma, acinar cell carcinoma, mucinous cystoadenocarcinoma, intraductal papillary mucinous carcinoma, serous cystoadenocarcinoma, carcinoma with osteoclastic-like giant cells, solid pseudopapillary carcinoma).

Among the rare cancers of the digestive tract we also describe
- **peritoneal mesothelioma**.

All together, rare epithelial cancers account for 16% of all cancers of the digestive system. Non epithelial tumours such as neuroendocrine tumours or sarcomas of the digestive system are not included here but in the sarcoma (p. 84) and neuroendocrine tumour (p. 90) groupings described in this monograph.

## RARE EPITHELIAL TUMOURS OF STOMACH, COLON AND RECTUM AND EPITHELIAL TUMOURS OF OESOPHAGUS, SMALL INTESTINE AND ANAL CANAL

### WHAT DO WE KNOW ABOUT THESE CANCERS?

All these cancers share similar risk factors: smoking, alcohol, and lifestyle habits, such as consumption of red meat, flour, and refined sugars, overweight, and limited physical activity.[1] Additional site-specific risk factors are: exposure to mycotoxins, human papillomavirus (HPV)[2] infection, and familial predisposition for squamous cell carcinoma of oesophagus; Barrett's oesophagus, gastroesophageal reflux, and bile reflux for adenocarcinoma of oesophagus;[3] Helicobacter pylori (HP) for epithelial tumours of stomach;[4] Crohn's disease, familial adenomatous polyposis for small intestine;[5] family history and hereditary syndromes for colon;[6] HPV infection (strains 16 and 18) for anal canal.

**In the oesophagus** squamous cell carcinoma is more frequent in the upper middle third part while adenocarcinoma occurs mainly in the lower third because of the different risk factors.

**In the stomach** squamous cell carcinoma and salivary gland type tumours are very rare. Undifferentiated carcinoma of the stomach is characterised by lesions that lack any differentiated features beyond an epithelial phenotype.

**In the small intestine** adenocarcinoma is the most common histotype and is located mainly in the second part of the duodenum. Diagnosis is often difficult, but recently videocapsule endoscopy has shown promising results in the diagnosis of disorders and tumours of the small intestine.

**Rectal squamous cell carcinoma** is more aggressive than adenocarcinoma and has a worse prognosis.

**Anal canal cancers**, because of their localisation, are often diagnosed when the disease is localised to the locoregional area. It has been shown that chemoradiation in squamous cell carcinoma of the anal canal may offer a good chance of cure without surgery. On the contrary, all other sites are rarely diagnosed as a localised disease. The number of randomised trials is scarce and the data to support evidence-based decisions are very limited. No effective and satisfactory treatment for this disease really exists, thus it is recommended to refer patients with these rare cancers to specialised centres.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

All epithelial tumours of the **oesophagus** are rare even if all together the epithelial tumours represent the 81% of all the tumours of the oesophagus. All epithelial tumours of the **small intestine** and of the **anal canal** are rare and represent the 56% and 97% of all tumours of small intestine and anal canal, respectively (incidence table, p. 44). In the stomach, colon, and rectum, rare epithelial cancers are 1.5%, 0.2%, and 1%, respectively, based on AIRTUM data.

The most frequent rare epithelial histotype is squamous cell carcinoma, but even common adenocarcinomas in some sites (oesophagus, small intestine, and anal canal) are rare. Most **rare epithelial cancers of the colon** are low grade mucinous adenocarcinoma of the appendix. The other histotypes (salivary gland type tumours, Paget's disease) are extremely rare. Squamous cell carcinoma is more frequent than adenocarcinoma in the oesophagus and anal canal; in the small intestine it is the opposite. We found an unexpectedly high frequency of adenocarcinomas among anal canal cancers. In hospital series they are exceptional, suggesting that some low rectal cancers were classified generically as anal canal cancers.

Rare epithelial tumours of the oesophagus, stomach, and small intestine are more common in males than females. The opposite is true for rare epithelial tumours of the colon, rectum, and anal canal. All these tumours are typical of old ages (>65 years old). Italian and European data of the RARECAREnet database (www.rarecarenet.eu) are similar, but in Italy the incidence of adenocarcinoma of the oesophagus is lower than in Europe and the incidence of adenocarcinoma of the anus is higher.

#### Survival

Survival of epithelial tumours of the oesophagus, stomach, and small intestine is poor. Five-year relative survival (RS) for these sites, regardless of the histotype, is 13% for the oesophagus, 18% for the stomach, and 29% for the small intestine. RS of rare epithelial tumours of the colon, rectum, and anal canal is slightly better, with almost half of patients alive after 5 years from diagnosis. However, squamous cell carcinoma of the colon has a 5-year RS of 31%, while that of low grade mucinous adenocarcinoma of the appendix is 66% (survival figure, p. 45). Thus, the latter mainly influence the survival of rare epithelial tumours of the colon. Italian and European data of the RARECAREnet database are similar.

### Prevalence

About 7,700 persons were estimated to be living with a diagnosis of anal canal tumour (about two thirds with squamous cell carcinomas) at the beginning of 2010. Persons living with a diagnosis of **rare epithelial tumours of the oesophagus** were about 5,000; among these, squamous cell carcinomas are the most frequent (mainly for their relatively high incidence).

Persons with a diagnosis of **small intestine tumours** were about 2,500 (87% with adenocarcinoma). Estimated numbers of prevalent cases of **rare tumours of the stomach, colon, and rectum** were 550, 600, and 650, respectively. Among prevalent cases, the proportion of patients that survived more than 15 years from diagnosis is similar among sites, lower than 30%. Prevalence estimates are coherent with the relatively low incidence and poor prognosis of the majority of these tumours. Prevalence estimates for the oesophagus are a bit higher than those published in the AIRTUM monograph on prevalence[7] because of the different methodology used (see «Materials and methods», pp. 14-21). The other sites are difficult to compare with published data because rare epithelial tumours represent only a small fraction of all the tumours of the site.

## RARE EPITHELIAL TUMOURS OF PANCRES

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Pancreatic cancer is an aggressive disease with an extremely poor prognosis. It is mainly diagnosed in advanced stage; however, increased use of radiological modalities has led to incidental findings of pancreatic cancer, as well as the detection of precursor lesions which can be monitored and/or resected as necessary. A combination of biochemical tests, radiological imaging, endoscopic ultrasound fine needle aspiration and multidisciplinary discussion in specialised centres is necessary for accurate diagnosis, staging, and for the definition of the appropriate management plan. An example of this approach is the experience of the Province of Reggio Emilia (Emilia-Romagna Region, Central Italy), where since 2012 it has been possible to submit all cases of pancreatic tumours that access the various hospitals in the province to multidisciplinary discussion, both through regular meetings and using a specially created discussion blog.

Risk factors include:[8] excess body weight, chronic inflammation of the pancreas, diabetes, family history of genetic syndromes, personal or family history of pancreatic cancer, smoking.

**Squamous cell carcinoma** clinical presentation is similar to that of adenocarcinoma.

**Acinar cell carcinoma** shows different clinical symptoms at presentation, different morphological features, different outcomes, and different molecular alterations, creating difficulties in the clinical and pathological diagnosis and in the therapeutic choice.[9] **Mucinous cystadenocarcinoma** is the malignant form of a mucinous cystic neoplasm. Correct and early characterisation of a premalignant or malignant mucinous cystic neoplasm with surgical resection offers a favourable prognosis. However, once it has become invasive or metastasised, the outcome of a cystic pancreatic carcinoma is poor.

**Intraductal papillary mucinous carcinomas** comprise a histologic spectrum ranging from adenoma with mild dysplasia to invasive carcinoma. Although the overall outcome is good, a significant proportion of resected patients develop pancreatic adenocarcinoma in the pancreatic remnant.

**Solid pseudopapillary carcinoma** derives from a solid-pseudopapillary neoplasm; it has been recognised with increasing frequency in recent years. It is characterised by tumour recurrence and/or metastasis.

**Serous cystadenocarcinoma** of the pancreas is a malignant cystic tumour which, in most cases, shows synchronous or metachronous liver metastases.

**Carcinoma with osteoclast-like giant cells** is an extraskeletal tumour containing multinucleated osteoclast-like giant cells, which morphologically resemble those found in giant cell tumours of the bone. The clinical features of these tumours remain obscure, as many cases are already advanced when detected. Long-term follow-up of patients with these rare tumours is essential in order to compile a body of literature to help guide treatment, since the rarity of this tumour renders prospective studies unlikely. The development of specialist registries can strongly contribute to the study of pancreatic diseases and the identification of an appropriate approach for diagnosis and treatment.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Rare epithelial cancers include several histotypes, which all together represent only 1% of pancreatic tumours. The proportion of rare cancers is so low partly because histological proof is not always obtained. In the AIRTUM database less than 50% of cases have histological verification. This is a problem which leads to an underestimation of the rare histotypes of the pancreas. In addition, 57% of pancreatic cancers have a non-specified morphology, which means that often pathologists do not report/identify the specific histotype, contributing to underestimate the real incidence of rare tumours.

In Italy in the AIRTUM database, in 11 years, 241 cases of rare epithelial tumours of pancreas were observed. The most common histotype is acinar cell carcinoma (39% of cases), followed by mucinous cystadenocarcinoma (23%), squamous cell carcinoma (16%), and invasive intraductal papillary mucinous carcinoma (14%). The other histotypes are extremely rare, with 13 or fewer cases observed in 11 years. Rare epithelial pancreatic cancers are more frequent in males than females and are typical of old age (65-75 years old). Italian and European (RARECAREnet database) are similar.

#### Survival

Survival of rare epithelial pancreatic cancers is low for all histotypes. Mucinous cystoadenocarcinoma and acinar cell carcinoma have the best 5-year relative survival (RS), which, in any case, is 33% and 25%, respectively. The number of cases of the other histotypes is not enough to provide reliable estimates (see figure p. 45). However, the estimates of the wider RARECAREnet database confirm the poor prognosis expected for solid pseudopapillary carcinoma, which has a 5-year RS of 65% (based on 42 cases only). Again, in the RARECAREnet database the number of cases was not enough to estimate the RS of serous cystadenocarcinoma and carcinoma with osteoclast-like giant cells.

#### Prevalence

Slightly more than 300 people were estimated to be alive in 2010 with a diagnosis of rare epithelial tumours of the pancreas, with acinar cell

carcinomas being the most prevalent cases (42%). The prevalence estimates are low because of the rarity and poor prognosis of these tumours.

## EPITHELIAL TUMOURS OF LIVER AND INTRAHEPATIC BILE DUCT AND OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Over 70% of primary liver cancers are attributable to Hepatitis C virus (HCV), Hepatitis B virus (HBV), alcohol, smoking, and, for cholangiocarcinoma, primary sclerosing cholangitis (PSC), cirrhosis, diabetes, obesity, and Caroli's disease.[10,11]

**For gallbladder cancer** the most common risk factors are gallstones, porcelain gallbladder, gallbladder adenoma, bile duct cysts, and abnormalities of the biliopancreatic junction. The risk increases in the case of obesity and a diet high in carbohydrates and low in fibres.

**For cancer of the bile ducts** the risk factors are chronic inflammation of the bile duct, bile duct cysts, congenital dilatation of intrahepatic bile ducts and cirrhosis.[12]

Histological proof is not always easy to obtain for these sites. Liver, extrahepatic bile duct, and gallbladder are not easily accessible, therefore biopsy and surgery are infrequently performed. In the absence of histological verification, diagnosis is based on operative findings or medical imaging. In the AIRTUM database, 60% of patients have a liver cancer and 40% have a gallbladder cancer diagnosed without histological verification. The proportion of unspecified morphology is high (>40%) and increases in older people (>65 years). Thus, some concerns regarding our analysis should be noted, as the high proportion of unspecified morphology may lead to underestimation of rare liver and gallbladder cancers (which are defined by the combination of topography and morphology). The accuracy of diagnosis of these tumours should increase regardless of the poor prognosis of liver cancers.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

**All epithelial tumours of liver and gallbladder** are rare because rare cancers are defined on the basis of the European population and not of the country-specific incidence rate. Thus, even hepatocellular carcinoma of the liver and all tumours of the gallbladder, which in Italy are not perceived as rare, fall into the rare category, since in Europe their incidence is 3 and 4 per 100,000, respectively.

Among the **epithelial tumours of liver and intrahepatic bile duct** (IBTs), the hepatocellular is the most frequent (85%) followed by cholangiocarcinoma (8%), and adenocarcinoma (6%) (see table p. 44). Around 200 cases of fibrolamellar hepatocellular carcinoma were observed in 11 years in the AIRTUM database. The other entities are extremely rare. All histotypes are more common in males than females and are typical of the older age group (>65 years). The incidence of all epithelial tumours of the liver does not include the unspecified morphology, which for this site is high. All liver histotypes show higher rates in Italy than in Europe (RARECAREnet database).

**Epithelial tumours of gallbladder and extrahepatic bile duct** (EBTs) are mainly adenocarcinomas; only 84 cases of squamous cell carcinoma were observed in 11 years in the AIRTUM database. Even in these sites there is a high proportion of unspecified morphologies, however, contrary to liver cancers, the incidence of epithelial tumours of the gallbladder includes the unspecified types (this is the reason why the sum of the proportion of adenocarcinomas of the gallbladder and EBTs do not add up to 100%). The incidence is slightly higher in females, especially for gallbladder tumours and increases with age. The incidence in Italy is slightly higher than in Europe (RARECAREnet database).

#### Survival

Prognosis of epithelial tumours of the liver, IBTs, epithelial tumours of the gallbladder, and EBTs is poor. One-year RS is 76% and 58% for fibrolamellar hepatocellular carcinoma and hepatocellular carcinoma, respectively. However for all other epithelial tumours of the liver and gallbladder, IBTs, and EBTs, 1-year RS is ≤44%. Survival drops to ≤20% 5 years after diagnosis (except for fibrolamellar hepatocellular carcinoma, for which it is 36%) (see figure p. 45). Survival estimates of undifferentiated carcinoma, squamous cell carcinoma, and bile duct cystadenocarcinoma of liver and IBTs are based on a limited number of cases. In Italy, survival for all these tumours is slightly higher than in Europe, probably because of the screening of high-risk patients (chronic HCV or HBC infection). Moreover, great attention is paid in Italy to the prevention of viral infections through blood work and blood products, donated organs and tissues, and all medical and surgical procedures.

#### Prevalence

Around 16,000 people were estimated to be alive in Italy in 2010 with a diagnosis of epithelial tumours of the liver. The prevalent cases are mainly due to the relatively high incidence of hepatocellular carcinomas. These data are slightly lower than those presented in the AIRTUM monograph on prevalence,[7] because we do not include cases with unspecified morphology of the liver, which are a high number. Around 9,700 people were estimated to be alive with a diagnosis of epithelial tumours of the gallbladder and were mainly people with adenocarcinomas of gallbladder and EBTs.

## MESOTHELIOMA OF PERITONEUM

### WHAT DO WE KNOW ABOUT THESE CANCERS?

**Peritoneal mesothelioma** can have the same morphology as pleural forms (epithelioid, sarcomatoid, and mixed). The tumour may grow, giving only nonspecific signs and symptoms. Patients with peritoneal mesothelioma access different hospital departments from those used by patients with lung mesothelioma. Thus, many different structures must be investigated in epidemiological survey of these tumours (internal medicine and general surgery, as well as thoracic surgery).

Asbestos is the main risk factor for peritoneal mesothelioma. An additional risk factor is radiation used for diagnosis and treatment (Thorotrast) and irradiation of abdominal lymph nodes in prostate cancer.[13] People exposed to asbestos have a risk of mesothelioma of the peritoneum that appears to constantly grow over time, even after cessation of exposure.

### THE EPIDEMIOLOGICAL DATA IN ITALY

Only 449 cases of mesothelioma of the peritoneum were observed in the AIRTUM database in 11 years. One-year RS is 43% and drops to 11% at five years. In some population-based studies, a shorter median survival was observed in peritoneal as compared with pleural mesothelioma, but in others there were contrasting results. A possible explanation is that peritoneal mesothelioma has both a shorter survival in most cases and a larger proportion of long-term survivors.[14]

## GENERAL REMARKS

In general, if you consider the number of observed cases in the AIRTUM database during the period 2000-2010 and expected cases in 2015 (see table p. 44), you may notice that there are entities with less than 100 yearly diagnosed patients in Italy. The treatment of rare neoplastic conditions is challenging, especially because studies providing high levels of evidence are often lacking especially for the small number of incident cases.[15]

The current reality, for better or for worse, is that patients with a rare tumour consult different hospital centres, and thus the already few incident cases disperse more; also, each hospital centre may lead to use different existing therapies off-label, and although the response to such treatments may be either overwhelmingly positive or negative, there is currently no systematic way to collect this clinical information and learn from it. The creation of a network of centres that deal with special rare cancers, capitalizing on the access of patients in all centres, could serve as a basis to accumulate and consolidate knowledge of the natural history, molecular biology, and treatment of rare cancers: as more drugs and treatments for rare cancers emerge, there will still remain a need for randomised trials or observational studies to compare strategies.[16]

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# RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY

**8%**
**OF ALL TUMOURS OF THE THORACIC CAVITY ARE RARE EPITHELIAL TUMOURS**

## INCIDENCE

**3 590**
ESTIMATED NEW CASES
ITALY, 2015

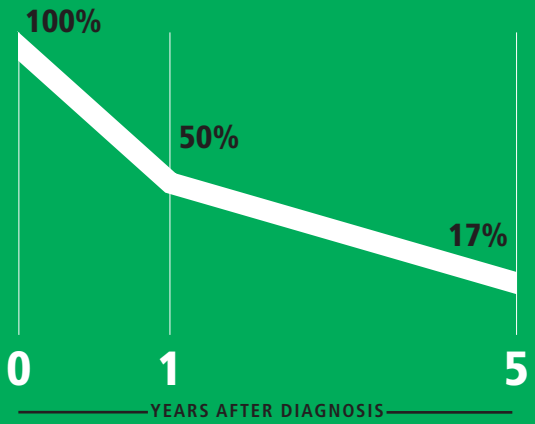
| | |
|---|---|
| 113 | EPITHELIAL TUMOURS OF TRACHEA |
| 1 699 | RARE EPITHELIAL TUMOURS OF LUNG |
| 232 | EPITHELIAL TUMOURS OF THYMUS |
| 1 546 | MESOTHELIOMA OF PLEURA AND PERICARDIUM |

| | |
|---|---|
| 95 % | OF RARE EPITHELIAL TUMOURS OUT OF ALL TUMOURS IN EACH SITE |
| 4 | |
| 97 | |
| 74 | |

## PREVALENCE

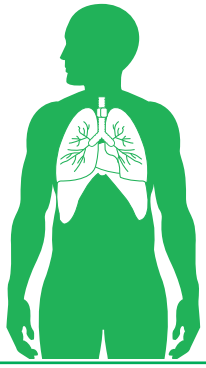
**9 933**
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY



# INCIDENCE

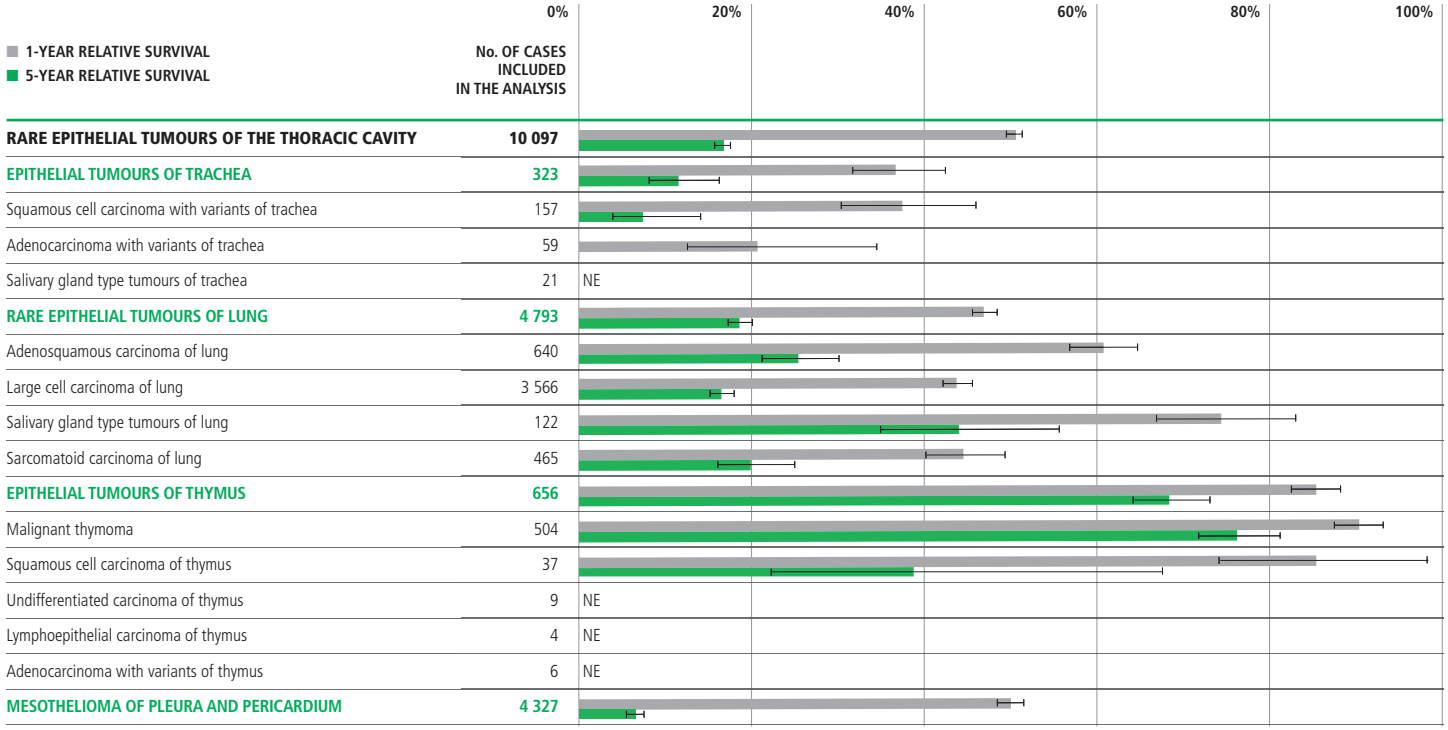
**RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY** | **5.42** | **5.33-5.52** | **12 027** | **8%** | **8.57** | **8.39-8.74** | **2.48** | **2.39-2.57** | **0.87** | **0.82-0.92** | **10.14** | **9.77-10.53** | **18.08** | **17.69-18.49** | **3 590** |
| EPITHELIAL TUMOURS OF TRACHEA | 0.17 | 0.15-0.19 | 374 | 95% | 0.27 | 0.24-0.30 | 0.07 | 0.06-0.09 | 0.03 | 0.02-0.04 | 0.33 | 0.27-0.41 | 0.55 | 0.48-0.62 | 113 |
| Squamous cell carcinoma with variants of trachea | 0.08 | 0.07-0.09 | 175 | | 0.14 | 0.11-0.16 | 0.03 | 0.02-0.04 | 0.01 | 0.01-0.02 | 0.16 | 0.12-0.22 | 0.26 | 0.21-0.31 | 53 |
| Adenocarcinoma with variants of trachea | 0.03 | 0.02-0.04 | 64 | | 0.05 | 0.04-0.06 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.08 | 0.05-0.12 | 0.08 | 0.06-0.11 | 19 |
| Salivary gland type tumours of trachea | 0.01 | 0.01-0.02 | 26 | | 0.01 | 0.01-0.02 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.02 | 0.01-0.04 | 0.03 | 0.02-0.05 | 8 |
| RARE EPITHELIAL TUMOURS OF LUNG | 2.58 | 2.51-2.65 | 5 722 | 4% | 4.37 | 4.24-4.49 | 0.91 | 0.85-0.96 | 0.40 | 0.36-0.43 | 4.97 | 4.71-5.25 | 8.57 | 8.30-8.85 | 1 699 |
| Adenosquamous carcinoma of lung | 0.41 | 0.38-0.44 | 909 | | 0.66 | 0.61-0.71 | 0.18 | 0.15-0.20 | 0.06 | 0.05-0.08 | 0.76 | 0.66-0.87 | 1.39 | 1.28-1.50 | 268 |
| Large cell carcinoma of lung | 1.84 | 1.78-1.89 | 4 071 | | 3.18 | 3.07-3.29 | 0.58 | 0.54-0.62 | 0.26 | 0.23-0.28 | 3.53 | 3.31-3.76 | 6.20 | 5.97-6.43 | 1 213 |
| Salivary gland type tumours of lung | 0.06 | 0.05-0.07 | 140 | | 0.09 | 0.07-0.11 | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | 0.12 | 0.09-0.17 | 0.15 | 0.11-0.19 | 41 |
| Sarcomatoid carcinoma of lung | 0.27 | 0.25-0.29 | 602 | | 0.44 | 0.40-0.48 | 0.11 | 0.09-0.13 | 0.05 | 0.04-0.06 | 0.56 | 0.48-0.66 | 0.85 | 0.76-0.94 | 177 |
| EPITHELIAL TUMOURS OF THYMUS | 0.36 | 0.34-0.39 | 804 | 97% | 0.41 | 0.38-0.45 | 0.32 | 0.28-0.35 | 0.18 | 0.16-0.20 | 0.73 | 0.64-0.84 | 0.75 | 0.67-0.84 | 232 |
| Malignant thymoma | 0.28 | 0.25-0.30 | 612 | | 0.31 | 0.28-0.35 | 0.24 | 0.21-0.27 | 0.15 | 0.13-0.17 | 0.56 | 0.47-0.65 | 0.54 | 0.47-0.61 | 175 |
| Squamous cell carcinoma of thymus | 0.02 | 0.02-0.03 | 46 | | 0.02 | 0.02-0.03 | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | 0.06 | 0.04-0.10 | 0.05 | 0.03-0.08 | 13 |
| Undifferentiated carcinoma of thymus | <0.01 | 0.00-0.01 | 9 | | NE | – | NE | – | NE | – | NE | – | NE | – | 2 |
| Lymphoepithelial carcinoma of thymus | <0.01 | 0.00-0.01 | 6 | | NE | – | NE | – | NE | – | NE | – | NE | – | 2 |
| Adenocarcinoma with variants of thymus | <0.01 | 0.00-0.01 | 7 | | NE | – | NE | – | NE | – | NE | – | NE | – | 2 |
| MESOTHELIOMA OF PLEURA AND PERICARDIUM | 2.31 | 2.25-2.38 | 5 127 | 74% | 3.51 | 3.40-3.63 | 1.19 | 1.12-1.25 | 0.27 | 0.24-0.29 | 4.10 | 3.86-4.35 | 8.21 | 7.94-8.48 | 1 546 |

**NE:** not estimable because 15 or less incident cases were observed

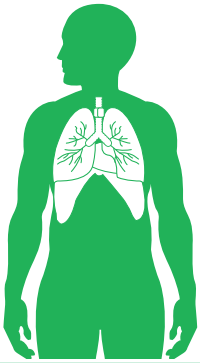
# SURVIVAL

**RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY** | **10 097** |
| EPITHELIAL TUMOURS OF TRACHEA | 323 |
| Squamous cell carcinoma with variants of trachea | 157 |
| Adenocarcinoma with variants of trachea | 59 |
| Salivary gland type tumours of trachea | 21 |
| RARE EPITHELIAL TUMOURS OF LUNG | 4 793 |
| Adenosquamous carcinoma of lung | 640 |
| Large cell carcinoma of lung | 3 566 |
| Salivary gland type tumours of lung | 122 |
| Sarcomatoid carcinoma of lung | 465 |
| EPITHELIAL TUMOURS OF THYMUS | 656 |
| Malignant thymoma | 504 |
| Squamous cell carcinoma of thymus | 37 |
| Undifferentiated carcinoma of thymus | 9 |
| Lymphoepithelial carcinoma of thymus | 4 |
| Adenocarcinoma with variants of thymus | 6 |
| MESOTHELIOMA OF PLEURA AND PERICARDIUM | 4 327 |

**NE:** not estimable because 30 or less incident cases were observed



# PREVALENCE

**RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **RARE EPITHELIAL TUMOURS OF THE THORACIC CAVITY** | **6.69** | **6.16-7.25** | **2.79** | **2.45-3.16** | **14.22** | **13.44-15.04** | **17.29** | **16.31-18.27** | **9 933** |
| **EPITHELIAL TUMOURS OF TRACHEA** | **0.15** | **0.08-0.26** | **0.09** | **0.04-0.18** | **0.34** | **0.23-0.49** | **0.42** | **0.27-0.57** | **240** |
| Squamous cell carcinoma with variants of trachea | 0.07 | 0.03-0.15 | 0.03 | 0.01-0.10 | 0.14 | 0.07-0.24 | 0.15 | 0.06-0.23 | 80 |
| Adenocarcinoma with variants of trachea | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.06 | 0.03 | 0.01-0.10 | 0.04 | 0.00-0.08 | 24 |
| Salivary gland type tumours of trachea | 0.05 | 0.01-0.12 | 0.02 | 0.00-0.08 | 0.13 | 0.06-0.23 | 0.20 | 0.08-0.32 | 120 |
| **RARE EPITHELIAL TUMOURS OF LUNG** | **2.87** | **2.53-3.25** | **1.44** | **1.20-1.72** | **7.34** | **6.78-7.93** | **9.12** | **8.40-9.84** | **5 218** |
| Adenosquamous carcinoma of lung | 0.40 | 0.28-0.56 | 0.21 | 0.12-0.33 | 0.94 | 0.75-1.17 | 1.12 | 0.88-1.37 | 635 |
| Large cell carcinoma of lung | 2.05 | 1.76-2.37 | 0.99 | 0.79-1.23 | 5.32 | 4.84-5.82 | 6.72 | 6.09-7.34 | 3 841 |
| Salivary gland type tumours of lung | 0.11 | 0.06-0.21 | 0.13 | 0.06-0.23 | 0.41 | 0.29-0.57 | 0.56 | 0.37-0.74 | 318 |
| Sarcomatoid carcinoma of lung | 0.31 | 0.20-0.45 | 0.11 | 0.06-0.21 | 0.67 | 0.51-0.86 | 0.73 | 0.54-0.91 | 425 |
| **EPITHELIAL TUMOURS OF THYMUS** | **0.72** | **0.56-0.93** | **0.57** | **0.43-0.76** | **2.46** | **2.14-2.81** | **3.31** | **2.86-3.76** | **1 921** |
| Malignant thymoma | 0.61 | 0.46-0.80 | 0.48 | 0.35-0.65 | 2.15 | 1.85-2.48 | 2.93 | 2.50-3.36 | 1 698 |
| Squamous cell carcinoma of thymus | 0.03 | 0.01-0.10 | 0.02 | 0.00-0.08 | 0.06 | 0.02-0.13 | 0.09 | 0.01-0.18 | 52 |
| Undifferentiated carcinoma of thymus | NE | – | NE | – | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.03 | 6 |
| Lymphoepithelial carcinoma of thymus | 0.01 | 0.00-0.06 | NE | – | 0.02 | 0.00-0.08 | 0.03 | 0.00-0.08 | 21 |
| Adenocarcinoma with variants of thymus | NE | – | NE | – | NE | – | NE | – | NE |
| **MESOTHELIOMA OF PLEURA AND PERICARDIUM** | **2.94** | **2.59-3.32** | **0.68** | **0.52-0.88** | **4.08** | **3.67-4.53** | **4.44** | **3.97-4.90** | **2 554** |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

Rare epithelial tumours represent 8% of all tumours of the thoracic cavity and include:

- **epithelial tumours of trachea** (squamous cell carcinoma, adenocarcinoma, and salivary gland type tumours);
- **rare epithelial tumours of lung** (adenosquamous carcinoma, large cell carcinoma, salivary gland type tumours, sarcomatoid carcinoma);
- **epithelial tumours of thymus** (malignant thymoma, squamous cell carcinoma, undifferentiated carcinoma, lymphoepithelial carcinoma, adenocarcinoma).

In this group we also describe

- **malignant pleural and pericardial mesothelioma**.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

Apart from mesothelioma, little information is available on patterns of incidence and survival for these tumours. This is largely because in the routine statistics these tumours are grouped together with other sites. **Tumours of the trachea** are grouped with lung and bronchus and tumours of the thymus are often grouped together with those of the heart, mediastinum, and pleura.[1] These tumour types have a different aetiology. Cancer of the trachea is associated with active and passive smoking, occupational exposure (to arsenic, asbestos, chromium, welding fumes) and environmental exposure (air pollution from traffic and industrial emissions).[2] Its usually insidious onset often leads to a delay in diagnosis, making these potentially treatable lesions difficult to treat and often fatal. Thus, early diagnosis is the most important factor affecting survival. Cigarette smoking is the most important risk factor of **lung cancer**, including its rare epithelial forms, together with occupational or environmental exposure to radon, asbestos, and heavy metals such as chromium, cadmium, and arsenic.[3] Adenosquamous carcinoma of the lung exhibits highly aggressive biological behaviour with early lymph node metastasis (46%) and its prognosis is worse than that of both squamous cell carcinoma and adenocarcinoma.[4] Large cell carcinomas often occur in the outer regions of the lungs and tend to grow rapidly and spread more quickly than some other forms of non-small cell lung cancer: they are more strongly associated with smoking than some other types of non-small cell lung cancers.

Many autoimmune syndromes are associated with **thymic epithelial tumours** (TETs); myasthenia gravis is the most common one, followed by autoimmune pure red cell aplasia, hypogammaglobulinaemia, and paraneoplastic autoimmune syndromes.[5] According to the 2004 World Health Organization classification, TETs are divided into thymomas (Ts: A, A/B, B1, B2, B3 subtypes) and thymic carcinomas (TCs: C) depending on cancer cell shape, degree of atypia, and extent of intratumoural thymocytes.[6] Available data demonstrate a poor prognosis for lesions classified as B3 and C, intermediate prognosis for B2, and favourable outcomes for A, AB, and B1 tumours. Squamous, undifferentiated, and lymphoepithelial carcinomas are not included among TETs, but are included in the list of rare cancers proposed by RARECARE as separate entities.[1] All subtypes of **malignant mesothelioma** (MM) **of the pleura and pericardium** are rare. In Italy, population-based registration of MM is carried out by the AIRTUM general cancer registries and by the Italian National Mesothelioma Registry (ReNaM) (https://ricercascientifica.inail.it/renam/Index.asp). The main risk factor of pleural MM is asbestos exposure. Other risk factors implicated in the pathogenesis of MM are ionising radiation and exposure to Thorotrast 9. Family clusters linked to the polymorphism of the genes involved in the repair process of DNA11,12 seem to make patients more vulnerable, still in the presence of asbestos exposure.[7] Pericardial mesothelioma cases have been associated with chest radiation treatment.[8] Microscopic diagnosis, which today has standardised the immunohistochemical panel, recognises three main subtypes of MM: epithelioid (more than half of the cases of MM), sarcomatoid (a worse prognosis), and biphasic (both components).

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

**All cancers of the trachea** are rare and overall only 374 cases were observed in the AIRTUM database in 11 years (2000-2010). Squamous cell carcinoma is the most common histotype (47%), followed by adenocarcinoma. Salivary gland type tumours represent a particularly rare histological type (only 26 cases in the period 2000-2010) (incidence table, p. 52). All histotypes are more common in males than females and their incidence increases with age, peaking in the 75-84-year age group (data not shown). Approximately 110 Italians are estimated to be diagnosed with cancers of the trachea in 2015.

**Rare epithelial tumours of the lung** represent only 4% of all cancers of this site. Among the rare forms, large cell carcinoma is the most common (71%), followed by adenosquamous carcinoma (16%), sarcomatoid carcinoma (11%), and salivary gland type tumours (2%). As in the case of the more frequent forms, even rare epithelial tumours of the lung are more common in males and increase with age (see table p. 52). Often the morphology of these tumours is not well specified: the percentage of unspecified forms, though reduced in the last few years, is still very high (29% of cancers of the lung; 35% in people >65 years old; data not shown). This is important because it could lead to an underestimation of the incidence of the rare epithelial cancer described here. In 2015, 1,699 new cases were estimated (see table p. 52).

**Thymus cancers** are all rare. Malignant thymoma is the most common form (76%), followed by squamous cell carcinoma (6%). Undifferentiated carcinoma, lymphoepithelial carcinoma, and adenocarcinoma represent particularly rare histological types (only 9, 6, and 7 cases were observed in the period 2000-2010, respectively). Malignant thymoma is more frequent in males than females; incidence peaks in the 65-74-year age group (data not shown). Squamous cell carcinoma incidence is similar in males and females; it has the highest incidence rate in the 60-69-year age group (data not shown). Even in Europe these cancers are extremely rare. Approximately 230 Italians are estimated to be diagnosed with cancers of the thymus in 2015.

The incidence of **pleural and pericardial MM** is higher in males than in females and in the over 65 age group. In the period 2000-2010, 5,127 cases were observed in the AIRTUM dataset (see table p. 52). The occurrence of MM showed an increasing trend in recent decades; in Italy different models have predicted a peak in incidence between 2010 and 2020.[9] All cancers of the thoracic cavity have a slightly higher incidence in Italy than in Europe (RARECAREnet database, www.rarecarenet.eu), except large cell carcinoma and salivary gland type tumours of the lung.

### Survival

Prognosis of patients diagnosed with an **epithelial tumour of the trachea** is poor, with less than half of the patients surviving the first year, and 12% alive 5 years after diagnosis. All histotypes share this poor prognosis, except salivary gland type tumours (survival figure, p. 52). In the AIRTUM database we do not have an appropriate number of cases of salivary gland tumours to estimate 5-year relative survival (RS); however, according to the European RARECAREnet database, it is 70%. Prognosis of patients with a tracheal malignancy is poor, however, surgical treatment can lead to good survival rates. Thus, the lower prognosis of these rare cancers is due to delay in diagnosis (due to its aspecific and asthma-mimicking symptoms), advanced stage at diagnosis, and limited experience among clinicians. Centralising the care and treatment of tracheal cancers could make surgery accessible to a larger number of patients, leading to better survival of these patients.[10] One-year and 5-year RS of **rare epithelial tumours of the lung** is 47% and 19%, respectively. Salivary gland type tumours have the highest 1- and 5-year RS (74% and 44%, respectively, see figure p. 52). For these rare forms, as well as for the most common cancers of the lung, no significant improvements in survival were reported over the last decades.[11] The worse prognosis of these cancers is mainly due to the more advanced stage at diagnosis and advanced age of the patients, which often condition radical surgery. For the early forms, if well treated, survival is significantly higher than the advanced forms.[12,13] However, there is considerable heterogeneity in the management of these patients, sometimes even in the same region.[14] Relative survival is rather good for patients diagnosed with an **epithelial tumour of the thymus**, with a 1- year RS of 85% and a 5-year RS of 68% (see figure p. 52). A combination of stage and histologic subtype should be considered in predicting survival. Types A, AB, and B1 have an excellent overall survival rate of between 90% and 95% at 10 years. Five-year RS for types B2, B3, and C is 75%, 70%, and 48%, respectively. Thymomas rarely metastasise, whereas TCs display a more aggressive phenotype, with distant metastases in liver, lymph nodes, and bones.[15] It is difficult to trace a standard treatment for thymomas. Although thymomas have a relatively good prognosis, they include a heterogeneous group of histologies, with different prognosis and for which there are no clear guidelines; so even for thymoma it would be appropriate to support a network that brings together experts to define common guidelines for better treatment. In France there is a national initiative named RYTHMIC, Réseau tumeurs THYmiques et Cancer (www.rythmic.org); in Italy, a network for thymic malignancies, TYME (TYmic MalignanciEs), was launched by the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, in 2014. One-year and 5-year RS of **pleural and pericardial MM** is 50% and 7%, respectively (see figure p. 52). Tools for early diagnosis and effective screening programs regarding MM are not available. Chest radiography and computer tomography (CT) were evaluated as ineffective in screening for MM in asbestos-exposed workers.[16,17] For pleural MM an optimal strategy is far from being standardised. Management of this disease requires a multidisciplinary team and it is recommended that patients who are considered candidates for a multimodal approach be included in a prospective trial at a specialised centre.

Among rare epithelial tumours of the thoracic cavity, squamous cell carcinoma of the thymus and mesothelioma of the pleura and pericardium show the most important differences between 1- year and 5-year RS (46 and 43 points, respectively).

Italian data and European RARECAREnet data are similar for all these tumours, except for pleural MM which has slightly higher survival in Italy than in Europe.

### Prevalence

About 10,000 persons were estimated alive in 2010 with a diagnosis of rare epithelial tumours of the thoracic cavity in Italy. Most prevalent cases are patients with a previous diagnosis of large cell carcinomas of the lung, mainly because of the relatively high incidence of these tumours compared to the others. The distribution of prevalence by time since diagnosis is fairly similar for the different types of tumours, except for those with poor prognosis (large cell carcinoma and sarcomatoid carcinoma of lung and mesothelioma of pleura and pericardium), that show a higher proportion of prevalent cases in the two years just after diagnosis.

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# RARE TUMOURS OF THE FEMALE GENITAL SYSTEM

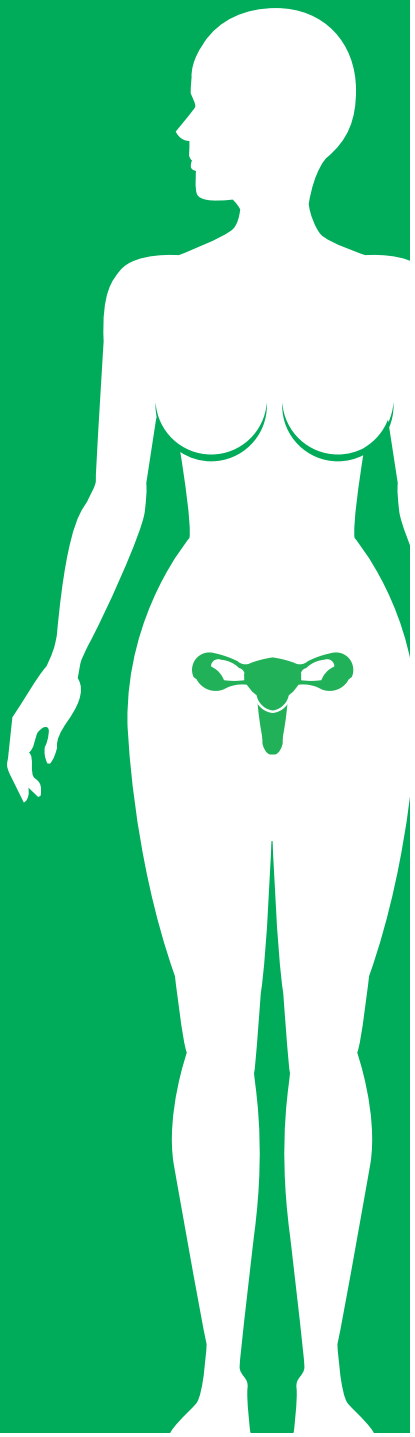
**17%**
**OF FEMALE GENITAL SYSTEM TUMOURS ARE RARE**

## INCIDENCE

**11 970**
ESTIMATED NEW CASES
ITALY, 2015

| | | |
|---|---|---|
| 3 093 | RARE EPITHELIAL TUMOURS OF BREAST | 6 |
| 553 | RARE EPITHELIAL TUMOURS OF CORPUS UTERI | 7 |
| 2 499 | EPITHELIAL TUMOURS OF CERVIX UTERI | 90 |
| 4 283 | EPITHELIAL TUMOURS OF OVARY AND FALLOPPIAN TUBE | 65 |
| 115 | NON EPITHELIAL TUMOURS OF OVARY | 2 |
| 1 414 | EPITHELIAL TUMOURS OF VULVA AND VAGINA | 95 |
| 12 | TROPHOBLASTIC TUMOURS OF PLACENTA | 82 |
| 246 | EPITHELIAL TUMOURS OF MALE BREAST | 100 |

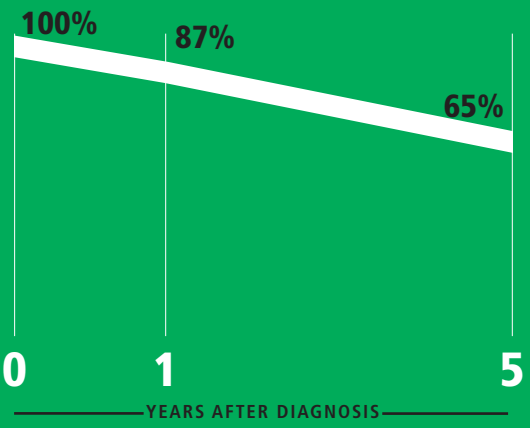
**%** **OF RARE TUMOURS OUT OF ALL TUMOURS IN EACH SITE**



## PREVALENCE

**154 397**
ESTIMATED PREVALENT CASES
ITALY, 2010

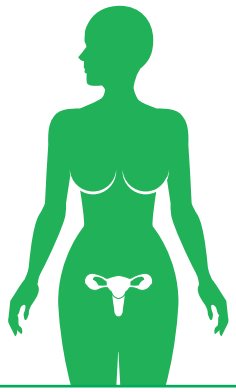
## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# RARE TUMOURS OF THE FEMALE GENITAL SYSTEM

# INCIDENCE

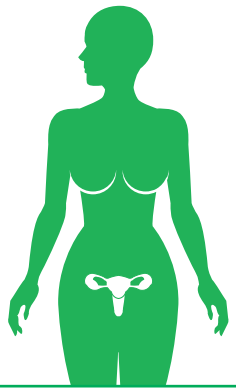


**RARE TUMOURS OF THE FEMALE GENITAL SYSTEM.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

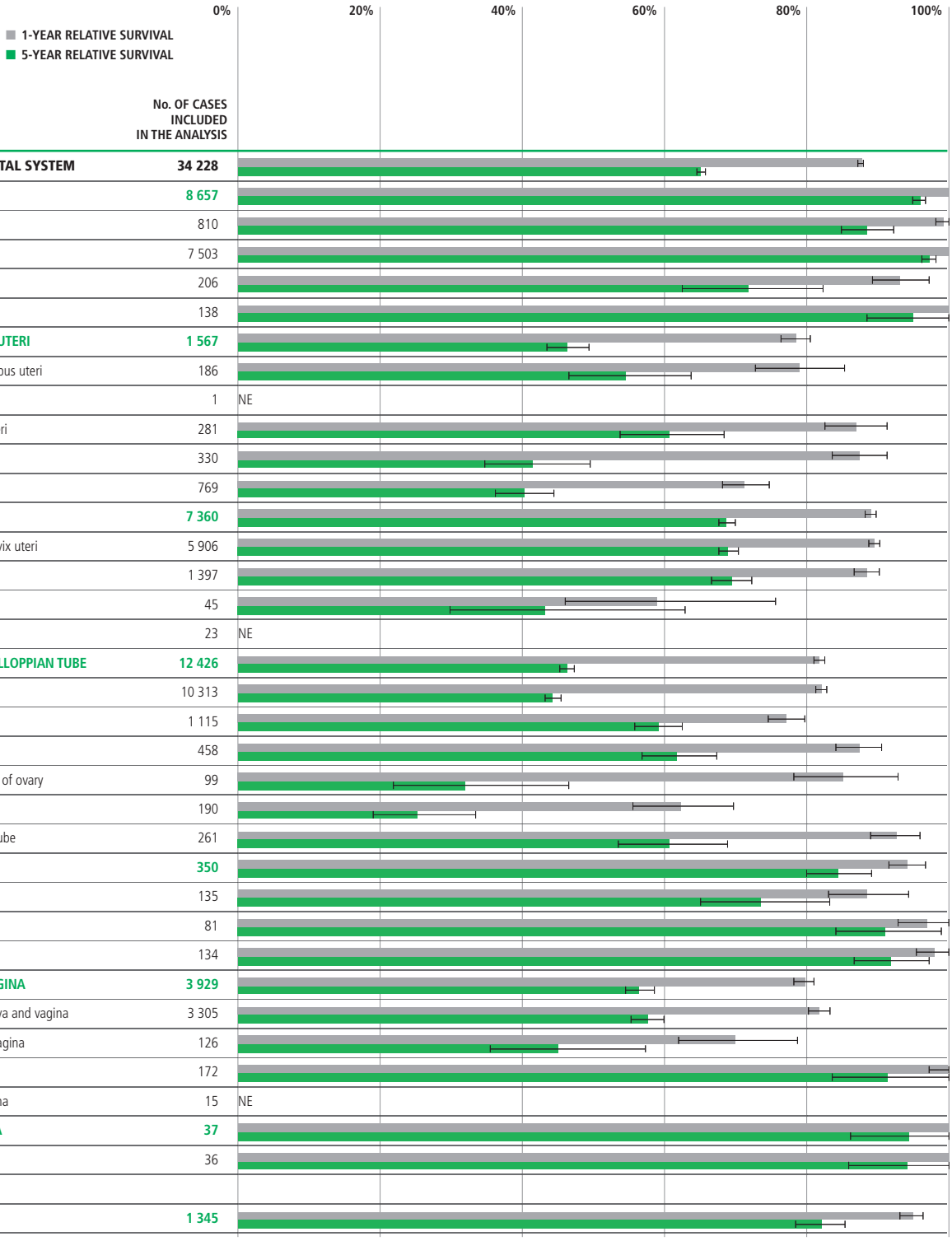
| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **RARE TUMOURS OF THE FEMALE GENITAL SYSTEM** | **18.55** | **18.37-18.73** | **41 141** | **17%** | **0.08** | **0.07-0.10** | **35.86** | **35.52-36.21** | **8.12** | **7.98-8.27** | **30.77** | **30.12-31.44** | **46.70** | **46.06-47.34** | **11 970** |
| **RARE EPITHELIAL TUMOURS OF BREAST** | **4.75** | **4.65-4.84** | **10 522** | **6%** | **0.08** | **0.06-0.10** | **9.12** | **8.94-9.29** | **1.94** | **1.87-2.01** | **7.77** | **7.45-8.11** | **12.47** | **12.14-12.80** | **3 093** |
| Mammary Paget's disease of breast | 0.43 | 0.41-0.46 | 963 | | 0.01 | 0.01-0.02 | 0.83 | 0.78-0.88 | 0.16 | 0.14-0.18 | 0.72 | 0.63-0.83 | 1.21 | 1.11-1.32 | 283 |
| Special types of adenocarcinoma of breast | 4.12 | 4.04-4.21 | 9 138 | | 0.06 | 0.05-0.08 | 7.92 | 7.76-8.09 | 1.70 | 1.64-1.77 | 6.75 | 6.44-7.06 | 10.77 | 10.47-11.09 | 2 687 |
| Metaplastic carcinoma of breast | 0.12 | 0.10-0.13 | 256 | | 0.00 | 0.00-0.01 | 0.22 | 0.20-0.25 | 0.05 | 0.04-0.06 | 0.17 | 0.12-0.23 | 0.30 | 0.25-0.36 | 75 |
| Salivary gland type tumours of breast | 0.07 | 0.06-0.09 | 165 | | 0.00 | 0.00-0.01 | 0.14 | 0.12-0.17 | 0.03 | 0.02-0.04 | 0.14 | 0.10-0.19 | 0.18 | 0.14-0.22 | 48 |
| **RARE EPITHELIAL TUMOURS OF CORPUS UTERI** | **0.86** | **0.82-0.90** | **1 907** | **7%** | | | **1.67** | **1.59-1.74** | **0.11** | **0.10-0.13** | **1.65** | **1.50-1.81** | **2.93** | **2.77-3.10** | **553** |
| Squamous cell carcinoma with variants of corpus uteri | 0.10 | 0.09-0.11 | 222 | | | | 0.19 | 0.17-0.22 | 0.03 | 0.02-0.04 | 0.22 | 0.16-0.28 | 0.27 | 0.23-0.33 | 65 |
| Adenoid cystic carcinoma of corpus uteri | <0.01 | 0.00-0.01 | 1 | | | | NE | – | NE | – | NE | – | NE | – | 0 |
| Clear cell adenocarcinoma, NOS of corpus uteri | 0.15 | 0.13-0.16 | 327 | | | | 0.29 | 0.26-0.32 | 0.02 | 0.02-0.03 | 0.23 | 0.18-0.30 | 0.51 | 0.45-0.59 | 94 |
| Serous (papillary) carcinoma of corpus uteri | 0.20 | 0.18-0.22 | 447 | | | | 0.39 | 0.36-0.43 | 0.01 | 0.01-0.02 | 0.43 | 0.35-0.51 | 0.72 | 0.64-0.80 | 129 |
| Mullerian mixed tumours of corpus uteri | 0.41 | 0.38-0.44 | 910 | | | | 0.79 | 0.74-0.85 | 0.05 | 0.04-0.06 | 0.77 | 0.67-0.89 | 1.42 | 1.31-1.54 | 264 |
| **EPITHELIAL TUMOURS OF CERVIX UTERI** | **3.94** | **3.85-4.02** | **8 726** | **90%** | | | **7.62** | **7.46-7.78** | **2.80** | **2.72-2.89** | **5.88** | **5.59-6.17** | **6.61** | **6.37-6.85** | **2 499** |
| Squamous cell carcinoma with variants of cervix uteri | 3.13 | 3.05-3.20 | 6 932 | | | | 6.06 | 5.91-6.20 | 2.24 | 2.16-2.32 | 4.68 | 4.42-4.94 | 5.20 | 4.99-5.42 | 1 987 |
| Adenocarcinoma with variants of cervix uteri | 0.78 | 0.74-0.81 | 1 721 | | | | 1.50 | 1.43-1.58 | 0.55 | 0.51-0.59 | 1.17 | 1.04-1.30 | 1.31 | 1.20-1.42 | 491 |
| Undifferentiated carcinoma of cervix uteri | 0.02 | 0.02-0.03 | 47 | | | | 0.04 | 0.03-0.05 | 0.01 | 0.01-0.02 | 0.03 | 0.01-0.06 | 0.05 | 0.03-0.08 | 14 |
| Mullerian mixed tumours of cervix uteri | 0.01 | 0.01-0.02 | 26 | | | | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.02 | 0.05 | 0.03-0.07 | 8 |
| **EPITHELIAL TUMOURS OF OVARY AND FALLOPPIAN TUBE** | **6.68** | **6.58-6.79** | **14 819** | **65%** | | | **12.94** | **12.74-13.15** | **2.78** | **2.69-2.86** | **13.28** | **12.85-13.72** | **15.97** | **15.60-16.35** | **4 283** |
| Adenocarcinoma with variants of ovary | 5.53 | 5.43-5.63 | 12 261 | | | | 10.71 | 10.52-10.90 | 2.25 | 2.17-2.32 | 11.11 | 10.72-11.52 | 13.30 | 12.96-13.65 | 3 550 |
| Mucinous adenocarcinoma of ovary | 0.60 | 0.57-0.63 | 1 326 | | | | 1.16 | 1.10-1.22 | 0.31 | 0.28-0.34 | 0.94 | 0.83-1.07 | 1.37 | 1.26-1.48 | 380 |
| Clear cell adenocarcinoma of ovary | 0.25 | 0.23-0.28 | 565 | | | | 0.49 | 0.45-0.54 | 0.14 | 0.13-0.16 | 0.61 | 0.52-0.71 | 0.41 | 0.36-0.48 | 163 |
| Primary peritoneal serous/papillary carcinoma of ovary | 0.05 | 0.04-0.06 | 115 | | | | 0.10 | 0.08-0.12 | 0.02 | 0.01-0.02 | 0.08 | 0.05-0.13 | 0.16 | 0.13-0.20 | 33 |
| Mullerian mixed tumours of ovary | 0.10 | 0.09-0.12 | 231 | | | | 0.20 | 0.18-0.23 | 0.02 | 0.01-0.03 | 0.23 | 0.18-0.30 | 0.32 | 0.27-0.38 | 66 |
| Adenocarcinoma with variants of falloppian tube | 0.14 | 0.13-0.16 | 321 | | | | 0.28 | 0.25-0.31 | 0.04 | 0.03-0.05 | 0.30 | 0.24-0.37 | 0.40 | 0.35-0.47 | 91 |
| **NON EPITHELIAL TUMOURS OF OVARY** | **0.19** | **0.17-0.21** | **424** | **2%** | | | **0.37** | **0.34-0.41** | **0.21** | **0.19-0.24** | **0.17** | **0.12-0.22** | **0.14** | **0.11-0.18** | **115** |
| Sex cord tumours of ovary | 0.07 | 0.06-0.08 | 155 | | | | 0.14 | 0.11-0.16 | 0.05 | 0.04-0.06 | 0.14 | 0.10-0.19 | 0.10 | 0.07-0.14 | 45 |
| Malignant/Immature teratomas of ovary | 0.05 | 0.04-0.05 | 100 | | | | 0.09 | 0.07-0.11 | 0.06 | 0.05-0.07 | 0.01 | 0.00-0.04 | 0.02 | 0.01-0.04 | 26 |
| Germ cell tumours of ovary | 0.08 | 0.07-0.09 | 169 | | | | 0.15 | 0.13-0.17 | 0.11 | 0.09-0.12 | 0.01 | 0.00-0.03 | 0.01 | 0.01-0.03 | 44 |
| **EPITHELIAL TUMOURS OF VULVA AND VAGINA** | **2.12** | **2.06-2.18** | **4 697** | **95%** | | | **4.10** | **3.99-4.22** | **0.25** | **0.22-0.27** | **2.03** | **1.86-2.20** | **8.59** | **8.31-8.86** | **1 414** |
| Squamous cell carcinoma with variants of vulva and vagina | 1.77 | 1.71-1.82 | 3 921 | | | | 3.43 | 3.32-3.53 | 0.19 | 0.17-0.22 | 1.63 | 1.48-1.79 | 7.24 | 6.99-7.50 | 1 176 |
| Adenocarcinoma with variants of vulva and vagina | 0.06 | 0.05-0.08 | 142 | | | | 0.12 | 0.10-0.15 | 0.02 | 0.01-0.03 | 0.08 | 0.05-0.13 | 0.21 | 0.17-0.25 | 42 |
| Paget's disease of vulva and vagina | 0.09 | 0.08-0.10 | 202 | | | | 0.18 | 0.15-0.20 | 0.01 | 0.01-0.02 | 0.15 | 0.10-0.20 | 0.33 | 0.27-0.38 | 58 |
| Undifferentiated carcinoma of vulva and vagina | 0.01 | 0.00-0.01 | 16 | | | | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.00 | 0.01 | 0.00-0.03 | 0.03 | 0.02-0.05 | 5 |
| **TROPHOBLASTIC TUMOURS OF PLACENTA** | **0.02** | **0.02-0.03** | **46** | **82%** | | | **0.04** | **0.03-0.05** | **0.03** | **0.02-0.04** | **<0.01** | **0.00-0.02** | **<0.01** | **0.00-0.01** | **12** |
| Choriocarcinoma of placenta | 0.02 | 0.01-0.03 | 45 | | | | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | <0.01 | 0.00-0.02 | <0.01 | 0.00-0.01 | 12 |
| | | | | | | | | | | | | | | | |
| **EPITHELIAL TUMOURS OF MALE BREAST** | | | **1 604** | **100%** | **1.50** | **1.42-1.57** | | | **0.31** | **0.27-0.35** | **2.63** | **2.36-2.93** | **5.65** | **5.31-6.00** | **246** |

**NE:** not estimable because 15 or less incident cases were observed **NOS:** not otherwise specified

# SURVIVAL



**RARE TUMOURS OF THE FEMALE GENITAL SYSTEM.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.

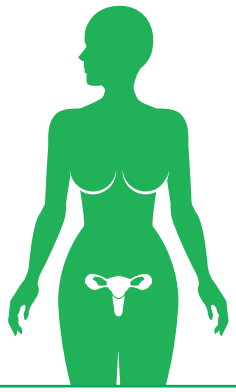



| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **RARE TUMOURS OF THE FEMALE GENITAL SYSTEM** | **34 228** |
| **RARE EPITHELIAL TUMOURS OF BREAST** | **8 657** |
| Mammary Paget's disease of breast | 810 |
| Special types of adenocarcinoma of breast | 7 503 |
| Metaplastic carcinoma of breast | 206 |
| Salivary gland type tumours of breast | 138 |
| **RARE EPITHELIAL TUMOURS OF CORPUS UTERI** | **1 567** |
| Squamous cell carcinoma with variants of corpus uteri | 186 |
| Adenoid cystic carcinoma of corpus uteri | 1 |
| Clear cell adenocarcinoma, NOS of corpus uteri | 281 |
| Serous (papillary) carcinoma of corpus uteri | 330 |
| Mullerian mixed tumours of corpus uteri | 769 |
| **EPITHELIAL TUMOURS OF CERVIX UTERI** | **7 360** |
| Squamous cell carcinoma with variants of cervix uteri | 5 906 |
| Adenocarcinoma with variants of cervix uteri | 1 397 |
| Undifferentiated carcinoma of cervix uteri | 45 |
| Mullerian mixed tumours of cervix uteri | 23 |
| **EPITHELIAL TUMOURS OF OVARY AND FALLOPPIAN TUBE** | **12 426** |
| Adenocarcinoma with variants of ovary | 10 313 |
| Mucinous adenocarcinoma of ovary | 1 115 |
| Clear cell adenocarcinoma of ovary | 458 |
| Primary peritoneal serous/papillary carcinoma of ovary | 99 |
| Mullerian mixed tumours of ovary | 190 |
| Adenocarcinoma with variants of falloppian tube | 261 |
| **NON EPITHELIAL TUMOURS OF OVARY** | **350** |
| Sex cord tumours of ovary | 135 |
| Malignant/Immature teratomas of ovary | 81 |
| Germ cell tumours of ovary | 134 |
| **EPITHELIAL TUMOURS OF VULVA AND VAGINA** | **3 929** |
| Squamous cell carcinoma with variants of vulva and vagina | 3 305 |
| Adenocarcinoma with variants of vulva and vagina | 126 |
| Paget's disease of vulva and vagina | 172 |
| Undifferentiated carcinoma of vulva and vagina | 15 |
| **TROPHOBLASTIC TUMOURS OF PLACENTA** | **37** |
| Choriocarcinoma of placenta | 36 |
| **EPITHELIAL TUMOURS OF MALE BREAST** | **1 345** |

NE

**NE:** not estimable because 30 or less incident cases were observed **NOS:** not otherwise specified

# PREVALENCE



**RARE TUMOURS OF THE FEMALE GENITAL SYSTEM.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | ESTIMATED PREVALENT CASES 2010 |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | |
| **RARE TUMOURS OF THE FEMALE GENITAL SYSTEM** | **34.26** | **33.04-35.51** | **39.74** | **38.42-41.08** | **161.23** | **158.58-163.92** | **264.54** | **259.45-269.62** | **154 397** |
| **RARE EPITHELIAL TUMOURS OF BREAST** | **10.58** | **9.90-11.28** | **14.46** | **13.67-15.28** | **58.22** | **56.63-59.84** | **80.24** | **77.60-82.89** | **46 858** |
| Mammary Paget's disease of breast | 0.94 | 0.75-1.17 | 1.25 | 1.03-1.51 | 4.78 | 4.33-5.26 | 6.81 | 6.14-7.49 | 3 961 |
| Special types of adenocarcinoma of breast | 9.29 | 8.66-9.95 | 12.84 | 12.10-13.62 | 51.48 | 49.98-53.01 | 70.99 | 68.46-73.52 | 41 472 |
| Metaplastic carcinoma of breast | 0.23 | 0.14-0.35 | 0.20 | 0.11-0.31 | 0.74 | 0.57-0.95 | 1.02 | 0.76-1.27 | 595 |
| Salivary gland type tumours of breast | 0.11 | 0.06-0.21 | 0.17 | 0.10-0.28 | 1.22 | 1.00-1.47 | 1.42 | 1.14-1.71 | 830 |
| **RARE EPITHELIAL TUMOURS OF CORPUS UTERI** | **1.63** | **1.37-1.92** | **1.25** | **1.03-1.51** | **4.92** | **4.47-5.41** | **6.45** | **5.78-7.12** | **3 742** |
| Squamous cell carcinoma with variants of corpus uteri | 0.13 | 0.06-0.23 | 0.18 | 0.11-0.30 | 0.67 | 0.51-0.86 | 1.12 | 0.82-1.42 | 643 |
| Adenoid cystic carcinoma of corpus uteri | NE | – | NE | – | 0.01 | 0.00-0.06 | 0.08 | 0.00-0.33 | 46 |
| Clear cell adenocarcinoma, NOS of corpus uteri | 0.36 | 0.24-0.51 | 0.30 | 0.20-0.44 | 1.11 | 0.90-1.36 | 1.38 | 1.10-1.65 | 821 |
| Serous (papillary) carcinoma of corpus uteri | 0.31 | 0.20-0.45 | 0.29 | 0.19-0.42 | 0.77 | 0.59-0.97 | 0.80 | 0.61-1.00 | 460 |
| Mullerian mixed tumours of corpus uteri | 0.84 | 0.65-1.05 | 0.48 | 0.35-0.65 | 2.36 | 2.05-2.71 | 3.07 | 2.64-3.50 | 1 772 |
| **EPITHELIAL TUMOURS OF CERVIX UTERI** | **6.98** | **6.43-7.55** | **8.59** | **7.99-9.23** | **40.14** | **38.82-41.50** | **92.32** | **88.80-95.84** | **53 952** |
| Squamous cell carcinoma with variants of cervix uteri | 5.52 | 5.04-6.04 | 7.16 | 6.61-7.74 | 33.33 | 32.13-34.57 | 76.94 | 73.72-80.16 | 44 975 |
| Adenocarcinoma with variants of cervix uteri | 1.43 | 1.19-1.71 | 1.43 | 1.19-1.71 | 6.77 | 6.24-7.34 | 15.12 | 13.71-16.53 | 8 819 |
| Undifferentiated carcinoma of cervix uteri | NE | – | 0.02 | 0.00-0.08 | 0.07 | 0.03-0.16 | 0.20 | 0.04-0.37 | 117 |
| Mullerian mixed tumours of cervix uteri | 0.02 | 0.00-0.08 | 0.01 | 0.00-0.06 | 0.05 | 0.01-0.12 | 0.06 | 0.00-0.12 | 41 |
| **EPITHELIAL TUMOURS OF OVARY AND FALLOPPIAN TUBE** | **11.56** | **10.86-12.30** | **11.39** | **10.69-12.12** | **42.61** | **41.25-44.01** | **61.30** | **59.24-63.36** | **35 633** |
| Adenocarcinoma with variants of ovary | 9.50 | 8.86-10.17 | 9.20 | 8.58-9.86 | 33.32 | 32.12-34.56 | 45.94 | 44.21-47.66 | 26 690 |
| Mucinous adenocarcinoma of ovary | 1.08 | 0.87-1.32 | 1.09 | 0.88-1.33 | 5.68 | 5.19-6.21 | 10.56 | 9.57-11.55 | 6 157 |
| Clear cell adenocarcinoma of ovary | 0.39 | 0.27-0.55 | 0.54 | 0.40-0.72 | 1.94 | 1.66-2.25 | 2.59 | 2.19-2.99 | 1 497 |
| Primary peritoneal serous/papillary carcinoma of ovary | 0.11 | 0.06-0.21 | 0.13 | 0.06-0.23 | 0.26 | 0.17-0.40 | 0.27 | 0.16-0.38 | 159 |
| Mullerian mixed tumours of ovary | 0.17 | 0.10-0.28 | 0.16 | 0.09-0.27 | 0.42 | 0.30-0.58 | 0.62 | 0.41-0.82 | 357 |
| Adenocarcinoma with variants of falloppian tube | 0.31 | 0.20-0.45 | 0.28 | 0.18-0.41 | 0.99 | 0.79-1.22 | 1.34 | 1.05-1.62 | 774 |
| **NON EPITHELIAL TUMOURS OF OVARY** | **0.44** | **0.31-0.60** | **0.45** | **0.32-0.61** | **2.38** | **2.06-2.72** | **5.04** | **4.31-5.77** | **2 970** |
| Sex cord tumours of ovary | 0.21 | 0.12-0.33 | 0.17 | 0.10-0.28 | 0.95 | 0.76-1.18 | 1.32 | 1.03-1.61 | 787 |
| Malignant/Immature teratomas of ovary | 0.08 | 0.03-0.17 | 0.10 | 0.05-0.20 | 0.40 | 0.28-0.56 | 0.98 | 0.61-1.35 | 590 |
| Germ cell tumours of ovary | 0.15 | 0.08-0.25 | 0.17 | 0.10-0.28 | 1.02 | 0.82-1.26 | 2.74 | 1.92-3.56 | 1 595 |
| **EPITHELIAL TUMOURS OF VULVA AND VAGINA** | **3.13** | **2.76-3.52** | **3.63** | **3.24-4.05** | **13.27** | **12.52-14.06** | **18.62** | **17.54-19.70** | **10 906** |
| Squamous cell carcinoma with variants of vulva and vagina | 2.77 | 2.43-3.14 | 3.18 | 2.82-3.58 | 11.38 | 10.69-12.11 | 16.44 | 15.41-17.47 | 9 645 |
| Adenocarcinoma with variants of vulva and vagina | 0.05 | 0.01-0.12 | 0.09 | 0.04-0.18 | 0.41 | 0.28-0.57 | 0.56 | 0.37-0.74 | 329 |
| Paget's disease of vulva and vagina | 0.15 | 0.08-0.26 | 0.20 | 0.11-0.31 | 0.83 | 0.65-1.04 | 0.95 | 0.72-1.17 | 546 |
| Undifferentiated carcinoma of vulva and vagina | NE | – | NE | – | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.04 | 8 |
| **TROPHOBLASTIC TUMOURS OF PLACENTA** | **0.02** | **0.00-0.08** | **0.09** | **0.04-0.18** | **0.26** | **0.17-0.40** | **0.56** | **0.28-0.83** | **335** |
| Choriocarcinoma of placenta | 0.02 | 0.00-0.08 | 0.09 | 0.04-0.18 | 0.26 | 0.17-0.40 | 0.56 | 0.28-0.83 | 335 |
| | | | | | | | | | |
| **EPITHELIAL TUMOURS OF MALE BREAST** | **3.11** | **2.60-3.69** | **3.58** | **3.03-4.20** | **12.94** | **11.87-14.07** | **15.41** | **14.11-16.71** | **4 334** |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

**NOS:** not otherwise specified

This group includes heterogeneous invasive cancers with different behaviour and prognosis:

- **rare epithelial breast cancers of females** (mammary Paget's disease, special types of adenocarcinoma of breast, metaplastic carcinoma of breast, salivary gland type tumours of breast);
- **epithelial breast cancers of males** (all histotypes are rare, including ductal and lobular carcinomas);
- **rare epithelial tumours of corpus and cervix uteri** (squamous cell carcinoma of cervix and corpus uteri; Mullerian mixed tumour of cervix and corpus uteri; clear cell adenocarcinoma; NOS of corpus uteri; serous/papillary carcinoma of corpus uteri; adenoid cystic carcinoma of corpus uteri; adenocarcinoma with variants of cervix uteri and undifferentiated carcinoma of cervix uteri);
- **epithelial tumours of ovary and falloppian tubes** (adenocarcinoma with variants of ovary, mucinous adenocarcinoma of ovary, clear cell adenocarcinoma of ovary, primary peritoneal serous/papillary carcinoma of ovary, MMMT of ovary, and adenocarcinoma with variants of the fallopian tubes);
- **non epithelial tumours of ovary and falloppian tubes** (sex cord, germ cell tumours, and immature teratomas);
- **epithelial tumours of vulva and vagina** (squamous cell carcinoma with variants of vulva and vagina, adenocarcinoma with variants of vulva and vagina, and Paget's disease of vulva and vagina);
- **trophoblastic placenta tumours**.

With a number of 41,141 incident cases (in the period 2000-2010), rare cancers represent 17% of all female genital system cancers, corresponding to about 12,000 new cases per year in Italy (incidence table, p. 57). It must be noted that, as reported in the «Materials and methods» chapter (pp. 14-21), rates are provided for both sexes with the exception of male breast cancer. In any case, sex-specific incidence rates are provided in the incidence table.

## RARE EPITHELIAL BREAST CANCERS

### WHAT DO WE KNOW ABOUT THESE CANCERS?

**Mammary Paget's disease** (PD) occurs almost exclusively in women. The typical pathologic finding is represented by Paget cells within the epidermis of the nipple.[1]

**Special types of adenocarcinoma** of the breast are a mixture of different types (tubular, mucinous, medullary, papillary, secretory, glycogen-rich clear cell, lipid-rich and oncocytic carcinoma).

**Metaplastic carcinoma of the breast:** part or all of the carcinomatous epithelium is transformed into a nonglandular (metaplastic) growing tissue; these tumours are often clinically palpable, large, and appear well circumscribed. Metaplastic carcinomas are mainly negative for oestrogen and progesterone receptors and for HER2/neu overexpression.[2]

**Salivary gland type tumour of the breast** is a very rare histological type including adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, and polymorphous low-grade adenocarcinoma; a high percentage of triple negative breast cancer is reported, too.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Rare epithelial breast cancers (10,522 cases) account for 26% of rare cancers of the female genital system, but only 6% of breast cancer. Special types of adenocarcinoma are the most common (87%), followed by mammary PD (9%), metaplastic carcinoma (2%), and salivary gland type tumours (2%). Distribution of the different types is similar to that observed in the European data from RARECAREnet (www.rarecarenet.eu), except for special types of adenocarcinoma, showing a slightly higher rate in Italy than in Europe (4% vs. 3%, respectively). More than 50% (5,425) of cases involves subjects aged over 65 years, with the highest rate in the 80-84 age class (24.5 per 100,000, data not shown).

In males, all breast tumours are rare and have a sex-specific IR of 1.5 per 100,000. The age trend is similar to that observed for females (see table p. 57). Approximately 3,500 Italians were estimated to be diagnosed with a rare cancer of the breast in 2015; of these 250 were males.

#### Survival

Five-year relative survival (RS) for rare female breast cancer is relatively high and varies from 88% for mammary PD to 72% for metaplastic carcinoma (survival figure, p. 58). Lower prognosis of metaplastic carcinoma is due to more advanced stage at diagnosis and the high percentage of "triple negative" subtypes.[3] One-year RS is similar to 5-year RS except for mammary PD and metaplastic tumours. Rare epithelial cancers of the breast have a similar prognosis to the more common ductal and lobular invasive carcinomas of the breast (85% at 5 years in European RARECAREnet data). Prognosis is worse in males than in females, probably because of the different biological patterns in males compared to females.[4] This result highlights the need for new treatment protocols for these specific cancers.

#### Prevalence

Around 47,000 persons were estimated to be alive in 2010 with a past diagnosis of one of these rare epithelial tumours of the breast in Italy.

## RARE EPITHELIAL TUMOURS OF CORPUS AND CERVIX UTERI

### WHAT DO WE KNOW ABOUT THESE CANCERS?

**Squamous cell carcinoma with variants of corpus and cervix uteri** include different types of cancers (papillary squamous cell carcinoma, squamous cell carcinoma NOS, keratinizing and nonkeratinizing squamous cell carcinoma, spindle cell squamous cell carcinoma, lymphoepithelial carcinoma) and is more frequent in the cervix than in the corpus uteri. Based on histopathology, molecular profile and clinical course of endometrial cancers are divided into two categories.

**Uterine clear-cell carcinoma** (UCC) is a type II endometrial cancer (not hormone dependent and usually grade III endometrioid adenocarcinomas, papillary serous and clear cell carcinomas and carcinosarcomas, or malignant mixed Mullerian tumours) and it typically occurs in older patients, as it is not hormone dependent. These tumours are generally more aggressive and have a

worse prognosis than type I endometrial cancer (typically low-grade (I-II) adenocarcinomas that are usually oestrogen related, diagnosed early, and with a favourable prognosis) and usually display p53 mutations.[5]

**Serous (papillary) carcinoma of corpus uteri** (USC) is characterised by nipple-shaped structures (papillae) with fibrovascular cores, marked nuclear atypia, psammoma bodies, and cilia. It has been associated with women of African-American ethnicity, tamoxifen use, and BRCA gene mutations.[6] About 60% of USCs overexpress the HER2/neu protein, showing some benefits with trastuzumab (Herceptin) treatment.[7]

**Malignant mixed Mullerian tumour** (MMMT) of the uterine corpus and cervix is an extremely rare and aggressive malignancy with a dedifferentiated or metaplastic form containing both carcinomatous and sarcomatous components, affecting postmenopausal women. Risk factors for the development of MMMT are similar to those of endometrial carcinoma and include nulliparity, advanced age, obesity, exposure to exogenous estrogens, pelvic irradiation, and long-term use of tamoxifen.[4]

**Adenocarcinoma of the cervix** is a mixture of different cancer types (adenocarcinoma NOS, adenocarcinoma with squamous metaplasia, mucinous, clear cell, or endometrioid adenocarcinoma, serous cystadenocarcinoma, signet ring cell, mesonephroma, villous, intestinal type and mixed cell adenocarcinoma) showing an incidence increase over time, probably attributable to cervix screening implementation. The causal role of human papillomavirus (HPV) in all cancers of the uterine cervix has been firmly established both biologically and epidemiologically. The status of current tobacco smoking is associated with an increased risk of squamous cell adenocarcinoma but not of adenocarcinoma in the cervix. No differences between the two most common histological types of invasive cervical cancer with respect to the role of number of sexual partners, age at first intercourse, age at first birth, body mass index, or use of oral contraceptives were observed.[9]

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

In the **cervix**, squamous carcinoma represents 79% of epithelial tumours, followed by adenocarcinoma (20%) (see table p. 57). The other histotypes are very rare. In the **corpus uteri**, MMMT are the most common (48%) followed by USC (23%), UCC (17%), and squamous cell carcinoma (12%). The other histotypes are very rare. The same distribution is reported in the European RARECAREnet data. Rare epithelial cancers of corpus uteri are typical of elderly, with the highest incidence rate in the 80-84 age class (3.6 per 100,000, data not shown). Epithelial cancers of cervix uteri show a bimodal distribution with two peaks: one in the perimenopausal age group 45-49 years (6.1 per 100,000, data not shown) and the other in the 80-84-year age group (8.1 per 100,000, data not shown). Approximately 3,000 Italians were estimated to be diagnosed with rare cancers of the uterus in 2015.

### Survival

One-year and 5-year RS of cervix uteri cancer are 89% and 69%, respectively. These results are mainly due to squamous cell carcinoma and adenocarcinoma of cervix uteri (see figure p. 58). The RS of undifferentiated carcinomas is much lower at both 1 and 5 years after diagnosis: 59% and 43%, respectively (based on 45 cases). It is not possible to provide an RS of MMMT because of the few cases available for analysis. However, in RARECAREnet data, 5-year RS is 34%. The RS of corpus uteri cancer is 78% at 1 year, but goes down to 46% at 5 years. This pattern is constant for all histotypes. After 5 years from diagnosis the RS is highest for UCC (61%), followed by squamous cell carcinoma (54%), USC, and MMMT (40%) (see figure p. 58). The results are coherent with European RARECAREnet data. Adenoid cystic carcinoma of the corpus uteri is so rare that no data are available in Italy and Europe. The availability of improved genetic and/or pathological characterisation by specialized laboratories could improve the prognosis of these rare tumours, enabling the development of specific therapeutic protocols.

### Prevalence

Around 54,000 persons were estimated to be alive in 2010 with a past diagnosis of epithelial tumours of the cervix (43% survived more than 15 years from diagnosis) and around 4,000 with a diagnosis of rare epithelial tumours of the corpus uteri (76% survived more than 15 years from diagnosis).

## EPITHELIAL TUMOURS OF OVARY AN FALLOPPIAN TUBES AND NON EPITHELIAL TUMOURS OF OVARY

The list of rare cancers separate epithelial and non epithelial tumours. Thus, this group includes epithelial tumours of the ovary and fallopian tubes and non epithelial tumours of the ovary.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**Epithelial ovarian cancers (EOC)** are a heterogeneous group of tumours. To explain this heterogeneity a new classification is used distinguishing type I and type II ovarian carcinoma. Type I includes low-grade carcinomas, frequently diagnosed in early stages, with indolent behaviour. Type II includes high-grade carcinomas, diagnosed in advanced stages, and characterised by genomic instability. Recent evidence suggests that the different histotypes of epithelial ovarian cancers originate from three different sites (fimbria, endometrial tissue, and tubal-mesothelium junction), while serous ovarian cancer originates from the fallopian tubes.[10] New promising molecular targeted drugs are bevacizumab (monoclonal antibody directed against VEGF) and PARP inhibitor.[11]

**MMMT of the ovary** is an exceedingly rare cancer, accounting for 1% to 3% of ovarian malignancies. These tumours are carcinosarcoma characterised by malignant epithelial and stromal elements. MMMTs are very aggressive tumours usually diagnosed at an older age and at advanced stages.[12] MMMT diagnosis is difficult; there are no useful biochemical markers and diagnostic imaging methods do not provide specific data.[13]

**Sex cord tumours of the ovary** include malignant granulosa cell tumour, Sertoli-Leydig cell tumour, poorly differentiated and malignant steroid cell tumour, which show areas with unequivocal gonadal stromal differentiation.[14]

**Ovarian germ cell tumours** (OGCT) include several types of cancer (dysgerminoma/seminoma, yolk sac tumour, mixed germ cell tumour, embryonal adenocarcinoma, choriocarcinoma, and

polyembryoma). Most OGCTs are benign, unilateral with the exception of dysgerminomas, are usually diagnosed at stage I, and are responsive to chemotherapy. Several reports suggest a genetic susceptibility.[15]

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

The risk for **EOCs** increases with age: the highest incidence rate (IR) occurs in postmenopausal women, with 47% of all cases diagnosed in patients older than 65 years (data not shown). Adenocarcinoma of the ovary is the most common histotype, with 12,261 incident cases in the period 2000-2010, followed by mucinous adenocarcinoma, clear cell adenocarcinoma, and MMMT (see table p. 57). Primary peritoneal serous/papillary carcinoma of the ovary is very rare (115 cases in 11 years). The relative frequency of histological variants observed in the Italian database is similar to the one documented by RARECAREnet. Fallopian tube includes all rare cancers and it is rare per se.

**Non EOCs** typically affect young people, with a peak of incidence in the 15-19 age group (0.47 per 100,000 data not shown). OGCT represents the most frequent subtype (40%), although European RARECAREnet data showed a higher frequency of sex cord tumours of the ovary (50%) compared to OGCT. Around 4,500 Italians were estimated to be diagnosed with rare cancers of the ovary in 2015.

#### Survival

**EOC** 1- and 5-year RS is 82% and 46%. All epithelial tumours of the ovary have a poor prognosis, with a 5-year RS ranging from 62% for clear cell adenocarcinoma to 25% for MMMT. This is probably due to the fact that the majority of these tumours are aggressive and become symptomatic at advanced stage. The Italian database shows better RS for EOC than European RARECAREnet data (70% and 37% at 1 and 5 years, respectively).

**Non EOC** has better prognosis than EOC, probably attributable to young age and early-stage at diagnosis and to the fact that the majority of these tumours are germ cell tumours, which are among the most curable diseases (see figure p. 58).

#### Prevalence

Around 35,000 persons were estimated to be alive in 2010 with a past diagnosis of **EOC**; 30% survived more than 15 years from diagnosis. Most prevalent cases were adenocarcinomas, mainly because of their relatively higher incidence compared to the other histotypes.

Around 3,000 persons were estimated to be alive with a diagnosis of **Non EOC**; 53% survived more than 15 years from diagnosis, coherently with young age at diagnosis and prognosis (prevalence table, p. 59).

## EPITHELIAL TUMOURS OF VULVA AND VAGINA

### WHAT DO WE KNOW ABOUT THESE CANCERS?

**Squamous cell carcinoma** originates from epidermal squamous cells.

**Vulvar adenocarcinoma** most often originates from cells of the Bartholin glands, although it is often very difficult to identify the site of origin.[16]

**Vaginal adenocarcinoma** arises from the glandular (secretory) cells in the lining of the vagina. Clear cell adenocarcinoma is associated with in utero exposure to diethylstilbestrol (DES). The peak of incidence of DES-associated adenocarcinoma is at young ages (less than 30 years), otherwise these tumours occur primarily in post menopause. Human papillomavirus (HPV) infection in associated to development of vulvar and vaginal cancers.[17]

**Paget's disease of vulva and vagina** is an uncommon cancer characterised by a chronic eczema-like rash of the skin around the anogenital regions. It microscopically looks like mammary Paget's disease and is predominantly an intraepithelial lesion, even though it may be associated with an underlying invasive adenocarcinoma.[18]

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Vulvar and vaginal cancers most commonly occur in people over 65 years old, with adenocarcinomas occurring a decade earlier than squamous cancers (see table p. 57). Squamous cell carcinomas are the most common histotype in Italy (83%) and Europe (RARECAREnet database 85%). Paget's disease is typical of older people (>70 years of age) (data not shown). About 1,500 rare epithelial tumours of the vulva and vagina are estimated to occur during 2015 in Italy; few cases (4%) are Paget's disease (see table p. 57).

#### Survival

One- and 5-year RS is 79% and 56%, respectively. Adenocarcinoma has the worse outcomes (67% and 45% RS at 1 and 5 years, respectively) (see figure p. 58). The number of cases of undifferentiated carcinomas is too low to estimate survival; however, according to the RARECAREnet data, 5-year RS is 26% (based on 85 cases). Five-year RS of Paget's disease is very good (91%), most likely because it is not aggressive. Italian and European RARECAREnet data are the same.

#### Prevalence

In Italy, around 11,000 persons were estimated to be alive in 2010 with a past diagnosis of epithelial tumours of vulva and vagina, and 72% were still alive more than 15 years after diagnosis. The most prevalent were squamous cell carcinomas because of the relatively high incidence and survival (see table p. 59).

## TROPHOBLASTIC TUMOURS OF PLACENTA

**Trophoblastic tumours of placenta** (TTP) are very rare. There were only 46 cases in 11 years (2000-2010) in Italy (see table p. 57). These tumours are highly curable malignancies arising in relation to pregnancy. Treatment of TTP is a success story in medical oncology. When treated by surgery alone, the cure rate is only 40%.[19] With the use of chemotherapeutic agents, outcome becomes excellent for more than 98% of women.[20] Survival in Italy is 94% (based on 34 cases), whereas according to RARECAREnet, which has a higher number of cases to base an estimate on, it is 89%.

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# RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM

**6%**

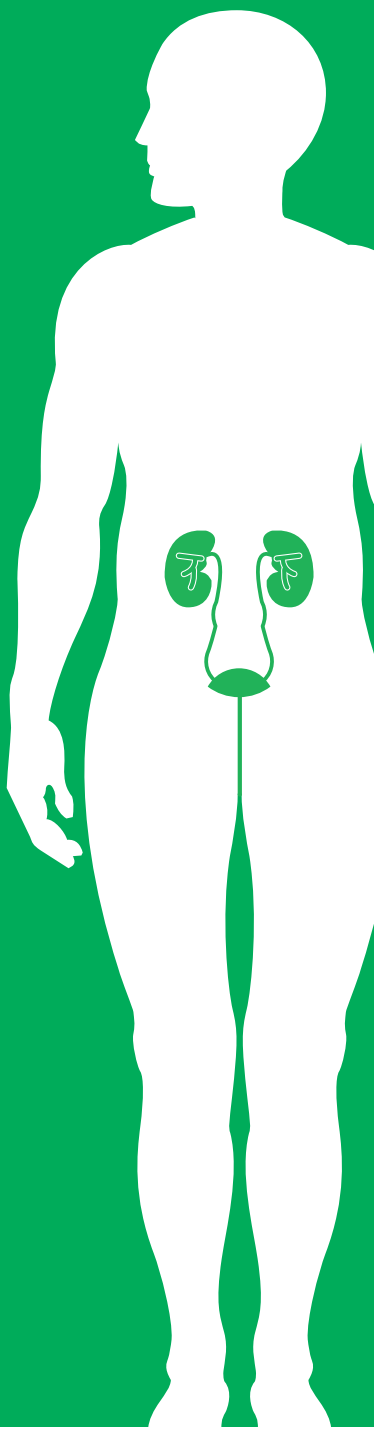
**OF THE URINARY SYSTEM TUMOURS ARE RARE EPITHELIAL TUMOURS**

## INCIDENCE

**1 948**

ESTIMATED NEW CASES
ITALY, 2015

| | | | |
|---|---|---|---|
| 39 | RARE EPITHELIAL TUMOURS OF KIDNEY | 0.04 | % OF RARE EPITHELIAL TUMOURS OUT OF ALL TUMOURS IN EACH SITE |
| 1 394 | EPITHELIAL TUMOURS OF PELVIS AND URETER | 99 | |
| 91 | EPITHELIAL TUMOURS OF URETHRA | 95 | |
| 424 | RARE EPITHELIAL TUMOURS OF BLADDER | 2 | |

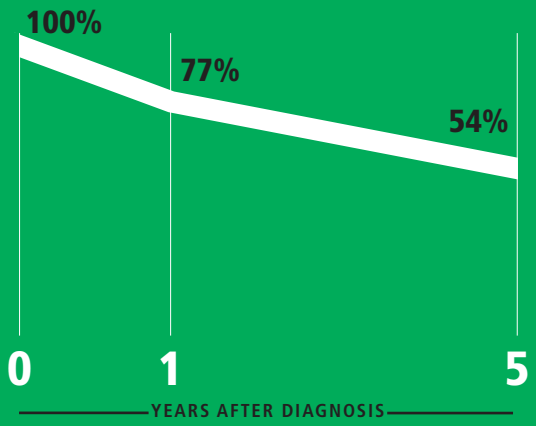


## PREVALENCE

**13 254**

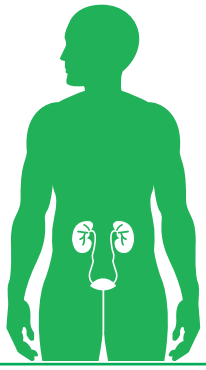
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM



# INCIDENCE

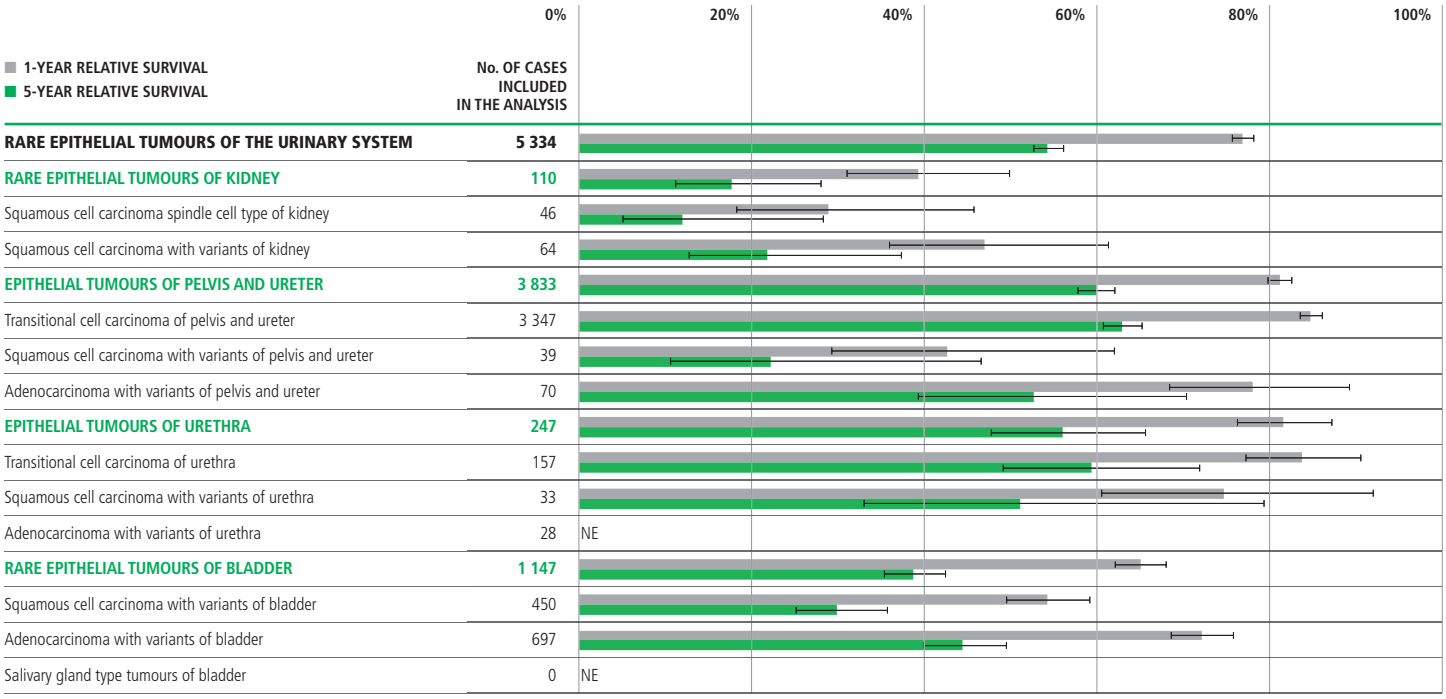
**RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE EPITHELIAL CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM** | **2.88** | **2.81-2.95** | **6 394** | **6%** | **4.17** | **4.05-4.29** | **1.68** | **1.60-1.75** | **0.34** | **0.31-0.37** | **4.09** | **3.86-4.34** | **10.84** | **10.54-11.15** | **1 948** |
| **RARE EPITHELIAL TUMOURS OF KIDNEY** | **0.06** | **0.05-0.07** | **132** | **0.04%** | **0.09** | **0.07-0.11** | **0.03** | **0.02-0.04** | **0.02** | **0.01-0.02** | **0.10** | **0.07-0.15** | **0.18** | **0.14-0.23** | **39** |
| Squamous cell carcinoma spindle cell type of kidney | 0.02 | 0.02-0.03 | 50 | | 0.03 | 0.02-0.05 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.04 | 0.02-0.08 | 0.06 | 0.04-0.09 | 15 |
| Squamous cell carcinoma with variants of kidney | 0.04 | 0.03-0.05 | 82 | | 0.06 | 0.04-0.07 | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | 0.06 | 0.03-0.10 | 0.12 | 0.09-0.16 | 25 |
| **EPITHELIAL TUMOURS OF PELVIS AND URETER** | **2.07** | **2.01-2.14** | **4 600** | **99%** | **2.94** | **2.84-3.05** | **1.26** | **1.20-1.33** | **0.22** | **0.20-0.25** | **3.00** | **2.80-3.21** | **7.84** | **7.58-8.10** | **1 394** |
| Transitional cell carcinoma of pelvis and ureter | 1.80 | 1.74-1.86 | 3 989 | | 2.57 | 2.47-2.66 | 1.08 | 1.02-1.14 | 0.19 | 0.17-0.22 | 2.67 | 2.48-2.88 | 6.75 | 6.51-7.00 | 1 200 |
| Squamous cell carcinoma with variants of pelvis and ureter | 0.02 | 0.02-0.03 | 50 | | 0.02 | 0.02-0.03 | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | 0.02 | 0.01-0.05 | 0.09 | 0.07-0.13 | 15 |
| Adenocarcinoma with variants of pelvis and ureter | 0.04 | 0.03-0.05 | 83 | | 0.06 | 0.04-0.07 | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | 0.08 | 0.05-0.12 | 0.12 | 0.09-0.16 | 25 |
| **EPITHELIAL TUMOURS OF URETHRA** | **0.13** | **0.12-0.15** | **292** | **95%** | **0.21** | **0.18-0.24** | **0.06** | **0.04-0.07** | **0.03** | **0.02-0.04** | **0.14** | **0.10-0.20** | **0.48** | **0.42-0.55** | **91** |
| Transitional cell carcinoma of urethra | 0.08 | 0.07-0.10 | 183 | | 0.15 | 0.12-0.17 | 0.02 | 0.02-0.03 | 0.01 | 0.01-0.02 | 0.08 | 0.05-0.12 | 0.32 | 0.27-0.38 | 57 |
| Squamous cell carcinoma with variants of urethra | 0.02 | 0.01-0.02 | 40 | | 0.03 | 0.02-0.04 | <0.01 | 0.00-0.02 | <0.01 | 0.00-0.01 | 0.03 | 0.01-0.05 | 0.06 | 0.04-0.08 | 12 |
| Adenocarcinoma with variants of urethra | 0.01 | 0.01-0.02 | 33 | | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.04 | 0.02-0.07 | 0.03 | 0.02-0.06 | 10 |
| **RARE EPITHELIAL TUMOURS OF BLADDER** | **0.62** | **0.59-0.65** | **1 370** | **2%** | **0.93** | **0.87-0.99** | **0.33** | **0.29-0.36** | **0.07** | **0.06-0.09** | **0.85** | **0.74-0.96** | **2.34** | **2.20-2.49** | **424** |
| Squamous cell carcinoma with variants of bladder | 0.24 | 0.22-0.26 | 537 | | 0.32 | 0.29-0.36 | 0.17 | 0.14-0.19 | 0.03 | 0.03-0.05 | 0.30 | 0.24-0.37 | 0.92 | 0.83-1.01 | 168 |
| Adenocarcinoma with variants of bladder | 0.38 | 0.35-0.40 | 833 | | 0.61 | 0.56-0.65 | 0.16 | 0.14-0.19 | 0.04 | 0.03-0.05 | 0.55 | 0.46-0.64 | 1.42 | 1.31-1.54 | 256 |
| Salivary gland type tumours of bladder | 0.00 | – | 0 | | NE | – | NE | – | NE | – | NE | – | NE | – | NE |

**NE:** not estimable because 15 or less incident cases were observed

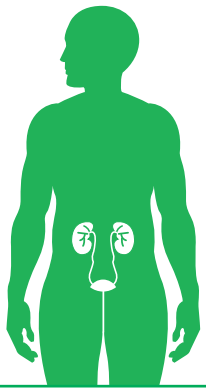
# SURVIVAL

**RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




**NE:** not estimable because 30 or less incident cases were observed

# PREVALENCE



**RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | ESTIMATED PREVALENT CASES 2010 |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | |
| **RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM** | **4.90** | **4.45-5.39** | **4.47** | **4.04-4.94** | **17.55** | **16.68-18.45** | **22.90** | **21.74-24.06** | **13 254** |
| **RARE EPITHELIAL TUMOURS OF KIDNEY** | **0.06** | **0.02-0.13** | **0.01** | **0.00-0.06** | **0.14** | **0.07-0.25** | **0.16** | **0.07-0.25** | **97** |
| Squamous cell carcinoma spindle cell type of kidney | 0.03 | 0.01-0.10 | 0.01 | 0.00-0.06 | 0.08 | 0.03-0.17 | 0.10 | 0.03-0.17 | 60 |
| Squamous cell carcinoma with variants of kidney | 0.02 | 0.00-0.08 | NE | – | 0.06 | 0.02-0.14 | 0.06 | 0.01-0.12 | 37 |
| **EPITHELIAL TUMOURS OF PELVIS AND URETER** | **3.86** | **3.46-4.29** | **3.61** | **3.22-4.03** | **14.11** | **13.33-14.92** | **18.23** | **17.20-19.27** | **10 533** |
| Transitional cell carcinoma of pelvis and ureter | 3.39 | 3.01-3.80 | 3.38 | 3.00-3.79 | 12.95 | 12.20-13.73 | 16.64 | 15.66-17.63 | 9 599 |
| Squamous cell carcinoma with variants of pelvis and ureter | 0.05 | 0.01-0.12 | NE | – | 0.06 | 0.02-0.13 | 0.07 | 0.01-0.14 | 44 |
| Adenocarcinoma with variants of pelvis and ureter | 0.14 | 0.07-0.24 | 0.05 | 0.01-0.12 | 0.28 | 0.18-0.41 | 0.31 | 0.19-0.44 | 181 |
| **EPITHELIAL TUMOURS OF URETHRA** | **0.31** | **0.20-0.45** | **0.15** | **0.08-0.26** | **0.80** | **0.63-1.02** | **1.03** | **0.78-1.27** | **600** |
| Transitional cell carcinoma of urethra | 0.22 | 0.13-0.34 | 0.11 | 0.06-0.21 | 0.56 | 0.42-0.74 | 0.71 | 0.51-0.92 | 415 |
| Squamous cell carcinoma with variants of urethra | 0.06 | 0.02-0.13 | 0.02 | 0.00-0.08 | 0.13 | 0.06-0.23 | 0.15 | 0.06-0.23 | 84 |
| Adenocarcinoma with variants of urethra | 0.01 | 0.00-0.06 | NE | – | 0.03 | 0.01-0.10 | 0.04 | 0.00-0.08 | 23 |
| **RARE EPITHELIAL TUMOURS OF BLADDER** | **0.67** | **0.51-0.87** | **0.70** | **0.54-0.90** | **2.52** | **2.19-2.87** | **3.48** | **3.01-3.95** | **2 025** |
| Squamous cell carcinoma with variants of bladder | 0.24 | 0.15-0.37 | 0.30 | 0.20-0.44 | 0.80 | 0.62-1.01 | 1.11 | 0.84-1.37 | 640 |
| Adenocarcinoma with variants of bladder | 0.43 | 0.31-0.60 | 0.40 | 0.28-0.56 | 1.71 | 1.45-2.01 | 2.36 | 1.98-2.74 | 1 376 |
| Salivary gland type tumours of bladder | NE | – | NE | – | NE | – | 0.01 | 0.00-0.04 | 0 |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

# RARE EPITHELIAL TUMOURS OF THE URINARY SYSTEM

This group includes the following tumours of the urinary system:
- **rare epithelial tumours of kidney** (squamous cell carcinoma, adenocarcinoma, and spindle cell type squamous cell carcinoma);
- **epithelial tumours of pelvis and ureter** (squamous cell carcinoma, adenocarcinoma and transitional cell carcinoma);
- **epithelial tumours of urethra** (squamous cell carcinoma and adenocarcinoma and transitional cell carcinoma);
- **rare epithelial tumours of bladder** (squamous cell carcinoma, adenocarcinoma, and salivary gland type tumours).

These tumours are usually well defined in terms of morphology, because they are diagnosed by imaging (cystoscopy, urography, or a computerised tomography scan for the kidney) and histopathological examination.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**Squamous-cell carcinoma** originates from squamous cells. These cells are typical of the epidermis of the skin, but can be found in different body sites for which symptoms at diagnosis, natural history, prognosis, and response to treatment can be extremely heterogeneous.[1] **Adenocarcinoma** is an undifferentiated and consequently malignant cancer of the epithelial tissue, which originates from the glandular epithelium.[2] It includes different histological types: tubulovillous, papillary, mucinous, and non-intestinal. The tubulovillous and mucinous variants are the most frequent and account for over 90% of cases.[3] **Transitional cell carcinoma** (also urothelial cell carcinoma) originates from the urothelium (layer of cells that lines the walls of the urinary tract: renal calices and pelvis, ureter, bladder, proximal urethra).[1] It can be diagnosed in the lower urinary tract (bladder and urethra) or in the upper urinary tract (renal calices, renal pelvis, and ureter). Upper tract urothelial carcinoma (UTUC) is rare and accounts for only 5%-10% of urothelial cancer. The estimated annual incidence of UTUC in Western countries is about two new cases per 100,000 inhabitants.[2] Cancers of the renal pelvis are about two times more common than ureteral tumours.[4] **Spindle cell tumours** of the kidney include a wide range of unrelated neoplasms with overlapping morphologic features and different prognostic/therapeutic implications. Diagnosis is supported mainly by the application of ancillary techniques, such as immunohistochemistry (IH) and in-situ hybridization (FISH). An accurate diagnosis is essential because early management by complete resection and adjuvant chemotherapy improves prognosis dramatically.[5]
Tobacco and occupational exposure to certain aromatic amines[2] remain the principal exogenous risk factors for the development of transitional cell carcinomas. For urethral cancers, various predisposing factors have been reported, including urethral strictures, chronic irritation after intermittent catheterisation/urethroplasty, external beam irradiation therapy, radioactive seed implantation, and chronic urethral inflammation/urethritis following sexually transmitted diseases.[6] In female patients, urethral diverticula and recurrent urinary tract infections have been associated with primary carcinoma.[7] For the renal pelvis and ureter, use of laxatives and analgesics are recognised risk factors.[8]

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

All rare epithelial tumours of the urinary system (kidney, renal pelvis, ureter, urethra, and bladder) are more common in males than females and are typical of the older age groups. The most common rare epithelial tumours of the urinary system are those of the renal pelvis and ureter (72%), followed by rare epithelial tumours of the bladder (21%), urethra (5%), and kidney (2%).
All cancers of the renal pelvis and ureter are rare and the most frequent morphology is transitional cell carcinoma (87%). The other two morphologies are squamous cell carcinoma and adenocarcinoma (1 and 1.8%, respectively). In the bladder, rare epithelial tumours represent only 2% of all bladder tumours and adenocarcinoma is the most frequent morphology (61%). In the AIRTUM database, no cases of salivary gland type cancers of the bladder were observed in Italy in the years 2000-2010; in the European RARECAREnet database (www.rarecarenet.eu) 7 cases were observed in Europe in the period 2000-2008, confirming the rarity of this entity. All cancers of the urethra are rare and the most frequent morphology is transitional cell carcinoma (63%), followed by squamous cell carcinoma (14%) and adenocarcinoma (11%). The latter two have a very similar incident rate. Finally, rare epithelial tumours of the kidney (squamous cell carcinomas and spindle cell carcinomas) are the rarest of urinary system cancers and represent only 0.4% of all tumours of the kidney. All these tumours, in each site, are more common in males than females and have a peak of incidence in the 70-79-year age groups (data not shown). Epithelial tumours of the urethra show the highest male to female ratio, probably because of the longer length of the male urethra (15-20 cm versus 3-4 cm in females). The male to female ratio of cancer of the renal pelvis and ureter is 2.3 in this study and much lower than for bladder cancer in European data from Globocan (M/F: 4.7).[8] This different male to female ratio suggests a different importance of the various aetiological factors. Smoking is the most important factor for bladder cancer. Although smoking is also a risk factor for cancer of the renal pelvis and ureter, long-term use of analgesics and laxatives, which is a strong risk factor for cancer of the renal pelvis and ureter and which is probably as widespread among females as among males, reduces the male to female ratio.[9]
The incidence results described are in line with those observed in Europe in the RARECAREnet database. The incidence of epithelial tumours of the renal pelvis and ureter is slightly higher in Italy than in Europe (2.07 vs. 1.58), but the morphological distribution is the same in the two databases. It is worth mentioning that for cancer of the renal pelvis, ureter or urethra, comparison with other registries outside Italy may be biased by differences in registration and classification practices. In the 9th edition of the International Classification of Diseases and the 1st edition of the International Classification of Diseases for Oncology, these cancers are grouped together with kidney cancer and many registries still report these cancers combined. Approximately 2,000 cases of rare epithelial tumours of the urinary tract are estimated to be diagnosed in Italy in 2015: 1,394 epithelial tumours of the renal pelvis and ureter, 424 rare epithelial tumours of the bladder, 91 epithelial tumours of the urethra, and only 39 cases of rare epithelial tumours of the kidney.

### Survival

One- and 5-year relative survival (RS) of rare epithelial tumours of the urinary system is 77% and 54%, respectively.
Epithelial tumours of the renal pelvis and ureter and epithelial tumours of the urethra are those with the highest RS: 81% after 1

year and 60% (renal pelvis and ureter) and 56% (urethra) after 5 years from diagnosis. Transitional carcinomas are those with the highest RS at 1 and 5 years after diagnosis, followed by adenocarcinoma and squamous cell carcinoma. The RS of rare epithelial tumours of the bladder is the third highest survival rate among urinary system cancers (65% and 39% at 1 and 5 years after diagnosis, respectively), with adenocarcinoma having higher survival than squamous cell carcinoma. Finally, survival of rare epithelial tumours of the kidney is 39% after 1 year and falls to 18% after 5 years from diagnosis. In the kidney, squamous cell carcinoma has higher survival than spindle cell carcinoma.

In Italy, the RS of these tumours is slightly higher than that observed in Europe in the RARECAREnet database. Regarding the survival differences between transitional, squamous cell carcinoma, and adenocarcinoma observed in Italy and in Europe (RARECAREnet database), several studies have pointed out that the stage distribution of squamous cell carcinoma and adenocarcinoma of the renal pelvis and ureter is relatively unfavourable in comparison to transitional cell carcinoma, with consequent poor survival.[10] However, the reason for this unfavourable stage distribution is unclear. Possibly, transitional cell carcinoma causes bleeding at an earlier stage and therefore is discovered earlier.

Considering that roughly half of the patients with these cancers do not survive their illness and that these are very rare cancers, as already suggested at European level, centralisation of treatment to a select number of specialist centres should be promoted.[10]

### Prevalence

Over 13,000 persons were estimated to be living with a diagnosis of rare epithelial cancers of the urinary system in Italy in 2010; 23% of these cases were diagnosed 15 years or more from prevalence date. Most prevalent cases are represented by patients with a previous diagnosis of transitional cell carcinoma of the renal pelvis and ureter. Surgery remains the mainstay treatment for renal pelvis and ureter cancer. Conservative surgery of the urethra is technically demanding and, when indicated, requires highly specialised surgeons. Centres that display a high surgical volume of treatment for renal, ureteral, and retroperitoneal tumours and that involve a multidisciplinary team in the decisional process should be contacted for primary care, or at least for a second opinion prior to undergoing treatment. At any rate, as cancer registries come to collect more information on stage and treatment and place of treatment, evaluation of this recommendation should become a priority.

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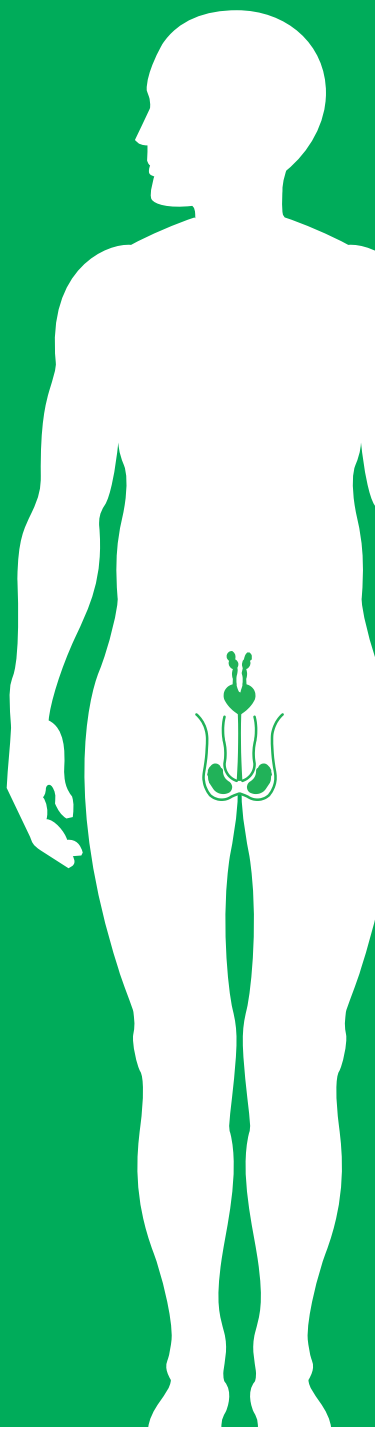
# RARE TUMOURS OF THE MALE GENITAL SYSTEM

**6%**
**OF MALE GENITAL SYSTEM TUMOURS ARE RARE**

## INCIDENCE

**2 413**
ESTIMATED NEW CASES
ITALY, 2015

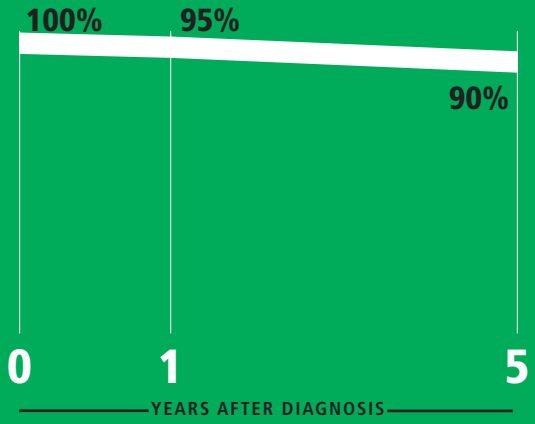
| | | |
|---|---|---|
| 116 | RARE EPITHELIAL TUMOURS OF PROSTATE | 0.3 % OF RARE TUMOURS OUT OF ALL TUMOURS IN EACH SITE |
| 1 746 | TESTICULAR AND PARATESTICULAR TUMOURS | 96 |
| 473 | EPITHELIAL TUMOURS OF PENIS | 96 |
| 76 | EXTRAGONADAL GERM CELL TUMOURS | 0.02 |
| 1 | MESOTHELIOMA OF TUNICA VAGINALIS | |



## PREVALENCE

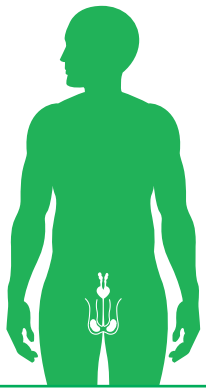
**51 030**
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# INCIDENCE



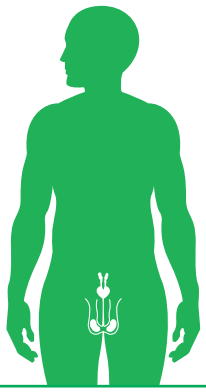
**RARE TUMOURS OF THE MALE GENITAL SYSTEM.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **RARE TUMOURS OF THE MALE GENITAL SYSTEM** | **4.08** | **4.00-4.17** | **9 049** | **6%** | **8.36** | **8.19-8.54** | **–** | **–** | **4.60** | **4.49-4.71** | **2.29** | **2.11-2.47** | **3.43** | **3.25-3.60** | **2 413** |
| **RARE EPITHELIAL TUMOURS OF PROSTATE** | **0.17** | **0.15-0.19** | **374** | **0.3%** | **0.35** | **0.31-0.39** | **–** | **–** | **<0.01** | **0.00-0.01** | **0.24** | **0.18-0.30** | **0.68** | **0.60-0.76** | **116** |
| Squamous cell carcinoma with variants of prostate | 0.01 | 0.00-0.01 | 16 | | 0.01 | 0.01-0.02 | – | – | 0.00 | – | 0.01 | 0.00-0.03 | 0.03 | 0.02-0.05 | 5 |
| Infiltrating duct carcinoma of prostate | 0.11 | 0.09-0.12 | 234 | | 0.22 | 0.19-0.25 | – | – | <0.01 | 0.00-0.01 | 0.16 | 0.11-0.21 | 0.42 | 0.36-0.49 | 72 |
| Transitional cell carcinoma of prostate | 0.05 | 0.04-0.06 | 119 | | 0.11 | 0.09-0.13 | – | – | <0.01 | 0.00-0.01 | 0.06 | 0.03-0.10 | 0.22 | 0.18-0.27 | 38 |
| Basal cell adenocarcinoma of prostate | <0.01 | 0.00-0.01 | 5 | | NE | – | – | – | NE | – | NE | – | NE | – | 1 |
| **TESTICULAR AND PARATESTICULAR TUMOURS** | **3.10** | **3.03-3.18** | **6 877** | **96%** | **6.41** | **6.26-6.56** | **–** | **–** | **4.27** | **4.17-4.38** | **0.83** | **0.72-0.94** | **0.50** | **0.43-0.57** | **1 746** |
| Paratesticular adenocarcinoma with variants | <0.01 | 0.00-0.00 | 2 | | NE | – | – | – | NE | – | NE | – | NE | – | 1 |
| Non seminomatous testicular tumours | 1.07 | 1.02-1.11 | 2 363 | | 2.20 | 2.11-2.29 | – | – | 1.53 | 1.47-1.60 | 0.12 | 0.08-0.17 | 0.06 | 0.04-0.08 | 586 |
| Seminomatous testicular tumours | 1.70 | 1.65-1.76 | 3 777 | | 3.52 | 3.41-3.64 | – | – | 2.35 | 2.27-2.42 | 0.55 | 0.47-0.65 | 0.22 | 0.17-0.26 | 964 |
| Spermatocytic seminoma | 0.05 | 0.04-0.06 | 103 | | 0.10 | 0.08-0.12 | – | – | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.06 | 0.08 | 0.05-0.11 | 29 |
| Teratoma with malignant transformation | <0.01 | 0.00-0.01 | 5 | | NE | – | – | – | NE | – | NE | – | NE | – | 1 |
| Testicular sex cord tumours | 0.02 | 0.02-0.03 | 55 | | 0.05 | 0.04-0.07 | – | – | 0.03 | 0.02-0.03 | 0.02 | 0.01-0.05 | 0.03 | 0.01-0.04 | 15 |
| **EPITHELIAL TUMOURS OF PENIS** | **0.68** | **0.65-0.72** | **1 509** | **96%** | **1.41** | **1.34-1.48** | **–** | **–** | **0.15** | **0.13-0.18** | **1.16** | **1.03-1.29** | **2.19** | **2.05-2.33** | **473** |
| Squamous cell carcinoma with variants of penis | 0.63 | 0.60-0.67 | 1 406 | | 1.31 | 1.24-1.38 | – | – | 0.14 | 0.13-0.16 | 1.10 | 0.98-1.23 | 2.02 | 1.89-2.16 | 438 |
| Adenocarcinoma with variants of penis | <0.01 | 0.00-0.01 | 13 | | NE | – | – | – | NE | – | NE | – | NE | – | 4 |
| **EXTRAGONADAL GERM CELL TUMOURS** | **0.13** | **0.11-0.14** | **284** | **0.02%** | **0.19** | **0.16-0.22** | **–** | **–** | **0.16** | **0.14-0.18** | **0.06** | **0.04-0.10** | **0.05** | **0.03-0.08** | **76** |
| Non seminomatous germ cell tumours | 0.06 | 0.05-0.08 | 142 | | 0.08 | 0.07-0.10 | – | – | 0.07 | 0.06-0.09 | 0.04 | 0.02-0.08 | 0.04 | 0.02-0.06 | 38 |
| Seminomatous germ cell tumours | 0.01 | 0.01-0.02 | 29 | | 0.02 | 0.02-0.04 | – | – | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.03 | 0.00 | – | 8 |
| Germ cell tumours of Central Nervous System (CNS) | 0.04 | 0.03-0.05 | 81 | | 0.06 | 0.04-0.07 | – | – | 0.05 | 0.04-0.06 | <0.01 | 0.00-0.02 | <0.01 | 0.00-0.02 | 22 |
| **MESOTHELIOMA OF TUNICA VAGINALIS** | **<0.01** | **0.00-0.01** | **5** | | **NE** | **–** | **–** | **–** | **NE** | **–** | **NE** | **–** | **NE** | **–** | **1** |

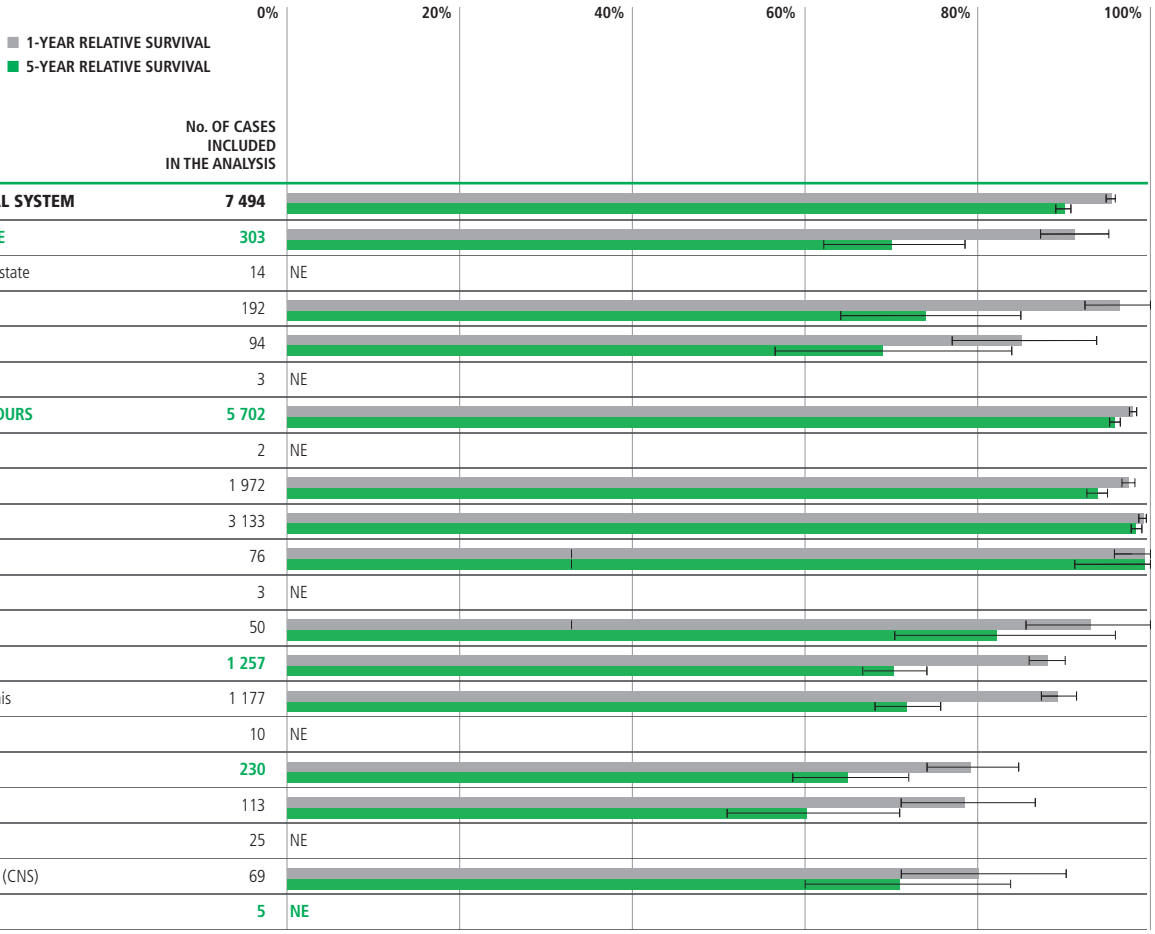
**NE:** not estimable because 15 or less incident cases were observed

# RARE TUMOURS OF THE MALE GENITAL SYSTEM

# SURVIVAL



**RARE TUMOURS OF THE MALE GENITAL SYSTEM.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.

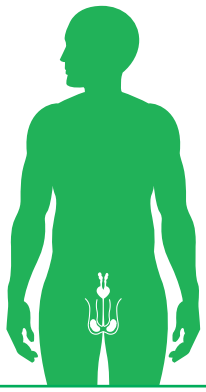



| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **RARE TUMOURS OF THE MALE GENITAL SYSTEM** | **7 494** |
| **RARE EPITHELIAL TUMOURS OF PROSTATE** | **303** |
| Squamous cell carcinoma with variants of prostate | 14 |
| Infiltrating duct carcinoma of prostate | 192 |
| Transitional cell carcinoma of prostate | 94 |
| Basal cell adenocarcinoma of prostate | 3 |
| **TESTICULAR AND PARATESTICULAR TUMOURS** | **5 702** |
| Paratesticular adenocarcinoma with variants | 2 |
| Non seminomatous testicular tumours | 1 972 |
| Seminomatous testicular tumours | 3 133 |
| Spermatocytic seminoma | 76 |
| Teratoma with malignant transformation | 3 |
| Testicular sex cord tumours | 50 |
| **EPITHELIAL TUMOURS OF PENIS** | **1 257** |
| Squamous cell carcinoma with variants of penis | 1 177 |
| Adenocarcinoma with variants of penis | 10 |
| **EXTRAGONADAL GERM CELL TUMOURS** | **230** |
| Non seminomatous germ cell tumours | 113 |
| Seminomatous germ cell tumours | 25 |
| Germ cell tumours of Central Nervous System (CNS) | 69 |
| **MESOTHELIOMA OF TUNICA VAGINALIS** | **5** |

| | NE |
|---|---|
| **RARE EPITHELIAL TUMOURS OF PROSTATE** | |
| Squamous cell carcinoma with variants of prostate | NE |
| Infiltrating duct carcinoma of prostate | |
| Transitional cell carcinoma of prostate | |
| Basal cell adenocarcinoma of prostate | NE |
| **TESTICULAR AND PARATESTICULAR TUMOURS** | |
| Paratesticular adenocarcinoma with variants | NE |
| Non seminomatous testicular tumours | |
| Seminomatous testicular tumours | |
| Spermatocytic seminoma | |
| Teratoma with malignant transformation | NE |
| Testicular sex cord tumours | |
| **EPITHELIAL TUMOURS OF PENIS** | |
| Squamous cell carcinoma with variants of penis | |
| Adenocarcinoma with variants of penis | NE |
| **EXTRAGONADAL GERM CELL TUMOURS** | |
| Non seminomatous germ cell tumours | |
| Seminomatous germ cell tumours | NE |
| Germ cell tumours of Central Nervous System (CNS) | |
| **MESOTHELIOMA OF TUNICA VAGINALIS** | **NE** |

**NE:** not estimable because 30 or less incident cases were observed

# PREVALENCE



**RARE TUMOURS OF THE MALE GENITAL SYSTEM**. Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **RARE TUMOURS OF THE MALE GENITAL SYSTEM** | **7.83** | **7.26-8.44** | **9.93** | **9.28-10.62** | **41.95** | **40.60-43.34** | **88.72** | **84.78-92.66** | **51 030** |
| **RARE EPITHELIAL TUMOURS OF PROSTATE** | **0.21** | **0.12-0.33** | **0.18** | **0.11-0.30** | **0.88** | **0.70-1.11** | **0.93** | **0.72-1.14** | **539** |
| Squamous cell carcinoma with variants of prostate | 0.01 | 0.00-0.06 | NE | – | 0.02 | 0.00-0.08 | 0.02 | 0.00-0.06 | 14 |
| Infiltrating duct carcinoma of prostate | 0.14 | 0.07-0.24 | 0.06 | 0.02-0.13 | 0.56 | 0.42-0.74 | 0.58 | 0.42-0.74 | 333 |
| Transitional cell carcinoma of prostate | 0.06 | 0.02-0.13 | 0.13 | 0.06-0.23 | 0.30 | 0.20-0.44 | 0.33 | 0.20-0.45 | 192 |
| Basal cell adenocarcinoma of prostate | NE | – | NE | – | NE | – | NE | – | NE |
| **TESTICULAR AND PARATESTICULAR TUMOURS** | **6.27** | **5.76-6.82** | **8.54** | **7.94-9.18** | **35.66** | **34.42-36.94** | **78.39** | **74.62-82.17** | **45 055** |
| Paratesticular adenocarcinoma with variants | NE | – | NE | – | NE | – | NE | – | NE |
| Non seminomatous testicular tumours | 1.92 | 1.64-2.23 | 2.80 | 2.46-3.18 | 11.86 | 11.14-12.60 | 29.53 | 26.37-32.69 | 16 779 |
| Seminomatous testicular tumours | 3.87 | 3.47-4.31 | 5.06 | 4.60-5.55 | 21.49 | 20.52-22.48 | 44.49 | 41.55-47.42 | 25 649 |
| Spermatocytic seminoma | 0.06 | 0.02-0.13 | 0.09 | 0.04-0.18 | 0.42 | 0.30-0.59 | 1.33 | 0.76-1.91 | 23 047 |
| Teratoma with malignant transformation | NE | – | NE | – | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.04 | 6 |
| Testicular sex cord tumours | NE | – | 0.06 | 0.02-0.13 | 0.20 | 0.11-0.31 | 0.41 | 0.21-0.60 | 232 |
| **EPITHELIAL TUMOURS OF PENIS** | **1.17** | **0.96-1.42** | **0.99** | **0.79-1.22** | **4.39** | **3.96-4.86** | **6.16** | **5.54-6.78** | **3 562** |
| Squamous cell carcinoma with variants of penis | 1.15 | 0.93-1.40 | 0.95 | 0.76-1.18 | 4.22 | 3.80-4.68 | 5.85 | 5.25-6.45 | 3 377 |
| Adenocarcinoma with variants of penis | NE | – | NE | – | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.04 | 7 |
| **EXTRAGONADAL GERM CELL TUMOURS** | **0.18** | **0.11-0.30** | **0.22** | **0.13-0.34** | **1.02** | **0.82-1.26** | **3.23** | **2.30-4.16** | **1 874** |
| Non seminomatous germ cell tumours | 0.08 | 0.03-0.17 | 0.09 | 0.04-0.18 | 0.47 | 0.34-0.64 | 1.11 | 0.73-1.49 | 652 |
| Seminomatous germ cell tumours | 0.03 | 0.01-0.10 | 0.05 | 0.01-0.12 | 0.17 | 0.10-0.28 | 0.25 | 0.12-0.39 | 150 |
| Germ cell tumours of Central Nervous System (CNS) | 0.06 | 0.02-0.13 | 0.05 | 0.01-0.12 | 0.30 | 0.20-0.44 | 0.42 | 0.22-0.62 | 244 |
| **MESOTHELIOMA OF TUNICA VAGINALIS** | **NE** | **–** | **NE** | **–** | **NE** | **–** | **NE** | **–** | **NE** |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

This group includes a heterogeneous number of rare cancers:
- **rare epithelial tumours of the prostate** (squamous cell carcinoma, infiltrating duct carcinoma, transitional cell carcinoma, basal cell adenocarcinoma);
- **testicular cancers** (paratesticular adenocarcinoma, non-seminomatous testicular cancer, seminomatous testicular cancer; spermatocytic seminoma, teratoma with malignant transformation, testicular sex cord cancers);
- **epithelial tumours of the penis** (squamous cell carcinomas, adenocarcinomas);
- **extragonadal germ cell tumours** (non-seminomatous germ cell tumours, seminomatous germ cell tumours, and germ cell tumours of the Central Nervous System);
- **mesothelioma of the tunica vaginalis testis**.

Extragonadal germ cell tumours include a few entities that occur even in women; these are also considered in this group since clinical management is the same for females as for males. Overall, rare cancers account for 6% of all male genital system cancers.

## RARE EPITHELIAL TUMOURS OF THE PROSTATE

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Tumours with **squamous cell differentiation** may arise from the urothelial cells of the prostatic urethra, the periurethral glands, as from a stem cell.[1] They may be in the pure squamous carcinoma form, which usually does not express serum PSA,[2] or associated with acinar adenocarcinoma (adenosquamous carcinoma), urothelial carcinoma, or sarcoma;[1] they are associated with early development of osteolytic metastases and poor responsiveness to antiandrogen therapy.[2]

Regarding infiltrating duct carcinomas, the mixed variant (adenocarcinoma-ductal carcinoma) is more common than pure ductal carcinoma; the latter arises in periurethral prostatic ducts and shows Gleason score 8;[2] this histotype may have a prevalent papillary, or solid or complex cribriform pattern of growth, and is more likely to metastasise to testis and penis.[2] **Transitional cell carcinoma** in the absence of bladder carcinoma may arise from the prostatic urethra or major prostatic ducts, which are lined by urothelial epithelium; it is often difficult to distinguish the origin of this neoplasm, due the possibility of an intraprostatic extension from bladder carcinoma.

**Basal cell adenocarcinoma of the prostate** is a very rare histological type described for the first time in 1974; it arises in the basal cell layer of the prostate gland and is very likely to cause urinary obstructive symptoms at clinical presentation; it is reported to behave less aggressively than other histotypes.[2] It is frequently associated with the acinar variant and only about 50 cases are described in the literature.[3]

Risk factors associated with common prostatic adenocarcinoma (age, familiarity, obesity, lifestyle, environmental exposure) most likely have a role even in the aetiology of rare prostatic cancers, except for squamous cell carcinoma. About half of squamous cell carcinomas arise after androgen deprivation therapy or radiation treatment for a conventional adenocarcinoma. However, some cases have been reported as *de novo* cancers in patients without prostate disease.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Infiltrating duct carcinoma is the most common (63%), followed by transitional carcinoma (32%), squamous (4%), and basal cell adenocarcinoma (1%). Like the common acinar adenocarcinoma of the prostate, even these rare epithelial tumours are typical of advanced age (>65 years), with exceptional cases of early-onset prostate cancer (diagnosed <55 years). Approximately 120 Italians were estimated to be diagnosed with rare tumours of the prostate in 2015.

#### Survival

Infiltrating duct carcinoma and transitional carcinomas have a good prognosis (5-year relative survival: 74% and 69%, respectively). In the AIRTUM database, the number of cases is too limited to provide survival of squamous cell carcinoma and basal cell adenocarcinoma. However, data from the European RARECAREnet database (www.rarecarenet.eu) show that squamous cell carcinomas have a poor survival rate (40% at 5 years), while basal cell adenocarcinoma have a good survival rate (80%).

The European RARECAREnet data show that rare epithelial cancers of the prostate are characterised by a worse prognosis than the common acinar adenocarcinoma of the prostate (88%). The lower prognosis of these rare cancers seems mainly due to the more advanced stage at diagnosis and some resistance to treatment, particularly to hormonal therapy. They usually occur in people older than those diagnosed with acinar adenocarcinoma and survival decreases with increasing age.

#### Prevalence

In Italy, slightly more than 500 persons were estimated to be alive in 2010 with a diagnosis of rare epithelial tumours of the prostate. The most prevalent cases are infiltrating duct carcinomas of the prostate, followed by transitional cell carcinomas.

## TESTICULAR CANCERS

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Testicular cancers are all rare, but are the most common cancers in young men, and their incidence is increasing.[4] The incidence varies in different geographical areas, thus testicular cancer may not be perceived as rare in countries of Northern and Western Europe.[4] However, as described in «Material and methods» (pp. 14-21), the definition of rarity is based on the European population and not on the country-specific incidence. Thus, even though the country-specific incidence rate of testicular cancer can be higher than 6 in some countries, testicular cancer is considered rare because its incidence is <6 per 100,000 in the EU.

**Seminomatous and non-seminomatous cancers** are the most common germ cell tumours of the testis. Seminomatous cancers are more often localised, metastasise via the lymphatic system, and are radiosensitive; they occur in somewhat older patients. By contrast, non-seminomatous cancers are prone to haematogenous as well as lymphatic spread and are less radiosensitive.[4] **Spermatocytic seminoma** is clinically and pathologically distinct from classic seminomatous cancer, in particular for its almost complete inability to metastasise.[4] On rare occasions, teratomas undergo somatic ma-

lignant transformation.[5] The most common transformations are to sarcoma, primitive neuroectodermal tumour, and adenocarcinoma. Most **sex cord cancers** have a benign clinical course following surgery, but about 20% are metastatic at diagnosis and 10%-12% behave aggressively, often with fatal outcome.[4]

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Seminomatous testicular cancer is the most common entity (55%), followed by non-seminomatous testicular cancer (34%). The other germ cell tumours are very rare. For seminomatous cancers, the incidence rate (IR) peaks in the 30-34 age group (0.5 per 100,000; data not shown). For non-seminomatous cancers, the IR peaks in the 25-29 age group (4 per 100,000; data not shown). Until around 24 years of age non-seminomatous cancers are the predominant histologic type, after around 29 years of age seminomas are more common than non seminomas. Among the elderly (65 years and over) 62% of germ cell tumours are seminomas. A total of 1,746 testicular cancers were estimated to be diagnosed in Italy at 2015; 90% of these cancers are germ cell tumours.

#### Survival

Among testicular and paratesticular cancers, seminomas and spermatocytic seminoma have the highest survival, followed by non seminomas. Five-year relative survival (RS) is also good for sex cord tumours. Survival differences between seminomatous and non-seminomatous cancers are explained by their different biology. The good prognosis of spermatocytic seminoma and sex cord tumours is mainly explained by their benign clinical course. The AIRTUM database has too few cases to provide survival of the other entities. However, regarding teratoma with malignant transformation, studies suggest that transformation has a negative impact on prognosis compared to the non-transformed counterpart.[5]

#### Prevalence

Around 45,000 persons were estimated to be living with a diagnosis of testicular cancers in Italy in 2010. The most prevalent testicular cancers are seminomatous and non-seminomatous cancers. Young age of patients may play an important role in so relatively high prevalence figures. For testicular cancers, however, the high survival rate appears as the most important contributor to the prevalence. Our estimates are slightly higher than those published in the AIRTUM monograph on prevalence[6] because of the different methodology used (see «Materials and methods», pp.14-21 ).

## EPITHELIAL TUMOURS OF THE PENIS

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Epithelial tumours of the penis are all rare. Risk factors for the development of penile cancer are multifactorial and include: phimosis, infection with human papilloma virus (HPV), HIV infection, cigarette smoking, history of trauma and chronic balanitis, lichen sclerosus, and PUVA treatment.[2] Circumcision in infancy is associated with a protective effect for penile cancer.[2] Penile cancer is a very rare tumour for which a referral to a centre of expertise is recommended, since it deserves special attention in the diagnosis process and treatment options. Penectomy is disfiguring and can have an intense effect on the patient's quality of life, sexual function, self-esteem, and general mental health. Therefore, there is an increased trend for penile preserving strategies (radiotherapy), despite the fact that recurrence rates may be higher than those of radical surgical procedures.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Cancer of the penis is the rarest cancer of the male genital system. The IR in Italy is 0.7 per 100,000 and it is equal to that observed in the European RARECAREnet database. As HPV infection is an important risk for penile cancer and circumcision is protective, the intermediate position of Italy and Europe can be explained by moderate rates of HPV-infection in a generally uncircumcised male population. Squamous cell carcinoma is the most common morphological type of penis cancer (93%). This tumour is very rare before 50 years old; the IR increases with age, with the highest IR in patients 75 years or older. About 470 penile cancers were estimated to be diagnosed in Italy in 2015.

#### Survival

Survival of squamous cell carcinoma of the penis is good and similar to that observed in the European RARECAREnet database. In the AIRTUM database the number of cases is too limited to provide data for adenocarcinoma of the penis. The European RARECAREnet database reports a 5-year RS of 50%. Although survival for penile cancers is relatively good, it has not improved in the past few years, probably because of the limited advances in curative treatment and the limited centralisation of treatment.[7,8]

#### Prevalence

In Italy, 3,500 persons were estimated to be alive with a diagnosis of penile cancer in 2010. The most prevalent penile cancer is squamous cell carcinoma.

## EXTRAGONADAL GERM CELL TUMOURS (EGCTs)

### WHAT DO WE KNOW ABOUT THESE CANCERS?

**Extragonadal germ cell tumours** are all rare. Germ cell tumours of the CNS are typical of children and adolescents and, therefore, are mainly managed by paediatric oncologists. EGCTs represent a minor part of all germ cell tumours and are more aggressive than those of the gonads. They usually occur along the midline of the body along which the primordial germ cells migrate from the proximal epiblast to the genital ridge.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

EGCTs account for 4% of all germ cell tumours in the AIRTUM database (data not shown). EGCTs are more common in males than females and, in all sites, non seminoma is the predominant histology. Germ cell tumours of the CNS are typical of children and adolescents (10-19 years old). Non seminomas have a first incidence peak in the 0-4-year age group and a second in the 25-29-year age group. Seminomas are very rare and have an incidence peak in the 35-39-year age group. Sites are predominantly the me-

diastinum (29%), CNS (17%), endocrine system (12%), female genital system (9%), retroperitoneum (5%), with primary site unknown in 3%. The remaining cases occur at disparate sites including head and neck, digestive tract, lung, prostate, urinary tract, and other not specified sites (ICD-O3 C76.0-76.8).

### Survival

Five-year RS of EGCTs is always worse than that of gonadal germ cell tumours. Five-year RS is 71% for CNS EGCTs and 60% for non-seminomatous EGCTs (data not shown). Among the latter, those of the mediastinum (most common site in the AIRTUM database) has the worst survival. This could be due to generally large tumour bulk at diagnosis, resistance to chemotherapy, difficulty of removing all residual disease after chemotherapy, and a predisposition to develop haematologic neoplasia and other non-germ cell malignancies. In the AIRTUM database the number of cases is too limited to provide data for seminomatous EGCTs. However, the European RARECAREnet database reports a 5-year RS of 85%.

### Prevalence

About 1,900 persons were estimated to be living with a diagnosis of extragonadal germ cell cancer in Italy in 2010.

## MESOTHELIOMA OF THE TUNICA VAGINALIS TESTIS

Only 5 cases of **malignant mesothelioma of the tunica vaginalis** (MTVT) were observed in the AIRTUM database in the period of diagnosis 2000-2010, confirming the extreme rarity of this tumour. The data of the National Italian malignant Mesothelioma Registry (ReNAM) reported 51 cases of MTVT diagnosed in the period 1993-2008, corresponding to 0.3% of all mesothelioma cases in Italy.[9] Differences in number of cases observed are due to the national coverage of the ReNAM, which is a mesothelioma-dedicated registry, and the partial coverage of the AIRTUM registries (which are general registries). The highest incidence is observed in the 65-75-year age group.

An Italian study found exposure to asbestos in 67% of cases of MTVT and clarified that the difference in the percentage of asbestos-related MTVT reported in the literature (30%-40%) might be the result of an incomplete investigation of exposure history for MTVT patients.[10] Thus, asbestos exposure is the main risk factor for MTVT, as well as for malignant mesotheliomas that occur at other sites, although the mechanism of involvement of the tunica vaginalis by asbestos fibres still remains unclear.

In the AIRTUM database the number of cases is too limited to estimate survival. However, according to the literature, survival is very bad, ranging from a minimum of 18 months without treatment[11] to a maximum of 23 months for patients treated with surgery.[12]

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# RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA

**0.2%**
**OF TUMOURS OF THE SKIN AND OF THE MUCOSA ARE RARE**

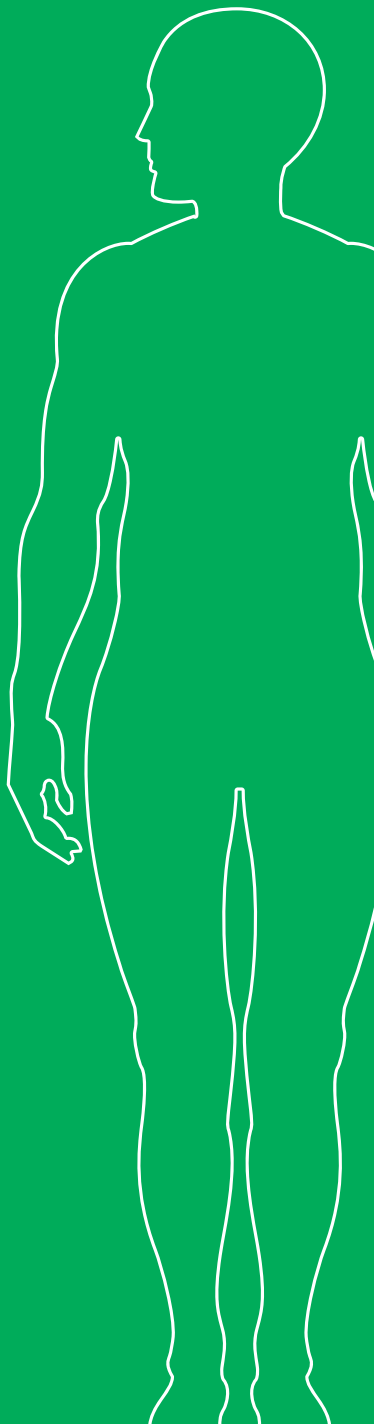
## INCIDENCE

**532**
ESTIMATED NEW CASES
ITALY, 2015

- **108** MALIGNANT MELANOMA OF MUCOSA (EXTRACUTANEOUS)
- **424** ADNEXAL CARCINOMA OF SKIN

**0.04** % OF RARE TUMOURS OUT OF ALL TUMOURS IN EACH SITE

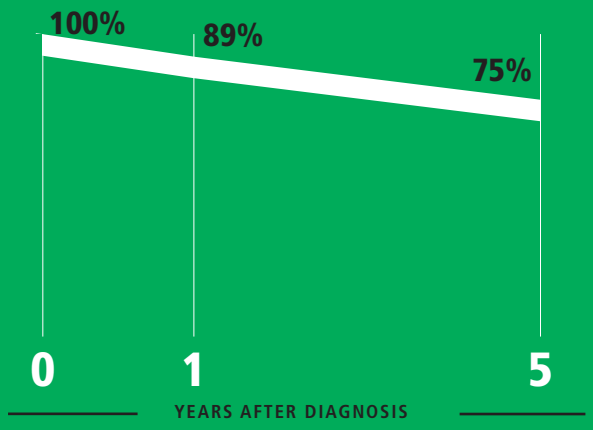
**3.4**



## PREVALENCE

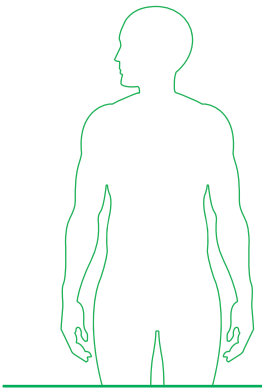
**4 403**
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

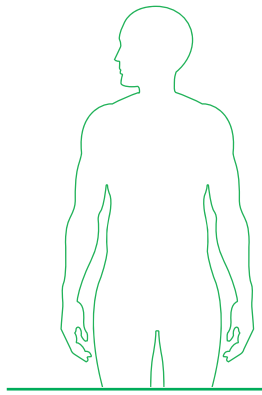
# RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA



# INCIDENCE

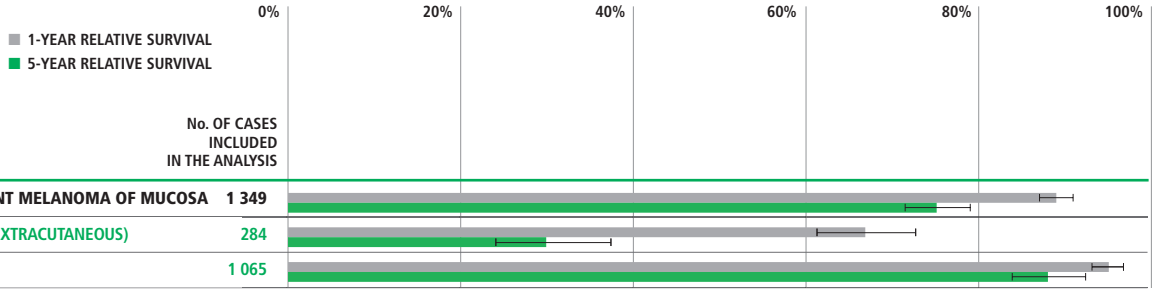
**RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

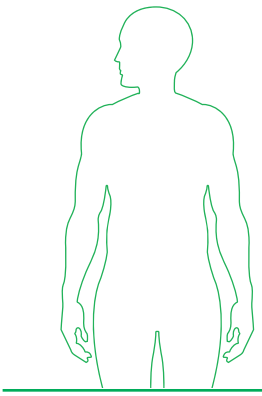
| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA** | **0.77** | **0.73-0.80** | **1 699** | **0.2%** | **0.83** | **0.78-0.89** | **0.70** | **0.66-0.75** | **0.13** | **0.11-0.15** | **0.93** | **0.82-1.05** | **2.86** | **2.70-3.02** | **532** |
| MALIGNANT MELANOMA OF MUCOSA (EXTRACUTANEOUS) | 0.16 | 0.14-0.18 | 356 | 0.04% | 0.12 | 0.10-0.15 | 0.19 | 0.17-0.22 | 0.04 | 0.03-0.05 | 0.25 | 0.19-0.31 | 0.54 | 0.47-0.61 | 108 |
| ADNEXAL CARCINOMA OF SKIN | 0.61 | 0.57-0.64 | 1 343 | 3.4% | 0.71 | 0.66-0.76 | 0.51 | 0.47-0.55 | 0.09 | 0.08-0.11 | 0.68 | 0.59-0.79 | 2.32 | 2.18-2.47 | 424 |



# SURVIVAL

**RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



# PREVALENCE

**RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA** | **1.40** | **1.16-1.67** | **1.70** | **1.44-2.00** | **5.66** | **5.17-6.18** | **7.50** | **6.83-8.17** | **4 403** |
| MALIGNANT MELANOMA OF MUCOSA (EXTRACUTANEOUS) | 0.25 | 0.16-0.38 | 0.16 | 0.09-0.27 | 0.61 | 0.46-0.80 | 0.87 | 0.63-1.11 | 524 |
| ADNEXAL CARCINOMA OF SKIN | 1.15 | 0.93-1.40 | 1.54 | 1.29-1.82 | 5.05 | 4.59-5.55 | 6.63 | 6.00-7.25 | 3 879 |

# RARE SKIN TUMOURS AND MALIGNANT MELANOMA OF MUCOSA

This group includes two tumour types which are rare and understudied:

- **malignant melanoma of the mucosa**;
- **skin adnexal tumours**.

Because of their rarity, even the basic descriptive epidemiology of these tumour types is sparse, restricted to specific anatomic sites and confined to case reports or clinical series.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**Primary mucosal melanomas** arise from melanocytes located in mucosal membranes. Although a majority of mucosal melanomas originate from the mucosa of the nasal cavity and accessory sinuses, oral cavity, anorectum, vulva, and vagina, they can arise in almost any part of mucosal membranes. In particular, primary oral melanomas may arise from nevi and pigmented areas such as amalgam tattoos, or post inflammatory pigmentations due to tobacco usage or drugs aberrant reactions.[1] Most mucosal melanomas occur in occult sites, which together with the lack of early and specific signs contribute to late diagnosis and poor prognosis. Because of their rareness the knowledge about their pathogenesis and risk factors is insufficient, and moreover there are no well-established protocols for staging and treatment. Surgery is the mainstay of treatment, with trends toward more conservative treatment since radical surgery has not proven an advantage for survival. Radiotherapy can provide better local control in some locations, but did not show improvement in survival. There is no effective systemic therapy for these aggressive tumours. Compared with cutaneous and ocular melanoma, mucosal melanomas have the lowest percentage of five-year survival. Recently revealed molecular changes underlying mucosal melanomas offer new hope for development of more effective systemic therapy for mucosal melanomas.[2]

**Skin adnexal tumours** (SATs) are a large and diverse group of benign and malignant neoplasms, which exhibit morphological differentiation towards one of the different types of adnexal epithelium present in normal skin: apocrine-eccrine differentiation (tumours of the sweat glands, mammary and extramammary Paget's disease ); follicular (tumours of hairs); and sebaceous (tumours of Zeis glands and meibomian glands of the eyelid). The histogenesis of adnexal tumours is still uncertain; however, the possibility of origin from a pluripotent stem cell is suggestive.[3-6]

Most SATs are benign, and local complete surgical excision is curative. However, diagnosing some of these tumours has important implications, as they might be markers for syndromes associated with internal malignancies, such as trichilemmomas in Cowden syndrome and sebaceous tumours in Muir-Torre syndrome.[7,8] Benign lesions are typical of the young. A malignant counterpart of almost every SAT has been described. These tumours are rare, locally aggressive, and have the potential for nodal involvement and distant metastasis, with a poor clinical outcome. Therefore, establishing a diagnosis of malignancy in SAT is important for therapeutic and prognostic purposes. Because pathologists may not frequently encounter SATs, and owing to their different derivation and broad histogenesis, diagnosing these tumours may be challenging even to an experienced pathologist. SATs appear as single nodular lesions resembling dermal melanocytic nevi, epidermoid cysts, and basal cell carcinoma. Thus, their diagnosis relies on histological evaluation, including immunohistochemistry to support differential diagnosis (podoplanin (D2-40) to distinguish basal cell carcinoma from trichoepithelioma, monoclonal antibody Ber-EP4 to reliably discriminate between microcystic adnexal carcinoma and basal cell carcinoma).[8]

In this study, we conducted the first comprehensive and largest analysis, to our knowledge, of incidence, prevalence and survival of these rare tumours in the Italian population. In the list of rare cancers proposed by RARECARE,[9] extramammary Paget's disease is not included among SATs, as it is often an epiphenomenon of another invasive malignancy and because the actual invasiveness of the lesion is still debated. Mammary Paget's disease is included and described among the rare cancers of the breast.

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

**All mucosal melanomas** are rare and are so rare that only 350 cases were observed in Italy in 11 years. These tumours are slightly more common in females than males and are typical of older people (peak in the eighth decade of life). In the AIRTUM database, mucosal melanoma occurs most frequently in the female genital tract and in the head and neck, as previously reported in Europe[1] and the USA.[10]

**All SATs** are rare and 1,300 cases were observed in Italy in the period 2000-2010 in the AIRTUM database. SATs are more common in males than females and the incidence rate (IR) increases exponentially with age, with peak frequencies in the eighth decade of life. The most frequent SATs are those with apocrine and eccrine differentiation, followed by sebaceous tumours and adenoid cystic carcinoma with skin appendage carcinoma, NOS, accounting for 20%. These results are similar to those observed in the SEER database (period of diagnosis 2001-2006), which reports a high IR of apocrine and eccrine followed by sebaceous and, differently from the Italian results, microcystic adnexal carcinoma. Skin appendage carcinoma, NOS, is lower in the SEER database (about 10%).[11] Interesting is the absence of follicular tumours in both the AIRTUM and SEER databases.

### Survival

Five-year relative (RS) of **mucosal melanomas** is 30%, most likely because of the late diagnosis and the lack of protocols for their treatment. Survival of **SAT** is good, as it is 95% after 1 year and 88% after 5 years from diagnosis. This is probably due to the fact that these tumours are mainly locally aggressive tumours. In the AIRTUM database there is no information on stage; however, according to the SEER database, 5-year RS is 99% in local SATs, 93% in SATs with regional involvement (which are 15% of all SATs) and 43% in SATs with distant metastases (which are very rare; 1.6% out of all SATs observed in the SEER database in the period 1992-2004). With regard to survival for the different differentiations, it seems that 5-year RS is slightly lower for tumours with sebaceous differentiation.[11]

These results are in line with those observed in Europe in the RARECAREnet database (www.rarecarenet.eu). As expected, for both mucosal melanomas and SATs, the observed survival (not shown in table) is lower than the relative one because these tumours affect mainly old people.

### Prevalence

Around 4,400 persons were estimated to be alive in 2010 with a past diagnosis of one of these rare cancers in Italy. The most prevalent cancers are SATs (88% of cases), coherently with the high incidence and survival of these tumours.

## GENERAL REMARKS

SATs affect mainly old people, have high survival, are rarely metastatic at diagnosis, and surgery is the mainstay treatment. However, diagnosing these tumours may be challenging. Survival of mucosal melanoma is low because of lack of treatment protocols and delay in diagnosis.

A possible solution to address the challenges for diagnosis and treatment of these tumours is the identification of an expert centre, with a multidisciplinary team, able to support the therapeutic decision for locally advanced and metastatic SATs and mucosal melanoma. The expert centre should also be able to provide a second pathological opinion to ensure the appropriate diagnosis of SATs. For melanoma of the mucosa, revision of the pathological sample is important, but not as essential as for SATs.

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# EMBRYONAL TUMOURS

**100%**
**OF EMBRYONAL TUMOURS ARE RARE**

## INCIDENCE

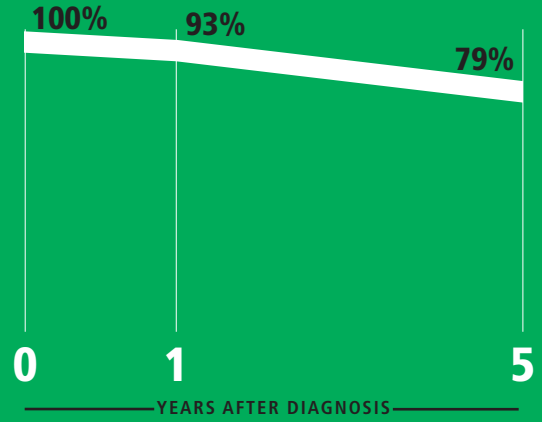
**234**
ESTIMATED NEW CASES
ITALY, 2015

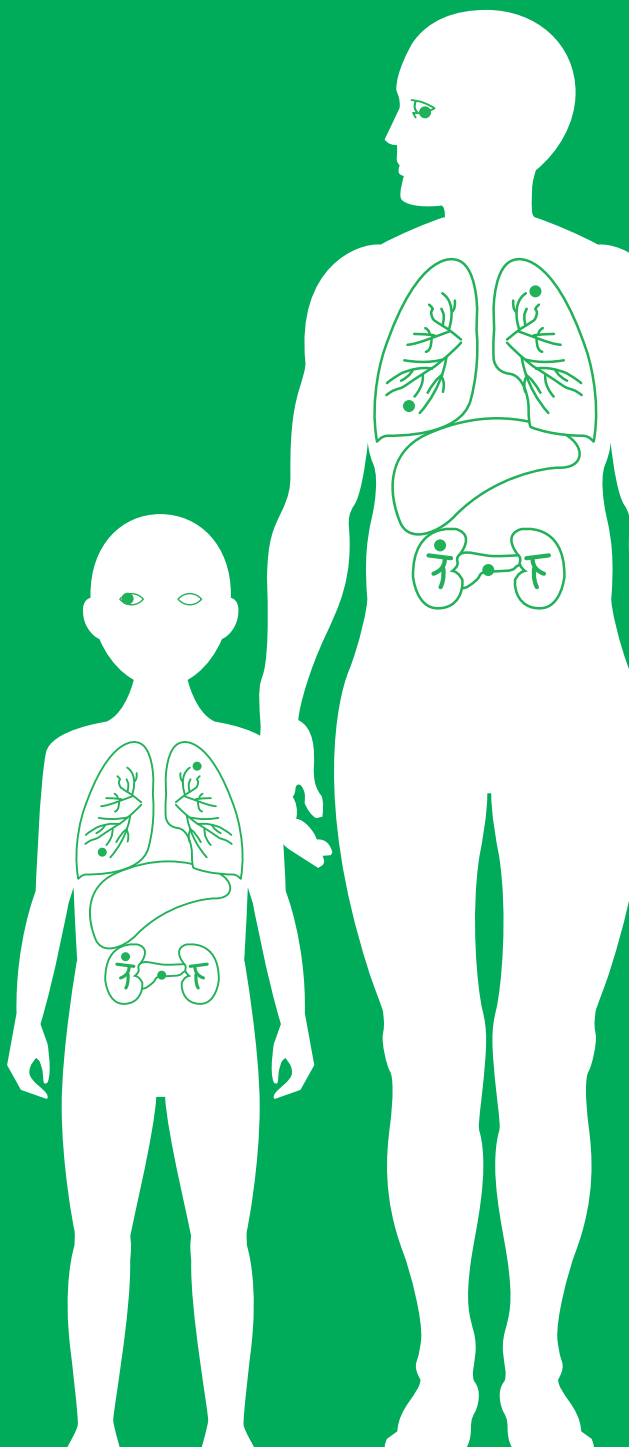
| | |
|---|---|
| 99 | NEUROBLASTOMA AND GANGLIONEUROBLASTOMA |
| 68 | NEPHROBLASTOMA |
| 30 | RETINOBLASTOMA |
| 11 | HEPATOBLASTOMA |
| 1 | PLEUROPULMONARY BLASTOMA |
| 1 | PANCREATOBLASTOMA |
| 20 | OLFACTORY NEUROBLASTOMA |
| 4 | ODONTOGENIC MALIGNANT TUMOURS |

## PREVALENCE

**6 085**
ESTIMATED PREVALENT CASES
ITALY, 2010

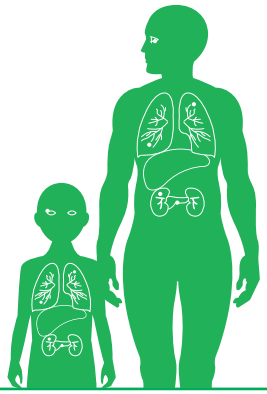
## SURVIVAL



SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# EMBRYONAL TUMOURS



# INCIDENCE

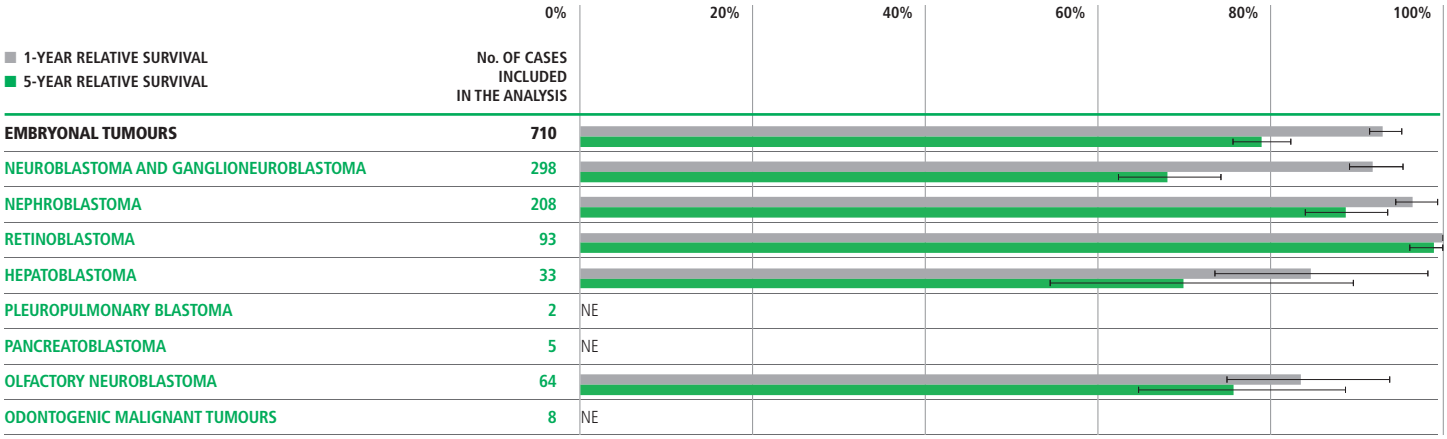
**EMBRYONAL TUMOURS.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-4 yrs | | 5-14 yrs | | 15+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **EMBRYONAL TUMOURS** | **0.39** | **0.36-0.41** | **859** | **100%** | **0.41** | **0.37-0.45** | **0.37** | **0.34-0.41** | **5.92** | **5.46-6.41** | **0.65** | **0.54-0.77** | **0.06** | **0.05-0.07** | **234** |
| NEUROBLASTOMA AND GANGLIONEUROBLASTOMA | 0.17 | 0.15-0.18 | 370 | NA | 0.19 | 0.16-0.22 | 0.15 | 0.12-0.17 | 2.88 | 2.56-3.23 | 0.29 | 0.22-0.38 | <0.01 | 0.00-0.01 | 99 |
| NEPHROBLASTOMA | 0.11 | 0.10-0.13 | 248 | NA | 0.10 | 0.08-0.12 | 0.12 | 0.10-0.15 | 1.67 | 1.43-1.94 | 0.30 | 0.23-0.38 | <0.01 | 0.00-0.01 | 68 |
| RETINOBLASTOMA | 0.05 | 0.04-0.06 | 111 | NA | 0.05 | 0.04-0.06 | 0.05 | 0.04-0.07 | 1.03 | 0.84-1.24 | 0.02 | 0.01-0.06 | 0.00 | – | 30 |
| HEPATOBLASTOMA | 0.02 | 0.01-0.02 | 40 | NA | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | 0.28 | 0.19-0.40 | 0.02 | 0.01-0.06 | <0.01 | 0.00-0.01 | 11 |
| PLEUROPULMONARY BLASTOMA | <0.01 | 0.00-0.00 | 2 | NA | NE | – | NE | – | NE | – | NE | – | NE | – | 1 |
| PANCREATOBLASTOMA | <0.01 | 0.00-0.01 | 5 | NA | NE | – | NE | – | NE | – | NE | – | NE | – | 1 |
| OLFACTORY NEUROBLASTOMA | 0.03 | 0.03-0.04 | 71 | NA | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | 0.02 | 0.00-0.07 | <0.01 | 0.00-0.03 | 0.04 | 0.03-0.05 | 20 |
| ODONTOGENIC MALIGNANT TUMOURS | <0.01 | 0.00-0.01 | 12 | NA | NE | – | NE | – | NE | – | NE | – | NE | – | 4 |

**NE:** not estimable because 15 or less incident cases were observed **NA:** not applicable

# SURVIVAL

**EMBRYONAL TUMOURS.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **EMBRYONAL TUMOURS** | **710** |
| NEUROBLASTOMA AND GANGLIONEUROBLASTOMA | 298 |
| NEPHROBLASTOMA | 208 |
| RETINOBLASTOMA | 93 |
| HEPATOBLASTOMA | 33 |
| PLEUROPULMONARY BLASTOMA | 2 |
| PANCREATOBLASTOMA | 5 |
| OLFACTORY NEUROBLASTOMA | 64 |
| ODONTOGENIC MALIGNANT TUMOURS | 8 |

NE

NE

NE

**NE:** not estimable because 30 or less incident cases were observed

# PREVALENCE

**EMBRYONAL TUMOURS.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **EMBRYONAL TUMOURS** | **0.76** | **0.59-0.96** | **0.87** | **0.69-1.09** | **3.74** | **3.35-4.17** | **9.46** | **3.78-15.15** | **6 085** |
| NEUROBLASTOMA AND GANGLIONEUROBLASTOMA | 0.38 | 0.26-0.53 | 0.34 | 0.23-0.49 | 1.47 | 1.23-1.75 | 2.89 | 1.78-3.99 | 1 922 |
| NEPHROBLASTOMA | 0.17 | 0.10-0.28 | 0.24 | 0.15-0.37 | 1.16 | 0.94-1.41 | 2.36 | 1.41-3.31 | 1 638 |
| RETINOBLASTOMA | 0.08 | 0.03-0.16 | 0.09 | 0.04-0.18 | 0.53 | 0.39-0.70 | 0.70 | 0.40-1.00 | 543 |
| HEPATOBLASTOMA | 0.05 | 0.01-0.12 | 0.08 | 0.03-0.17 | 0.18 | 0.11-0.30 | 2.63 | 0.00-8.08 | 1 474 |
| PLEUROPULMONARY BLASTOMA | 0.01 | 0.00-0.06 | NE | – | 0.01 | 0.00-0.06 | 0.01 | 0.00-0.01 | 6 |
| PANCREATOBLASTOMA | NE | – | NE | – | 0.01 | 0.00-0.06 | 0.34 | 0.00-1.01 | 180 |
| OLFACTORY NEUROBLASTOMA | 0.05 | 0.01-0.12 | 0.11 | 0.06-0.21 | 0.36 | 0.24-0.51 | 0.47 | 0.30-0.64 | 276 |
| ODONTOGENIC MALIGNANT TUMOURS | 0.02 | 0.00-0.08 | NE | – | 0.02 | 0.00-0.08 | 0.06 | 0.00-0.15 | 47 |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

Embryonal cancers are a heterogeneous group of cancers. They occur mainly in children, with the exception of some very rare types (olfactory neuroblastoma, odontogenic tumours). Several studies indicate that the incidence of embryonal cancer is increasing.[1-3] The risk of developing embryonal cancer is higher in children with certain genetic syndromes or congenital malformations,[4-6] which account for no more than 5% of all cases. Environmental factors, such as ionising radiation, toxic therapies, herbicides, tobacco smoke, and diet, have been investigated as potential causes of embryonal cancers, particularly for exposure in the womb or at a very young age.[1,2,7] Changing foetal growth conditions related to increasing age at first pregnancy, exposure to sex hormones, and increasing birth weight have also been investigated.[7] Childhood cancers such as nephroblastoma and retinoblastoma have been intensely studied: their clinical and biological characteristics are well known and numerous clinical trials have been conducted by cooperative groups, resulting in the development of effective therapies. By contrast, hepatoblastoma, pulmonary blastoma, pancreatoblastoma, olfactory neuroblastoma, and odontogenic tumours are rare, even among childhood cancers;[8] nevertheless, they, too, have been investigated by cooperative research programs[9] either in the context of rare paediatric tumours as a group, or as individual entities.

The embryonal tumours considered in this monograph are:

- **neuroblastoma and ganglioneuroblastoma;**
- **nephroblastoma;**
- **retinoblastoma;**
- **hepatoblastoma;**
- **olfactory neuroblastoma;**
- **pleuropulmonary blastoma;**
- **pancreatoblastoma;**
- **odontogenic tumours.**

## NEUROBLASTOMA AND GANGLIONEUROBLASTOMA

### Incidence

About 100 new diagnoses are estimated in 2015 in Italy. Incidence is 10% more frequent in boys than girls (not significant). The majority of cases occurs in children aged <5 years, with an incidence rate (IR) of 2.9 per 100,000. The annual crude IR is 0.2 per 100,000, higher than the IR observed if the European RARECAREnet database (www.rarecarenet.eu) (0.1 per 100,000). In Europe, incidence in children significantly increased between 1978 and 1997.[10]

### Survival

Survival significantly drops after the first year of diagnosis, from 92% to 68% at 5 years. Data from EUROCARE-5[11] show 5-year relative survival (RS) to be excellent in infants (91%) and worse in children 1-14 years of age, between 52% and 59%. Actually, the majority of low-risk neuroblastomas are among infants, most likely for the propensity of neuroblastomas of infancy to undergo spontaneous regression. According to the RARECAREnet database, 5-year RS in children is slightly better in Italy than in Europe (71% vs. 79%). In Europe from 1999 to 2007 no progress was reported for neuroblastoma in children.[11]

### Prevalence

Around 2,000 patients were estimated to be living with a diagnosis of neuroblastoma and ganglioblastoma in 2010. Almost 50% of prevalent cases were diagnosed 15 or more years before the prevalence date.

## NEPHROBLASTOMA

### Incidence

In Italy, about 70 children and adults are diagnosed with nephroblastoma each year; most (99%) nephroblastomas are diagnosed in children aged less than 5 years. The highest IR is in the first 2 years of life. Thus, the annual IR per 100,000 decreases from 1.7 to 0.01 across ages.

Incidence is slightly higher among females than males. European childhood IRs significantly increased among girls and among children aged 5 or less years only.[10]

According to the RARECAREnet database (www.rarecarenet.eu), there are no differences between Italian and European rates.

### Survival

One- and 5-year RS are 97% and 89%, respectively. In Europe, 5-year RS is better in children (92%) than in adults (64%).[12] According to the RARECAREnet database, there are no differences in prognosis between Europe and Italy, for the period 2000-2007.

### Prevalence

Around 1,600 people were estimated to be living with a diagnosis of nephroblastoma in 2010. Almost 50% of prevalent cases were diagnosed 15 or more years before the prevalence date.

## RETINOBLASTOMA

### Incidence

In Italy, approximately 30 children are diagnosed with retinoblastoma each year, with almost 95% occurring before five years of age. The annual IR per 100,000 for the period 2000-2007 is 1.0, in children <5 years of age. There are no differences between genders. The overall IR is 0.05 per 100,000 in Italy and Europe, according to the RARECAREnet database. In Europe, age-standardized rates were higher in Northern and Southern Europe and in the UK and Ireland.[12]

### Survival

The outcome of children diagnosed with retinoblastoma in the period 2000-2007 is favourable, with 99% alive five years after diagnosis.

### Prevalence

Slightly more than 500 people were estimated to be living with a diagnosis of retinoblastoma in 2010.

## HEPATOBLASTOMA

### Incidence

About 10 new cases are diagnosed in Italy each year, all occurring in children. The peak is in those aged <5 years, with an IR of about 3 cases per million. Incidence is slightly higher among boys than girls. There are no differences between the Italian and European rates, according to the RARECAREnet database. The incidence of hepatoblastoma increased during the period 1975-1995 in the US, while no increment was reported for Europe.[10,13]

### Survival

Based on 33 cases, 1- and 5-year RS are 85% and 70%, respectively. According to the RARECAREnet database, RS is slightly lower in Italy than Europe (76% at 5 years). There was an impressive progress in Europe: 5-year RS increased from 59% (1995-1999) to 82% (2004-2007). Cooperative research programs, such as the International Childhood Liver Tumour Strategy Group (SIOPEL), on hepatoblastoma are responsible for the excellent progress.[9]

### Prevalence

Around 1,500 children were estimated to be living with a diagnosis of hepatoblastoma in Italy in 2010; most of them were diagnosed 15 or more years before the prevalence date.

## OLOFACTORY NEUROBLASTOMA

### Incidence

In Italy, about 20 cases of olfactory neuroblastoma are diagnosed each year.

### Survival

Based on 64 cases, 1- and 5-year RS are 86% and 76%, respectively. According to the RARECAREnet database, RS is slightly better in Italy than Europe (1- and 5-year RS: 81% and 64%, respectively).

### Prevalence

Around 300 persons were estimated to be living with a diagnosis of olfactory neuroblastoma in Italy in 2010.

## PLEUROPULMONARY BLASTOMA, PANCREATOBLASTOMA, AND ODONTOGENIC TUMOURS

These tumours are so rare that in 11 years (2000-2010) in the AIRTUM dataset only 2, 5, and 12 cases, respectively, were observed. In the RARECAREnet database, in the period 2000-2007, there were 9, 39, and 69 cases. It is not possible to provide estimates of survival for these tumours on the basis of the Italian data. According to the RARECAREnet database, 5-year RS for pancreatoblastoma is 34% (based on 35 cases) and for odontogenic tumours it is 62% (based on 69 cases).

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# SARCOMAS

**100%**
**OF SARCOMAS ARE RARE**

## INCIDENCE

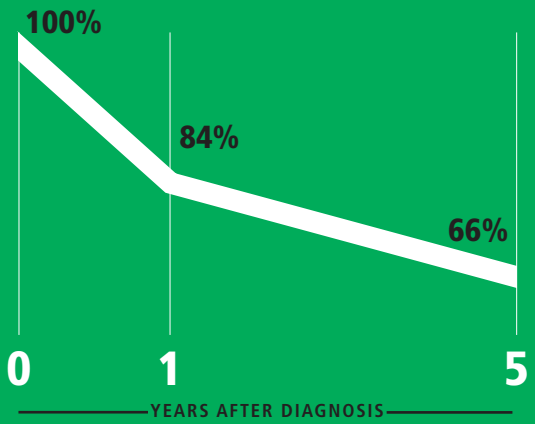
**5 883**
ESTIMATED NEW CASES
ITALY, 2015

- **4 072** SOFT TISSUE SARCOMAS
- **499** BONE SARCOMAS
- **386** GASTROINTESTINAL STROMAL TUMOURS
- **927** KAPOSI SARCOMA

## PREVALENCE

**68 931**
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# INCIDENCE

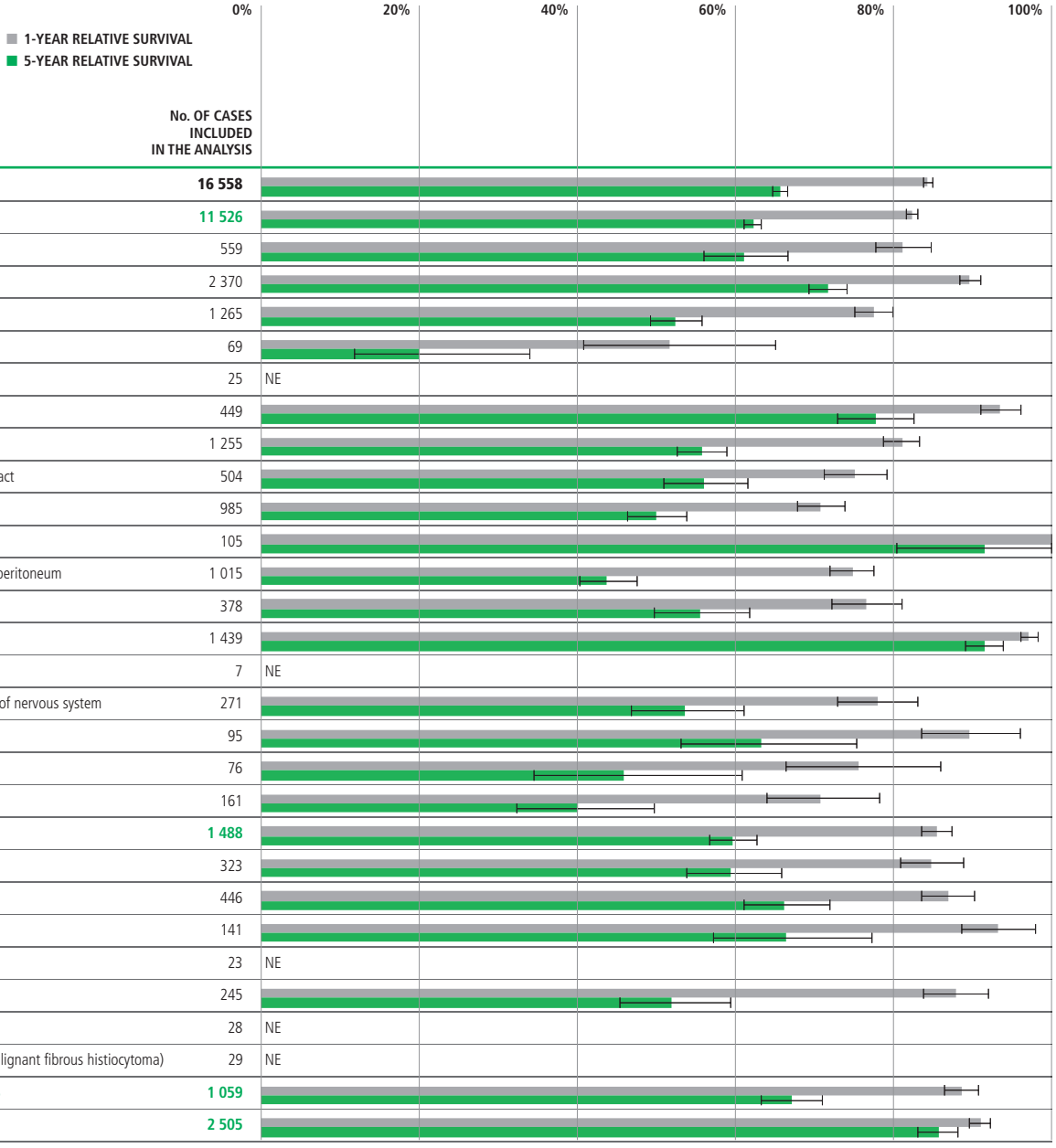
**SARCOMAS.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **SARCOMAS** | **9.03** | **8.90-9.15** | **20 019** | **100%** | **9.54** | **9.35-9.72** | **8.55** | **8.38-8.72** | **4.75** | **4.65-4.87** | **12.72** | **12.30-13.15** | **21.37** | **20.94-21.81** | **5 883** |
| **SOFT TISSUE SARCOMAS** | **6.27** | **6.17-6.38** | **13 914** | **NA** | **5.95** | **5.80-6.09** | **6.58** | **6.43-6.73** | **3.49** | **3.40-3.59** | **9.23** | **8.87-9.60** | **13.97** | **13.62-14.33** | **4 072** |
| Soft tissue sarcomas of head and neck | 0.31 | 0.29-0.33 | 683 | | 0.41 | 0.37-0.45 | 0.21 | 0.19-0.24 | 0.13 | 0.12-0.15 | 0.39 | 0.32-0.47 | 0.85 | 0.77-0.94 | 206 |
| Soft tissue sarcomas of limbs | 1.27 | 1.23-1.32 | 2 823 | | 1.38 | 1.31-1.45 | 1.17 | 1.11-1.24 | 0.67 | 0.63-0.71 | 1.74 | 1.58-1.90 | 3.05 | 2.88-3.21 | 827 |
| Soft tissue sarcomas of superficial trunk | 0.69 | 0.65-0.72 | 1 526 | | 0.81 | 0.76-0.86 | 0.57 | 0.53-0.62 | 0.33 | 0.30-0.36 | 1.09 | 0.97-1.22 | 1.68 | 1.56-1.81 | 447 |
| Soft tissue sarcomas of mediastinum | 0.04 | 0.03-0.04 | 79 | | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | 0.02 | 0.01-0.02 | 0.07 | 0.04-0.11 | 0.08 | 0.06-0.11 | 23 |
| Soft tissue sarcomas of heart | 0.01 | 0.01-0.02 | 32 | | 0.01 | 0.01-0.02 | 0.02 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.02 | 0.01-0.05 | 0.03 | 0.02-0.05 | 9 |
| Soft tissue sarcomas of breast | 0.24 | 0.22-0.27 | 543 | | <0.01 | 0.00-0.02 | 0.47 | 0.43-0.51 | 0.17 | 0.15-0.19 | 0.38 | 0.31-0.46 | 0.42 | 0.36-0.48 | 160 |
| Soft tissue sarcomas of uterus | 0.69 | 0.65-0.72 | 1 525 | | 0.00 | – | 1.33 | 1.27-1.40 | 0.50 | 0.46-0.54 | 1.21 | 1.09-1.35 | 1.01 | 0.92-1.11 | 447 |
| Other soft tissue sarcomas of genitourinary tract | 0.27 | 0.25-0.29 | 596 | | 0.26 | 0.23-0.29 | 0.28 | 0.25-0.31 | 0.11 | 0.09-0.13 | 0.43 | 0.35-0.51 | 0.71 | 0.64-0.80 | 176 |
| Soft tissue sarcomas of viscera | 0.53 | 0.50-0.56 | 1 183 | | 0.62 | 0.57-0.67 | 0.45 | 0.42-0.49 | 0.17 | 0.15-0.20 | 0.84 | 0.73-0.96 | 1.57 | 1.46-1.70 | 350 |
| Soft tissue sarcomas of paratestis | 0.05 | 0.04-0.06 | 120 | | 0.11 | 0.09-0.13 | 0.00 | – | 0.02 | 0.01-0.02 | 0.10 | 0.07-0.14 | 0.16 | 0.12-0.20 | 37 |
| Soft tissue sarcomas of retroperitoneum and peritoneum | 0.54 | 0.51-0.57 | 1 198 | | 0.53 | 0.49-0.58 | 0.55 | 0.50-0.59 | 0.19 | 0.17-0.21 | 1.08 | 0.96-1.21 | 1.40 | 1.29-1.52 | 349 |
| Soft tissue sarcomas of pelvis | 0.21 | 0.19-0.23 | 463 | | 0.22 | 0.20-0.25 | 0.20 | 0.17-0.22 | 0.11 | 0.10-0.13 | 0.35 | 0.28-0.43 | 0.45 | 0.39-0.52 | 137 |
| Soft tissue sarcomas of skin | 0.78 | 0.74-0.82 | 1 731 | | 0.87 | 0.82-0.93 | 0.69 | 0.65-0.74 | 0.58 | 0.54-0.62 | 0.75 | 0.65-0.86 | 1.48 | 1.37-1.60 | 502 |
| Soft tissue sarcomas of paraorbit | <0.01 | 0.00-0.01 | 8 | | NE | – | NE | – | NE | – | NE | – | NE | – | 2 |
| Soft tissue sarcomas of brain and other parts of nervous system | 0.14 | 0.13-0.16 | 318 | | 0.16 | 0.14-0.19 | 0.12 | 0.10-0.15 | 0.10 | 0.08-0.11 | 0.22 | 0.17-0.28 | 0.26 | 0.21-0.31 | 91 |
| Embryonal rhabdomyosarcoma of soft tissue | 0.05 | 0.04-0.06 | 116 | | 0.06 | 0.05-0.08 | 0.04 | 0.03-0.05 | 0.07 | 0.06-0.09 | <0.01 | 0.00-0.03 | <0.01 | 0.00-0.02 | 32 |
| Alveolar rhabdomyosarcoma of soft tissue | 0.04 | 0.03-0.05 | 87 | | 0.04 | 0.03-0.05 | 0.04 | 0.03-0.05 | 0.05 | 0.04-0.06 | 0.03 | 0.01-0.06 | 0.03 | 0.01-0.04 | 25 |
| Ewing's sarcoma of soft tissue | 0.08 | 0.07-0.09 | 179 | | 0.09 | 0.07-0.11 | 0.08 | 0.06-0.09 | 0.08 | 0.06-0.09 | 0.10 | 0.06-0.14 | 0.08 | 0.06-0.11 | 49 |
| **BONE SARCOMAS** | **0.80** | **0.76-0.84** | **1 770** | **NA** | **0.93** | **0.87-0.99** | **0.67** | **0.63-0.72** | **0.67** | **0.63-0.72** | **0.88** | **0.78-1.00** | **1.17** | **1.07-1.28** | **499** |
| Osteogenic sarcoma | 0.17 | 0.16-0.19 | 383 | | 0.19 | 0.17-0.22 | 0.15 | 0.13-0.18 | 0.18 | 0.16-0.20 | 0.12 | 0.08-0.17 | 0.18 | 0.14-0.23 | 106 |
| Chondrogenic sarcomas | 0.24 | 0.22-0.26 | 536 | | 0.27 | 0.24-0.30 | 0.22 | 0.19-0.25 | 0.14 | 0.12-0.16 | 0.41 | 0.34-0.49 | 0.49 | 0.43-0.56 | 153 |
| Notochordal sarcomas, chordoma | 0.08 | 0.07-0.09 | 170 | | 0.10 | 0.08-0.12 | 0.05 | 0.04-0.07 | 0.03 | 0.03-0.04 | 0.13 | 0.09-0.18 | 0.19 | 0.15-0.24 | 49 |
| Vascular sarcomas | 0.01 | 0.01-0.02 | 28 | | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.01 | 0.01 | 0.00-0.04 | 0.03 | 0.01-0.04 | 8 |
| Ewing's sarcoma | 0.12 | 0.11-0.14 | 277 | | 0.16 | 0.14-0.19 | 0.09 | 0.07-0.11 | 0.17 | 0.15-0.20 | 0.03 | 0.01-0.06 | 0.02 | 0.01-0.03 | 74 |
| Epithelial tumours, adamantinoma | 0.01 | 0.01-0.02 | 32 | | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | 0.01 | 0.01-0.02 | 0.01 | 0.00-0.04 | 0.02 | 0.01-0.04 | 9 |
| Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma) | 0.02 | 0.01-0.02 | 36 | | 0.01 | 0.01-0.02 | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | 0.03 | 0.01-0.05 | 0.03 | 0.02-0.05 | 10 |
| **GASTROINTESTINAL STROMAL TUMOURS** | **0.59** | **0.56-0.62** | **1 307** | **NA** | **0.66** | **0.61-0.71** | **0.53** | **0.48-0.57** | **0.17** | **0.15-0.20** | **1.12** | **1.00-1.25** | **1.68** | **1.56-1.81** | **386** |
| **KAPOSI SARCOMA** | **1.37** | **1.32-1.42** | **3 028** | **NA** | **2.00** | **1.92-2.09** | **0.77** | **0.72-0.82** | **0.42** | **0.38-0.45** | **1.48** | **1.34-1.63** | **4.54** | **4.35-4.75** | **927** |

**NE:** not estimable because 15 or less incident cases were observed **NA:** not applicable

# SURVIVAL

**SARCOMAS.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **SARCOMAS** | **16 558** |
| **SOFT TISSUE SARCOMAS** | **11 526** |
| Soft tissue sarcomas of head and neck | 559 |
| Soft tissue sarcomas of limbs | 2 370 |
| Soft tissue sarcomas of superficial trunk | 1 265 |
| Soft tissue sarcomas of mediastinum | 69 |
| Soft tissue sarcomas of heart | 25 |
| Soft tissue sarcomas of breast | 449 |
| Soft tissue sarcomas of uterus | 1 255 |
| Other soft tissue sarcomas of genitourinary tract | 504 |
| Soft tissue sarcomas of viscera | 985 |
| Soft tissue sarcomas of paratestis | 105 |
| Soft tissue sarcomas of retroperitoneum and peritoneum | 1 015 |
| Soft tissue sarcomas of pelvis | 378 |
| Soft tissue sarcomas of skin | 1 439 |
| Soft tissue sarcomas of paraorbit | 7 |
| Soft tissue sarcomas of brain and other parts of nervous system | 271 |
| Embryonal rhabdomyosarcoma of soft tissue | 95 |
| Alveolar rhabdomyosarcoma of soft tissue | 76 |
| Ewing's sarcoma of soft tissue | 161 |
| **BONE SARCOMAS** | **1 488** |
| Osteogenic sarcoma | 323 |
| Chondrogenic sarcomas | 446 |
| Notochordal sarcomas, chordoma | 141 |
| Vascular sarcomas | 23 |
| Ewing's sarcoma | 245 |
| Epithelial tumours, adamantinoma | 28 |
| Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma) | 29 |
| **GASTROINTESTINAL STROMAL TUMOURS** | **1 059** |
| **KAPOSI SARCOMA** | **2 505** |

NE

**NE:** not estimable because 30 or less incident cases were observed

# PREVALENCE

**SARCOMAS.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **SARCOMAS** | **17.34** | **16.48-18.24** | **18.76** | **17.86-19.70** | **71.31** | **69.55-73.11** | **118.50** | **114.87-122.14** | **68 931** |
| **SOFT TISSUE SARCOMAS** | **12.67** | **11.93-13.44** | **12.52** | **11.78-13.28** | **49.46** | **47.99-50.96** | **85.25** | **82.67-87.84** | **49 580** |
| Soft tissue sarcomas of head and neck | 0.68 | 0.52-0.87 | 0.56 | 0.41-0.74 | 2.42 | 2.11-2.77 | 4.04 | 3.49-4.59 | 2 387 |
| Soft tissue sarcomas of limbs | 2.69 | 2.35-3.05 | 3.35 | 2.98-3.76 | 11.54 | 10.83-12.27 | 18.55 | 17.40-19.71 | 10 719 |
| Soft tissue sarcomas of superficial trunk | 1.50 | 1.26-1.78 | 1.20 | 0.99-1.46 | 4.91 | 4.46-5.40 | 9.20 | 8.31-10.09 | 5 368 |
| Soft tissue sarcomas of mediastinum | 0.03 | 0.01-0.10 | 0.03 | 0.01-0.10 | 0.10 | 0.05-0.20 | 0.28 | 0.08-0.49 | 161 |
| Soft tissue sarcomas of heart | 0.02 | 0.00-0.08 | 0.01 | 0.00-0.06 | 0.06 | 0.02-0.13 | 0.23 | 0.00-0.46 | 130 |
| Soft tissue sarcomas of breast | 0.57 | 0.42-0.75 | 0.63 | 0.48-0.82 | 2.86 | 2.52-3.24 | 4.59 | 3.99-5.18 | 2 681 |
| Soft tissue sarcomas of uterus | 1.15 | 0.93-1.40 | 1.28 | 1.05-1.54 | 4.90 | 4.45-5.39 | 8.70 | 7.72-9.69 | 5 096 |
| Other soft tissue sarcomas of genitourinary tract | 0.50 | 0.37-0.68 | 0.41 | 0.29-0.57 | 1.73 | 1.47-2.03 | 3.22 | 2.70-3.74 | 1 882 |
| Soft tissue sarcomas of viscera | 0.90 | 0.71-1.12 | 0.86 | 0.68-1.08 | 3.10 | 2.74-3.50 | 4.09 | 3.60-4.58 | 2 372 |
| Soft tissue sarcomas of paratestis | 0.07 | 0.03-0.15 | 0.15 | 0.08-0.26 | 0.59 | 0.44-0.77 | 0.68 | 0.49-0.87 | 384 |
| Soft tissue sarcomas of retroperitoneum and peritoneum | 1.08 | 0.87-1.32 | 0.85 | 0.66-1.06 | 3.16 | 2.80-3.56 | 3.79 | 3.34-4.25 | 2 185 |
| Soft tissue sarcomas of pelvis | 0.34 | 0.23-0.49 | 0.36 | 0.24-0.51 | 1.35 | 1.11-1.61 | 3.13 | 2.40-3.86 | 1 820 |
| Soft tissue sarcomas of skin | 2.07 | 1.78-2.39 | 2.05 | 1.76-2.37 | 9.00 | 8.38-9.65 | 15.36 | 14.20-16.53 | 8 901 |
| Soft tissue sarcomas of paraorbit | 0.02 | 0.00-0.08 | 0.01 | 0.00-0.06 | 0.07 | 0.03-0.15 | 0.35 | 0.03-0.67 | 206 |
| Soft tissue sarcomas of brain and other parts of nervous system | 0.25 | 0.16-0.38 | 0.24 | 0.15-0.37 | 0.98 | 0.78-1.21 | 1.93 | 1.51-2.35 | 1 136 |
| Embryonal rhabdomyosarcoma of soft tissue | 0.10 | 0.05-0.20 | 0.07 | 0.03-0.15 | 0.41 | 0.28-0.56 | 1.79 | 0.57-3.02 | 1 026 |
| Alveolar rhabdomyosarcoma of soft tissue | 0.11 | 0.06-0.21 | 0.05 | 0.01-0.12 | 0.23 | 0.14-0.35 | 0.37 | 0.18-0.56 | 256 |
| Ewing's sarcoma of soft tissue | 0.21 | 0.12-0.33 | 0.10 | 0.05-0.20 | 0.46 | 0.33-0.63 | 1.15 | 0.70-1.59 | 672 |
| **BONE SARCOMAS** | **1.20** | **0.98-1.46** | **1.69** | **1.42-1.98** | **6.39** | **5.87-6.95** | **11.41** | **10.41-12.41** | **6 639** |
| Osteogenic sarcoma | 0.23 | 0.14-0.35 | 0.29 | 0.19-0.42 | 1.32 | 1.09-1.58 | 3.41 | 2.67-4.16 | 1 990 |
| Chondrogenic sarcomas | 0.41 | 0.29-0.57 | 0.62 | 0.46-0.81 | 2.27 | 1.96-2.61 | 4.42 | 3.78-5.05 | 2 570 |
| Notochordal sarcomas, chordoma | 0.11 | 0.06-0.21 | 0.23 | 0.14-0.35 | 0.64 | 0.48-0.83 | 0.75 | 0.55-0.94 | 428 |
| Vascular sarcomas | 0.02 | 0.00-0.08 | NE | – | 0.10 | 0.05-0.20 | 0.19 | 0.06-0.31 | 102 |
| Ewing's sarcoma | 0.23 | 0.14-0.35 | 0.31 | 0.20-0.45 | 1.08 | 0.87-1.32 | 2.13 | 1.30-2.96 | 1 284 |
| Epithelial tumours, adamantinoma | 0.01 | 0.00-0.06 | 0.02 | 0.00-0.08 | 0.09 | 0.04-0.18 | 0.15 | 0.04-0.25 | 83 |
| Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma) | 0.02 | 0.00-0.08 | 0.02 | 0.00-0.08 | 0.14 | 0.08-0.25 | 0.29 | 0.13-0.45 | 158 |
| **GASTROINTESTINAL STROMAL TUMOURS** | **1.20** | **0.98-1.45** | **1.62** | **1.36-1.91** | **3.75** | **3.36-4.18** | **4.83** | **4.26-5.39** | **2 788** |
| **KAPOSI SARCOMA** | **2.28** | **1.98-2.63** | **2.96** | **2.60-3.34** | **11.84** | **11.12-12.58** | **17.01** | **14.73-19.30** | **9 924** |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE

Sarcoma is a malignant neoplasm arising from mesenchymal cells; it includes a heterogeneous group of tumours. It can be split up into dozens of histological categories, and it can occur in virtually any anatomic site. This gives rise to a huge number of possible combinations of histology and primary site which are of clinical importance. The anatomic site influences the therapeutic choice, in particular making surgery more or less viable or even impossible, but histology also influences prognosis and responsiveness to chemotherapy. It is important to consider the primary site as well as the histologic type when presenting soft tissue sarcomas (STSs) statistics.[1] These characteristics have made it almost impossible up now to have reliable statistics on incidence, mortality, prevalence, and survival per single type of sarcoma in each site even at the national level. In this study, for the first time we have the opportunity to estimate reliable incidence, prevalence, and survival statistics even for very rare sarcomas.

In this monograph we present:

- **soft tissue sarcomas** (STS) of organ-specific sites (head and neck, limbs, superficial trunk, mediastinum, heart, breast, uterus, genitourinary tract, viscera, paratestis, retroperitoneum and peritoneum, pelvis, skin, paraorbit, brain and other parts of the nervous system, embryonal rhabdomyosarcoma of soft tissue, alveolar rhabdomyosarcoma of soft tissue, Ewing's sarcoma of soft tissue);
- **bone sarcomas** (osteogenic and chondrogenic sarcomas, chordoma, vascular sarcomas, Ewing's sarcoma of bone, adamantinoma, other high grade sarcomas);
- **gastrointestinal stromal tumours** (GIST);
- **Kaposi sarcoma** (KS).

The latter is described in the group of sarcomas even if it is not properly a sarcoma.

We adopted the same classification used in the RARECARE project.[2] This classification renders the clinical importance of both anatomic site of origin and histology in these tumours.[2]

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**STSs** represent less than 1% of malignant tumours and show a broad range of differentiation according to the anatomic site they occur in: smooth muscle (leiomyosarcoma), adipocyte (liposarcoma), striated muscle (rhabdomyosarcoma), endothelium (angiosarcoma), or fibroblast (dermatofibrosarcoma).[3] In the last two decades, cytogenetic findings have provided a valuable and reproducible tool for STS classification. The use of the molecular classification makes it possible to report variation in incidence patterns of STS by histologic type, supporting the notion that these tumours are aetiologically distinct and that they should be considered separately in analytic studies.

Little is known about their aetiology, however few risk factors are known: ionising radiation, especially in the form of radiotherapy for a previous cancer, environmental factors (e.g., herbicides, dioxins), immunodeficiency (e.g., AIDS), and viral infections (Epstein Barr virus, human herpes virus type 8).[4-8] Several heritable syndromes are associated with increased risk of sarcomas. Those which account for the largest number of cases are neurofibromatosis 1 (nerve sheath tumours), heritable retinoblastoma (osteosarcoma and various STSs), and Li-Fraumeni syndrome (osteosarcoma and STS).[9]

**KS** is a virus-related malignancy which most frequently arises in the skin, though mucosal sites, lymph nodes, and viscera can also be involved. Infection with Kaposi sarcoma herpes virus (KSHV, previously known as human herpes virus type 8, HHV-8) is required for the development of KS. Historically, KS occurred as two clinically and epidemiologically distinct subtypes, classic and endemic. Classic KS is predominantly a disease of the elderly of Mediterranean or Middle Eastern origin without apparent immunosuppression; never smoking, diabetes, and use of oral corticosteroids are risk factors. Endemic KS occurs almost entirely in sub-Saharan Africa and it is difficult to disentangle endemic KS and HIV-related KS.[10]

Strong geographic variations have been observed for sarcoma survival among European countries. These differences are usually interpreted as differences in accessibility to effective care. In particular, the expertise of the centre has been recognised to be important for the outcome.[2] Sarcoma clinical management should be carried out in centres of expertise for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. This centralised referral should be pursued as early as the time of the clinical suspicion of sarcoma.

This is the first time that data on all sarcomas are shown separately and by site. Usually cancer statistics (ITACAN, GLOBOCAN, NORDCAN, SEER) give data only by site, and tumours of soft tissue and bone represent the best proxy to describe soft tissue and bone sarcomas.

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

**STSs** are the most frequent (70%) sarcomas; altogether, they are slightly higher in females than in males, but this is due to the relatively high incidence rate of sarcomas of the uterus and breast. In the other non-gender specific sites, sarcomas are slightly higher in males than females. The most frequent sites are limbs, followed by skin, uterus, and superficial trunk. **Bone sarcomas and GIST** are 9% and 7% of all sarcomas, respectively (incidence table, p. 85). Regarding **GIST**, the AIRTUM incidence rate (IR) is of 0.6 per 100,000 (see table p. 85). This result is close to the IR of 0.7 per 100,000 observed in an Italian population-based study based on a pathology review,[11] but still slightly below the IR (range of 1.0-1.5 per 100,000) reported in other population-based studies based on pathological reviews and performed in various European countries.[2] The IR increases with age for most STSs. The main exceptions are: embryonal rhabdomyosarcoma, which is the most frequent histology at age 0-14, with an IR of 0.3 per 100,000 and occurs mainly in the first 4 years of life, and alveolar rhabdomyosarcoma, which also occurs mainly at ages 0-14; soft tissue sarcomas of uterus have a peak at ages 45-49, Ewing's sarcomas of soft tissue shows an almost flat incidence curve with age (data not shown). The overall age incidence pattern for **bone sarcomas** is bimodal, with peaks at ages 10-19 and 65+. Of the three most frequent subtypes, osteosarcoma and Ewing's sarcoma of the bone have their highest incidence at ages 10-19 and incidence of chondrogenic sarcomas is greatest at age 65+.

**KS** is relatively frequent in Italy, with an IR of 1.4 per 100,000. The relatively high incidence of classic KS in Italy is known[12] and is confirmed even in our data, which show the highest IR of KS (4.5 per 100,000) in those aged 65+ (see table p. 85).

### Survival

Five-year relative survival (RS) is 62% for **STSs**, 60% for bone sarcomas, 67% for GIST. STSs of paratestis and skin (mainly dermatofibrosarcoma protuberans) have the highest survival rate (92% and 91%, respectively), while STSs of mediastinum have survival rates of 20%. Five-year RS from STSs of the uterus is 56% (survival figure, p. 86). In Europe 5-year RS from STSs of the uterus was 49% overall, but it was 65% for tumours of stromal histology (mainly endometrial stromal tumour) and 42% for other types, predominantly leiomyosarcoma and sarcoma NOS (not otherwise specified).[2]

In Italy, among **bone sarcomas**, survival rate is highest for chondrogenic sarcomas and chordoma (66%). The number of cases is too limited in the AIRTUM database to estimate 5-year RS of the rare adamantinoma and vascular sarcomas; however, according to previous European published data, the 5-year RS of these rare sarcomas was 83% and 34%, respectively.[2] There is general agreement that treatment of sarcomas should be concentrated in specialist centres with multidisciplinary expertise and knowledge of the disease, though the effect of such a policy on survival has seldom been evaluated. As cancer registries come to collect more information on stage and treatment and place of treatment, the evaluation of such a policy should become a priority.

For **GIST**, 5-year RS (67%; see figure p. 86) is similar to previous published data at European level,[2] thanks to the introduction of molecularly targeted therapies. It will be interesting to look at epidemiological data on GIST, when they become available from cancer registries in the next few years, to see how a major breakthrough involving a targeted agent can translate into prognostic improvements on a population basis in different settings. An important challenge for cancer registries will be to develop the ability to track, at the population level, the highly selective improvements resulting from this kind of "histology-driven" or "molecularly-driven" therapy, affecting single histologies or clinical presentations with low numbers of eligible patients. A proper pathologic diagnosis on a population basis would be crucial in this regard, and it is well known that this is still a challenge.

Five-year RS of **KS** (86%; see figure p. 86) is slightly higher in Italy than in Europe, but similar to that observed in Southern Europe.[10] Higher survival in Southern Europe (including Italy) may partially reflect predominantly less aggressive disease in patients with classic KS and greater clinical experience as a consequence of the higher incidence of both major subtypes of KS.[10]

### Prevalence

About 69,000 persons were estimated to be alive in 2010 with a past diagnosis of sarcoma in Italy. The most prevalent sarcomas were **STSs** (about 50,000 cases), followed by **bone sarcomas** (about 7,000 cases). The distribution of prevalence by time since diagnosis was fairly similar for the different sarcomas. We estimated about 10,000 prevalent cases of **KS**, which is slightly higher than the estimates published in the AIRTUM monograph on prevalence.[13] This is due to the method used to estimate complete prevalence, which leads to an overestimation of tumours, such as KS, which have different incidence across Italian areas (see «Materials and methods», pp. 14-21).

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# NEUROENDOCRINE TUMOURS

**100%**
**OF NEUROENDOCRINE TUMOURS ARE RARE**

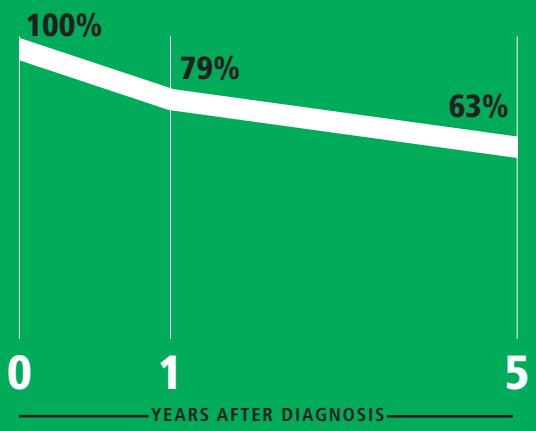
## INCIDENCE

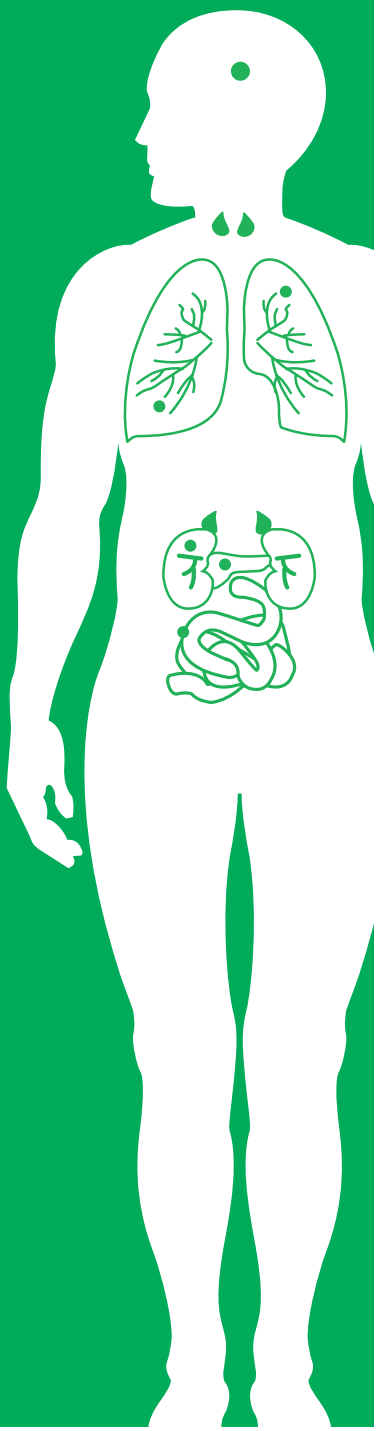
**2 697**
ESTIMATED NEW CASES
ITALY, 2015

## PREVALENCE

**23 937**
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL

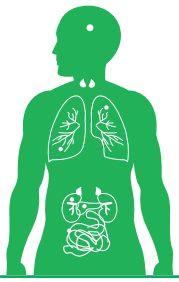


SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# NEUROENDOCRINE TUMOURS

# INCIDENCE



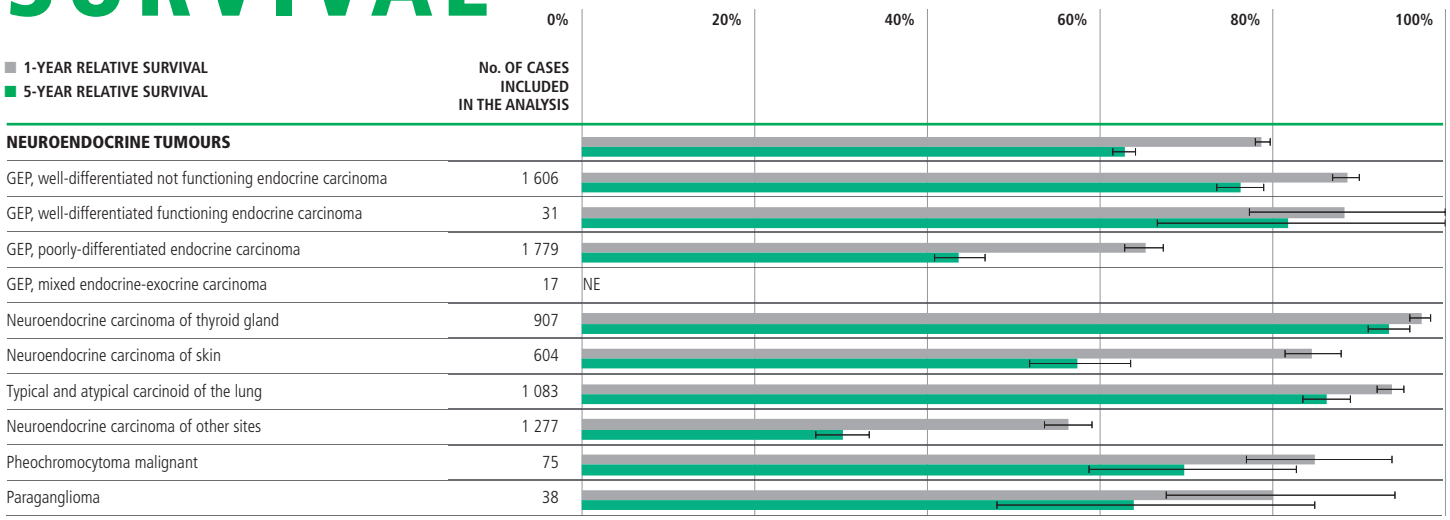
**NEUROENDOCRINE TUMOURS.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **NEUROENDOCRINE TUMOURS** | **4.15** | **4.06-4.23** | **9 196** | **NA** | **4.31** | **4.18-4.43** | **4.00** | **3.88-4.12** | **1.49** | **1.42-1.55** | **7.37** | **7.05-7.70** | **11.27** | **10.95-11.58** | **2 697** |
| GEP, well-differentiated not functioning endocrine carcinoma | 0.89 | 0.85-0.93 | 1 970 | | 0.97 | 0.91-1.03 | 0.81 | 0.76-0.87 | 0.34 | 0.31-0.37 | 1.58 | 1.44-1.74 | 2.34 | 2.20-2.49 | 576 |
| GEP, well-differentiated functioning endocrine carcinoma | 0.02 | 0.01-0.03 | 41 | | 0.02 | 0.01-0.03 | 0.02 | 0.01-0.03 | <0.01 | 0.01-0.02 | 0.06 | 0.03-0.09 | 0.03 | 0.01-0.05 | 12 |
| GEP, poorly-differentiated endocrine carcinoma | 1.01 | 0.97-1.05 | 2 233 | | 1.20 | 1.13-1.26 | 0.83 | 0.78-0.89 | 0.31 | 0.28-0.34 | 1.87 | 1.72-2.04 | 2.85 | 2.69-3.01 | 655 |
| GEP, mixed endocrine-exocrine carcinoma | <0.01 | 0.00-0.01 | 17 | | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.02 | <0.01 | 0.00-0.01 | <0.01 | 0.00-0.03 | 0.01 | 0.01-0.03 | 5 |
| Neuroendocrine carcinoma of thyroid gland | 0.51 | 0.48-0.54 | 1 125 | | 0.38 | 0.34-0.42 | 0.63 | 0.58-0.67 | 0.30 | 0.27-0.33 | 1.05 | 0.93-1.18 | 0.88 | 0.80-0.97 | 320 |
| Neuroendocrine carcinoma of skin | 0.34 | 0.32-0.37 | 759 | | 0.33 | 0.30-0.37 | 0.35 | 0.32-0.39 | 0.03 | 0.02-0.04 | 0.34 | 0.28-0.42 | 1.42 | 1.31-1.54 | 238 |
| Typical and atypical carcinoid of the lung | 0.60 | 0.57-0.63 | 1 328 | | 0.56 | 0.51-0.60 | 0.64 | 0.59-0.68 | 0.27 | 0.24-0.30 | 1.17 | 1.05-1.31 | 1.37 | 1.26-1.49 | 378 |
| Neuroendocrine carcinoma of other sites | 0.71 | 0.68-0.75 | 1 585 | | 0.77 | 0.72-0.83 | 0.66 | 0.61-0.71 | 0.18 | 0.16-0.21 | 1.16 | 1.03-1.29 | 2.26 | 2.12-2.41 | 474 |
| Pheochromocytoma, malignant | 0.04 | 0.03-0.05 | 94 | | 0.04 | 0.03-0.06 | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | 0.08 | 0.05-0.12 | 0.07 | 0.05-0.10 | 27 |
| Paraganglioma | 0.02 | 0.01-0.03 | 44 | | 0.02 | 0.02-0.03 | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | 0.05 | 0.03-0.08 | 0.03 | 0.02-0.05 | 13 |

**NA:** not applicable **GEP:** gastroenteropancreatic tract

# SURVIVAL

**NEUROENDOCRINE TUMOURS.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **NEUROENDOCRINE TUMOURS** | |
| GEP, well-differentiated not functioning endocrine carcinoma | 1 606 |
| GEP, well-differentiated functioning endocrine carcinoma | 31 |
| GEP, poorly-differentiated endocrine carcinoma | 1 779 |
| GEP, mixed endocrine-exocrine carcinoma | 17 |
| Neuroendocrine carcinoma of thyroid gland | 907 |
| Neuroendocrine carcinoma of skin | 604 |
| Typical and atypical carcinoid of the lung | 1 083 |
| Neuroendocrine carcinoma of other sites | 1 277 |
| Pheochromocytoma malignant | 75 |
| Paraganglioma | 38 |

NE: not estimable

**NE:** not estimable because 30 or less incident cases were observed **GEP:** gastroenteropancreatic tract

# PREVALENCE

**NEUROENDOCRINE TUMOURS.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **NEUROENDOCRINE TUMOURS** | **7.38** | **6.82-7.97** | **7.65** | **7.08-8.25** | **28.18** | **27.07-29.31** | **40.73** | **38.95-42.50** | **23 937** |
| GEP, well-differentiated not functioning endocrine carcinoma | 1.70 | 1.43-1.99 | 2.08 | 1.78-2.40 | 8.54 | 7.94-9.18 | 12.89 | 11.96-13.82 | 7 427 |
| GEP, well-differentiated functioning endocrine carcinoma | NE | – | 0.03 | 0.01-0.10 | 0.20 | 0.11-0.31 | 0.33 | 0.16-0.49 | 195 |
| GEP, poorly-differentiated endocrine carcinoma | 1.35 | 1.11-1.61 | 1.30 | 1.07-1.56 | 3.43 | 3.05-3.84 | 3.49 | 3.09-3.89 | 2 140 |
| GEP, mixed endocrine-exocrine carcinoma | 0.02 | 0.00-0.08 | 0.01 | 0.00-0.06 | 0.05 | 0.01-0.12 | 0.09 | 0.01-0.18 | 51 |
| Neuroendocrine carcinoma of thyroid gland | 1.24 | 1.01-1.49 | 1.48 | 1.24-1.76 | 4.93 | 4.47-5.42 | 9.45 | 8.51-10.39 | 5 455 |
| Neuroendocrine carcinoma of skin | 0.76 | 0.59-0.96 | 0.48 | 0.35-0.65 | 1.90 | 1.62-2.21 | 2.34 | 1.98-2.70 | 1 369 |
| Typical and atypical carcinoid of the lung | 1.33 | 1.10-1.60 | 1.38 | 1.14-1.65 | 6.07 | 5.57-6.61 | 8.34 | 7.62-9.06 | 4 995 |
| Neuroendocrine carcinoma of other sites | 0.96 | 0.77-1.19 | 0.76 | 0.59-0.96 | 2.77 | 2.43-3.14 | 3.16 | 2.76-3.56 | 1 932 |
| Pheochromocytoma, malignant | 0.02 | 0.00-0.08 | 0.08 | 0.03-0.17 | 0.28 | 0.18-0.41 | 0.47 | 0.28-0.66 | 275 |
| Paraganglioma | NE | – | 0.05 | 0.01-0.12 | 0.09 | 0.04-0.18 | 0.17 | 0.05-0.28 | 98 |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE **GEP:** gastroenteropancreatic tract

The list of rare cancers proposed by the European RARECARE project (www.rarecare.eu) is based on a combination of ICD-O-3 morphologies and topographies. This is appropriate for all rare cancers and especially for neuroendocrine tumours. Morphologic analyses, immunohistochemical studies, and, more recently, molecular studies have attempted to classify this family of neoplasms. These classifications properly group neuroendocrine tumours (NETs) according to grading, but diagnosis, treatment, and prognosis also depend on the site of origin. Thus, in addition to grading, the site of origin should always be considered to understand the different behaviour, clinical presentations, and prognosis of these tumours and to properly describe them.

The NET grouping proposed by RARECARE combines morphologies (as a proxy of the grading) and topographies as follows:

- gastroenteropancreatic (GEP), well-differentiated non functioning endocrine carcinoma;
- GEP, well-differentiated functioning endocrine carcinoma;
- GEP, poorly differentiated endocrine carcinoma;
- GEP, mixed endocrine-exocrine carcinoma;
- neuroendocrine carcinoma of thyroid gland;
- neuroendocrine carcinoma of skin;
- typical and atypical carcinoid of the lung;
- neuroendocrine carcinoma of other sites;
- malignant pheochromocytoma;
- paraganglioma.

Poorly differentiated endocrine carcinoma of the lung is not considered in this monograph, because it is not considered rare by the RARECARE cancer list (since its incidence is >6 per 100,000 at EU level).

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**NETs** are neoplasms that originate from the diffuse neuroendocrine cell system which is in many different organs, sharing common expression of neuroendocrine markers and characterised by amine, neuropeptide, or hormone production. NETs are rare tumours and aetiological factors are unknown, apart from familial syndromes like multiple endocrine neoplasia (MEN) and the reported familial risk for gastrointestinal carcinoids.[1] About 20% of thyroid neuroendocrine carcinomas are related to MEN. No association was found with smoking for lung NETs, which are associated with MEN in 8% of cases.[2] **Neuroendocrine carcinoma of the skin** is mostly represented by Merkel carcinoma, which is characterised by an aggressive behaviour. Ultraviolet radiation exposure plays an important role for the development of this cancer. Patients with AIDS have a higher risk to develop this tumour.[3] Polyomavirus infection has been detected in Merkel carcinoma and seems to be a contributing factor to its development.[4] **Pheochromocytoma and paraganglioma** are both very rare and have similar basic histopathological characteristics, but pheochromocytoma arises from the adrenal medulla and paraganglioma from nerve ganglia, mainly located in the head and neck. About 24%-27% of pheochromocytoma or paraganglioma are associated with known genetic mutations, which in children reach a prevalence of 40%.[5] NETs have in general been considered indolent tumours with low metastatic potential; however, some NET subtypes are highly malignant and carry a bad prognosis with the possibility to metastasise to regional lymph nodes and distant organs. In general, the current WHO guidelines divide NETs into well-differentiated, traditionally referred to as carcinoids and pancreatic islet cell tumours, and poorly differentiated tumours, with different prognosis.[6,7] Most poorly differentiated NETs (about 50%) have metastatic disease at diagnosis, in contrast with well-differentiated NETs (20%).[8]

NET incidence is in constant, gradual increase in the Western populations.[7-9] Improvement in classification and new immunohistochemical techniques could have contributed to this increase, but it is still unclear if this trend is due to an increased awareness among physicians and pathologists, improved diagnostic tools, or an actual real increase in NET incidence.[8] Furthermore, increasing clinical and biological knowledge has led to changes in the classification of these tumours, which could be responsible for the geographical differences in incidence reported in the literature, together with different awareness of clinicians, different expertise of pathologists, and availability of markers to identify these tumours across countries.[9] It should also be considered that registration is based on a morphology code of the ICD-O-10 with a malignant behaviour, so data may partly vary between clinical trial and population-based cancer registries.

Incidence rate and distribution by anatomic site are widely variable in the literature, depending on the specific code included in the studies, so it is very difficult to compare the results. As the pathology report is the basis for a correct diagnosis and for a correct identification and classification of NETs, it is essential that the pathological report contains all the necessary information to identify the NET and their different subtypes. Despite the lack of some clinical and histopathological variables, such as associated syndromes (ICD-O does not include any code for secretor function) or proliferation index or grading, the association of ICD-O-3 codes with the different sites proposed in this report properly captures the different clinical behaviours of these tumours and thus represents the first unselected study from a large population in Italy to describe the burden of these heterogeneous neoplasms in Italy.

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

NETs included in this monograph are all rare cancers. In Italy 9,197 cases were registered in the period 2000-2010 leading to an incidence rate (IR) of 4.15 per 100,000 (incidence table, p. 91). The incidence of all NETs is slightly higher in Italy than in the European RARECAREnet database (IR 3.5) (www.rarecarenet.eu), mainly due to a slightly higher incidence in Italy than in Europe of poorly differentiated GEP carcinoma, thyroid NETs, and well-differentiated carcinoids of the lung. NETs occur with similar frequency in males and females, except for neuroendocrine carcinoma of the thyroid, which has higher incidence in females than males, with an IR of 0.63 vs. 0.38, respectively (see table p. 91) and poorly differentiated GEP carcinoma, which is more frequent in males than females. The IR of NETs increases with age. In Italy about 2,700 new cases are expected in 2015. About 46% of NETs are in the GEP system with a marked heterogeneity in terms of biologic behaviour and histological differentiation.

Tumours can be functioning, causing a specific syndrome, or non-functioning. For tumours that arise mostly from the pancreas it is possible to attribute a specific code of functioning tumours, for other NETs it is not possible to identify syndrome-affected patients

(about 10%, variable in relation to the stage and primary site).
The most frequent primary GEP sites are the small intestine (25%), pancreas (22%), colon (19%), stomach (17%), and rectum (10%). NETs of the appendix comprise only 5% of all GEP NETs (data not shown). It is important to stress that carcinoid tumours of uncertain malignant potential of the appendix are not included in the data presented here. The most frequent morphologies of GEP NETs are poorly differentiated carcinoma (52%) and well-differentiated non functioning endocrine carcinoma (46%); well-differentiated functioning endocrine carcinomas are very rare, probably in part because of the lack of a code for functioning NETs arising in sites other than the pancreas. Typical and atypical carcinoids of lung are the second in order of frequency (14% of NETs). These tumours occur mainly in the over-54-year age group, with only a slight increase in those aged over 65 years, with an IR of 1.2 and 1.4, respectively (see table p. 91). Other lung NETs are not rare, and are therefore not included in this report. Neuroendocrine carcinoma of thyroid (12% of NETs) is mostly represented by medullary carcinoma, and occurs mainly in the fourth and fifth decade of life, with an IR of 1.1 (see table p. 91). NETs of skin (8% of NETs) typically occur in people over 64 years of age, with an IR of 1.4 (see table p. 91). Pheochromocytoma and paraganglioma are very rare tumours, with 94 and 44 cases observed over 11 years of observation in Italy. Neuroendocrine carcinoma of other sites is a very heterogeneous group including various primary sites, but also NETs of unknown origin, and represent in total about 18% of NETs, with an IR of 0.7 (see table p. 91). Of these, 13% are from the bladder, 11% from the breast, 9% from the female genital tract, 9% from the respiratory tract, 7% from head and neck, 3% from the prostate, 2% from the thymus, and 46% unknown origin. About 90% of all NETs of other sites have poorly differentiated morphology (data not shown).

### Survival

In Italy, 1- and 5-year relative survival (RS) of NETs is 79% and 63%, respectively (survival figure, p. 91); slightly higher than the European RARECAREnet database (71% and 54% at 1 and 5-year, respectively). Five-year RS is slightly higher in Italy than in the European RARECAREnet database for GEP poorly differentiated, well-differentiated functioning and non-functioning, for NETs of thyroid, and for typical and atypical carcinoids of the lung. For the others, no major differences are observed between Italy and Europe. For GEP NETs a great difference in 5-year RS is observed between well-differentiated non functioning carcinoma (RS: 76%) and poorly differentiated tumours (RS: 44%) (see figure p. 91). This result is due to the aggressiveness of poorly differentiated NETs. The small intestine is the NET site with the best prognosis, as reported in the literature,[8] which shows only a slight difference in RS between well-differentiated NETs (1-year RS: 90%; 5-year RS: 77%) and poorly differentiated NETs (1-year RS: 85%, 5-year RS: 71%) (data not shown). Absence of symptoms in non functioning GEP NETs can lead to a delay in diagnosis and increased probability of metastatic disease, which make surgical treatment with curative intent impossible. The very complex treatment, requiring multidisciplinary integration, may lead to a heterogeneous care of these patients that could partially explain the geographical difference in survival observed across European countries. One- and 5-year RS of typical and atypical carcinoids of the lung is high (1-year RS: 94%, 5-year RS: 84%) see figure p. 91), reflecting the good prognosis of these tumours. Survival is strongly influenced by the possibility of receiving surgery, since surgery is the only curative approach.[11] Neuroendocrine carcinoma of thyroid gland has a good prognosis, with 1- and 5-year RS >90% (see figure p. 91). Age and stage at diagnosis are strictly correlated with survival. NETs of skin have an RS of 85% at 1 year, which drops to 57% at five years (see figure p. 91) This could be attributed to the aggressiveness of this tumour.
Diagnosis of metastasised disease in elderly patients could limit treatments.[12] Pheochromocytoma has an RS of 85% at 1 year and 70% at 5 years from diagnosis (see figure p. 91). Therapy of choice is surgical resection after appropriate preoperative preparation. Radiotherapy with MIBG could have a role in diffuse metastatic disease.[13] Paraganglioma has a relatively good survival, although estimates are based on 38 cases only. The worst RS is observed for NETs of other sites (RS 56% at one year and 30% at five years) (see figure p. 91), slightly better than European data (RS 48% and 24%, respectively). The large proportion of NETs of unknown primary site and of poorly differentiated NETs in this group can contribute to explain their low RS.

### Prevalence

About 25,000 persons were estimated to be living with a NET diagnosis in Italyin 2010. GEP, well-differentiated, non functioning endocrine carcinomas are the most prevalent NETs, followed by neuroendocrine carcinomas of the thyroid gland, typical and atypical carcinoid of the lung, GEP, poorly differentiated endocrine carcinoma, and NETs of the skin. The remaining NETs accounted for a limited number of prevalent cases. The distribution of prevalent cases by time since diagnosis varied between the different tumour entities, depending on the prognosis of the specific histotype, site of origin, and mean age of incidence.

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# TUMOURS OF THE CENTRAL NERVOUS SYSTEM

**100%**
**OF CENTRAL NERVOUS SYSTEM TUMOURS ARE RARE**

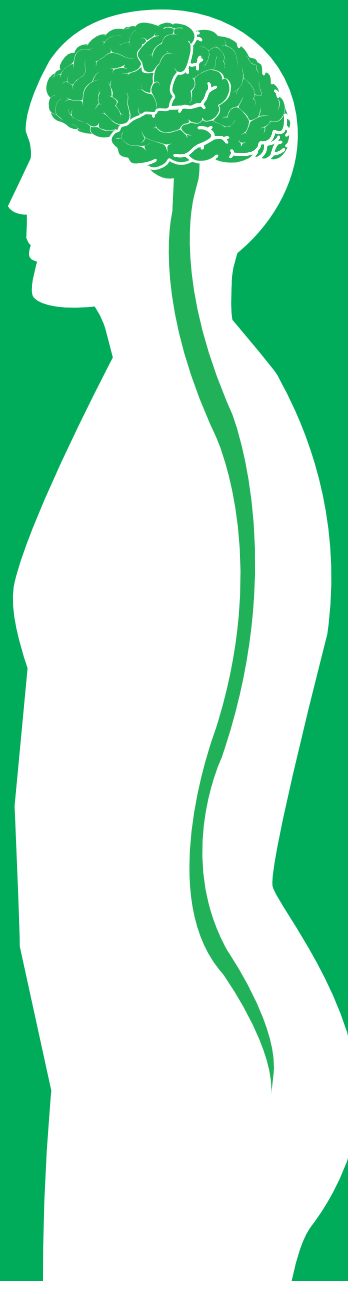
## INCIDENCE

**3 725**
ESTIMATED NEW CASES
ITALY, 2015

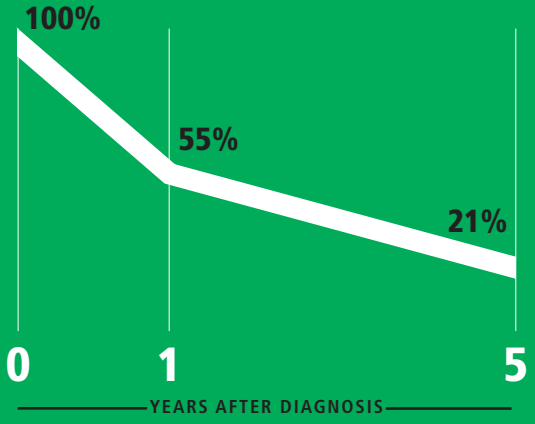
- **3 588** TUMOURS OF THE CENTRAL NERVOUS SYSTEM
- **137** EMBRYONAL TUMOURS OF THE CENTRAL NERVOUS SYSTEM

## PREVALENCE

**26 610**
ESTIMATED PREVALENT CASES
ITALY, 2010



## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# TUMOURS OF THE CENTRAL NERVOUS SYSTEM

# INCIDENCE

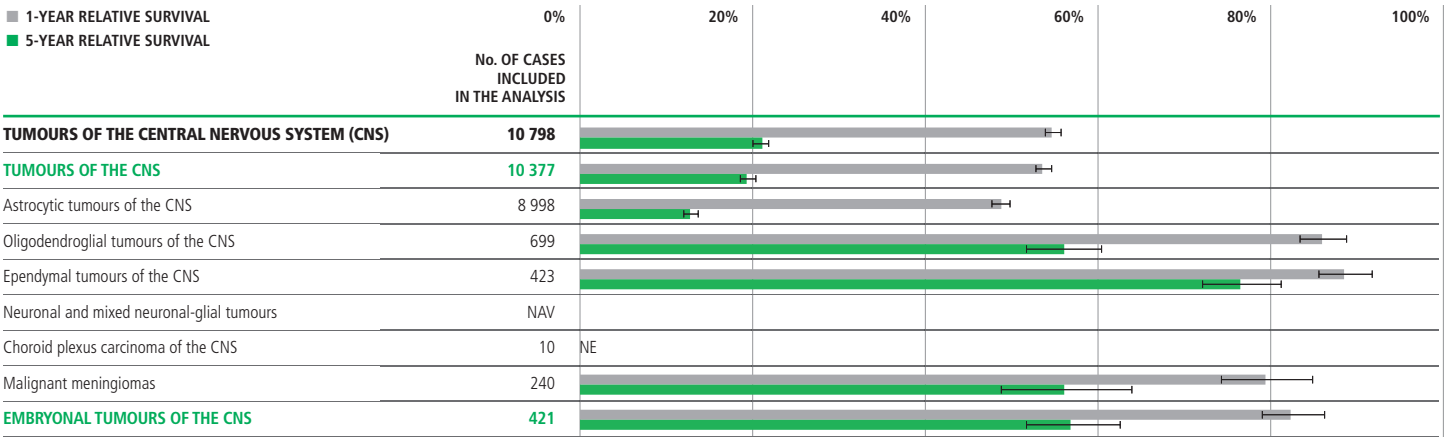
**TUMORUS OF THE CENTRAL NERVOUS SYSTEM.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **TUMOUR OF THE CENTRAL CENTRAL NERVOUS SYSTEM (CNS)** | **5.89** | **5.79-6.00** | **13 071** | **100%** | **6.99** | **6.84-7.15** | **4.87** | **4.74-4.99** | **3.17** | **3.08-3.26** | **11.64** | **11.24-12.05** | **11.67** | **11.36-12.00** | **3 725** |
| TUMOURS OF THE CNS | 5.67 | 5.57-5.77 | 12 566 | NA | 6.70 | 6.54-6.85 | 4.70 | 4.58-4.83 | 2.86 | 2.77-2.94 | 11.58 | 11.18-11.99 | 11.62 | 11.30-11.94 | 3 588 |
| Astrocytic tumours of the CNS | 4.92 | 4.83-5.01 | 10 904 | | 5.89 | 5.74-6.03 | 4.01 | 3.90-4.13 | 2.24 | 2.17-2.32 | 10.42 | 10.04-10.81 | 10.67 | 10.37-10.98 | 3 125 |
| Oligodendroglial tumours of the CNS | 0.38 | 0.35-0.40 | 836 | | 0.43 | 0.40-0.48 | 0.32 | 0.29-0.36 | 0.33 | 0.30-0.36 | 0.64 | 0.55-0.74 | 0.39 | 0.33-0.45 | 231 |
| Ependymal tumours of the CNS | 0.23 | 0.21-0.25 | 504 | | 0.24 | 0.21-0.27 | 0.21 | 0.19-0.24 | 0.23 | 0.21-0.26 | 0.29 | 0.23-0.36 | 0.18 | 0.14-0.22 | 139 |
| Neuronal and mixed neuronal-glial tumours | NAV | NAV | NAV | | NAV | – | NAV | – | NAV | – | NAV | – | NAV | – | NAV |
| Choroid plexus carcinoma of the CNS | <0.01 | 0.00-0.01 | 13 | | NE | – | NE | – | NE | – | NE | – | NE | – | 4 |
| Malignant meningiomas | 0.13 | 0.12-0.15 | 299 | | 0.12 | 0.10-0.14 | 0.15 | 0.13-0.17 | 0.05 | 0.04-0.06 | 0.22 | 0.17-0.29 | 0.37 | 0.32-0.43 | 86 |
| EMBRYONAL TUMOURS OF THE CNS | 0.23 | 0.21-0.25 | 505 | NA | 0.30 | 0.26-0.33 | 0.16 | 0.14-0.19 | 0.31 | 0.28-0.34 | 0.06 | 0.03-0.10 | 0.05 | 0.03-0.08 | 137 |

**NE:** not estimable because 15 or less incident cases were observed **NAV:** not available **NA:** not applicable

# SURVIVAL

**TUMOURS OF THE CENTRAL NERVOUS SYSTEM.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




**NE:** not estimable because 30 or less incident cases were observed **NAV:** not available

# PREVALENCE

**TUMOURS OF THE CENTRAL NERVOUS SYSTEM.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **TUMOURS OF THE CENTRAL NERVOUS SYSTEM (CNS)** | **7.19** | **6.64-7.78** | **4.28** | **3.86-4.74** | **19.14** | **18.23-20.08** | **45.66** | **42.34-48.98** | **26 610** |
| TUMOURS OF THE CNS | 6.93 | 6.39-7.50 | 3.93 | 3.53-4.37 | 17.61 | 16.74-18.51 | 39.70 | 36.84-42.63 | 23 121 |
| Astrocytic tumours of the CNS | 5.46 | 4.98-5.97 | 2.22 | 1.92-2.55 | 11.47 | 10.77-12.21 | 28.98 | 26.30-31.66 | 16 882 |
| Oligodendroglial tumours of the CNS | 0.91 | 0.72-1.13 | 0.72 | 0.56-0.93 | 2.82 | 2.47-3.19 | 3.45 | 3.01-3.89 | 1 973 |
| Ependymal tumours of the CNS | 0.39 | 0.27-0.55 | 0.61 | 0.46-0.80 | 2.45 | 2.13-2.80 | 6.09 | 5.14-7.05 | 3 565 |
| Neuronal and mixed neuronal-glial tumours | NAV | – | NAV | – | NAV | – | NAV | – | NAV |
| Choroid plexus carcinoma of the CNS | NE | – | 0.03 | 0.01-0.10 | 0.03 | 0.01-0.10 | 0.25 | 0.00-0.57 | 145 |
| Malignant meningiomas | 0.17 | 0.10-0.28 | 0.35 | 0.23-0.50 | 0.85 | 0.67-1.07 | 1.21 | 0.93-1.49 | 701 |
| EMBRYONAL TUMOURS OF THE CNS | 0.26 | 0.17-0.40 | 0.35 | 0.24-0.50 | 1.53 | 1.28-1.81 | 5.93 | 4.29-7.56 | 3 489 |

**NE:** not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE **NAV:** not available

# TUMOURS OF THE CENTRAL NERVOUS SYSTEM

Primary central nervous system tumours (CNS) are of ecto- and mesodermal origin and arise from the brain, cranial nerves, meninges, pituitary, pineal and vascular elements. The standard definition of CNS tumours is that of the 2007 WHO classification,[1] which is based on histological characteristics and lists approximately 100 subtypes of CNS malignancies in seven categories with different molecular biology, clinical behaviour, and, presumably, aetiology. Statistics on CNS tumours are estimated by grouping all malignancies arising in all CNS anatomic sites (ICD-10 topography codes C70-C72). However, rare tumours are more appropriately defined as a combination of topographical and morphological characteristics, according to the International Classification of Diseases for Oncology (ICD-O).
Thus, based on an adaptation of the WHO classification and further work by RARECAREnet:[2]
CNS tumours have been divided into:

- tumours of the CNS (major histological groups (astrocytic tumours, oligodendroglial tumours, ependymal tumours, neuronal and mixed neuronal-glial tumours, choroid plexus carcinoma, malignant meningiomas);
- embryonal tumours (including pineoblastoma).

The results presented in this section refer exclusively to malignant tumours of the CNS. Epidemiological features of the carcinomas of the pituitary gland are described in the endocrine tumours grouping.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

The aetiology of **CNS tumours** is not well established; common risk factors for other cancers (e.g., diet, smoking, physical activity, alcohol) do not seem to play a significant role. A relationship with exposure to chemical carcinogens has been reported, but the only environmental factor unequivocally associated with an increased risk is therapeutic irradiation, especially in children; exposure to non-ionizing radiation by cellular phones is controversial.[3] Finally, an increased risk is also attributed to hereditary syndromes.[4]
According to the WHO grading scheme, CNS tumours can be stratified by degree of malignancy:
Grade I: lesions with low proliferative potential and the possibility of cure by surgical resection alone;
Grade II: infiltrative neoplasms with low proliferative activity, but tendency to recur and progress to a higher grade;
Grade III: lesions with histological evidence of malignancy;
Grade IV: cytologically malignant, mitotically active, necrosis-prone, fatal neoplasms with rapid evolution.

**Astrocytomas** include a heterogeneous group of histotypes. WHO grade I refers to low-grade astrocytomas, such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. WHO Grade II includes infiltrating neoplasms such as pilomyxoid, diffuse, protoplasmic astrocytoma, as well as oligoastrocytoma. Negative prognostic factors include age ≥40 years, astrocytoma histology, maximum diameter ≥6 cm, baseline neurologic deficits, residual mass after surgery >1 cm. WHO Grade III includes anaplastic astrocytoma, which is (with glioblastoma, see next) one of the most common primary malignant brain tumours in adults.[4] WHO Grade IV includes glioblastoma (the most lethal brain tumour), gliosarcoma, and giant cell glioblastoma.

**Oligodendroglial tumours** express different levels of clinical aggressiveness: this category includes oligodendroglioma (WHO Grade II) and anaplastic oligodendroglioma (WHO Grade III), both deriving from the oligodendrocytic cell line. Highly prevalent cytogenetic alterations, namely mutations of the isocitrate dehydrogenase-1 (IDH1) and chromosomal arm 1p and 19q codeletion, are predictors of more favourable prognosis of these tumours.[6]
**Ependymal tumours** are derived from ependymal glial cells and include different subtypes, with varying degree of differentiation and malignancy: WHO Grade I: subependymoma, myxopapillary ependymoma; WHO Grade II/III: ependymoma NOS; WHO Grade III/IV: anaplastic ependymoma.
**Neuronal and mixed neuronal-glial tumours** are very rare and characterised by a variable degree of neuronal differentiation, with neoplastic neuronal cells alone (e.g., gangliocytoma) or mixed to neoplastic glial cells.
**Primary choroid plexus carcinomas** are rare aggressive WHO grade III tumours which usually occur in children under 12 years of age and account for nearly 20% of all choroid plexus tumours.[4,7] Since the choroid plexus is the neuroepithelial tissue that produces cerebrospinal fluid, these tumours are mostly located in the lateral ventricle (mainly in children) and less frequently in the fourth ventricle (mainly in adults).
**Malignant meningiomas** are WHO Grade III with a low tendency to metastasise but a high rate of recurrence and progression.[4,8] Higher grade meningiomas are often associated with neurofibromatosis type 2 (NF2) mutation, loss of chromosome 22, and additional chromosomal aberrations.[6] Prior radiation therapy to head and neck can be a risk factor.
**Embryonal tumours** include several tumours of embryonal origin – typically occurring in infants and young children – characterised by high malignancy and therefore classified as WHO Grade IV: medulloblastoma (MB) and its variants: e.g., desmoplastic/nodular-, anaplastic-, large cell-MB; primitive neuroectodermal tumours (PNETs) and variants: e.g., neuroblastoma, ganglioneuroblastoma, neuroepithelioma, medulloepithelioma; atypical teratoid/rhabdoid tumours (ATRTs).
**Pineoblastomas** are also included among embryonal tumours, although separately classified by WHO as pineal tumours (Grade IV). In summary: MBs, PNETs, ATRTs, and pineoblastomas probably represent biologically distinct entities, so the classification of embryonal tumours, currently debated, may be susceptible to further revisions.[4]

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

All CNS tumours are rare and are more frequent in males than in females, with an M/F ratio ranging from 1.14 to 1.81, with the sole exception of malignant meningiomas (M/F: 0.81). The most frequent histotype is astrocytoma – which accounts for 83% of the total –, followed by oligodendroglial tumours (6.4%), ependymal and embryonal tumours (both at 3.9%), and malignant meningiomas (2.3%).
Incidence of all tumours tends to increase after age 40 years, with a peak in the 65-75-year age group; however, astrocytomas and embryonal tumours also occur in young children. In particular, embryonal neoplasms in the first 15 years of age account for nearly

50% of all embryonal neoplasms at all ages. Among these, medulloblastomas – located exclusively in the cerebellum – are the most common (70%), followed by primitive neuroectodermal tumours (PNETs, 20%). Pineoblastoma (a malignant pineal parenchymal tumour) is very rare and accounts for less than 3% of all rare CNS tumours.
The Italian estimates for each subtype are fully in line with the corresponding European incidence estimates based on the RARECAREnet database (www.rarecarenet.eu).
The proportion of NOS cancer cases in the AIRTUM database in the study period (2000-2010) is estimated at 37%, with a differential distribution across age, ranging from 20% in the 0-24-year age group to 52% in the over 65 age group. This raises the issue of a potential underestimation of true incidence, mostly in the elderly, but does not jeopardise the overall description of the frequency of CNS tumours here presented.

### Survival

One and 5-year relative survival (RS) of CNS tumours is 55% and 21%, respectively. However, these results are strongly affected by astrocytic tumours, which are both the most common among these tumours and those with the worst survival (49% and 13% at 1 and 5 years, respectively). There is a striking difference in relative survival between each of the other CNS tumours and astrocytomas; namely, 5-year RS is 76% for ependymal tumours and 56%-57% for all other histotypes.
The poor prognosis of astrocytomas is at least partially explained by the high proportion (64%) of WHO grade IV tumours in this group. On the contrary, ependymal tumours and oligodendrogliomas have a high proportion of WHO grade II tumours (82% and 71%, respectively); oligodendrogliomas have a higher proportion of WHO grade III tumours compared to ependymal tumours, which can contribute to explain the estimated difference in survival between these two histotypes.
Italian estimates are in line with the corresponding European survival estimates based on the RARECAREnet database for most of the subtypes, with the only exceptions of astrocytomas (in which 1-year survival is 48% in Italy vs. 41% in Europe) and – to a lesser extent – oligodendroglial tumours. This finding is consistent with other reports where geographical differences have been measured;[2] whether this can be attributed to different case-mix, timeliness of diagnosis, access to treatment (especially radiotherapy) or is rather the effect of differential case selection or classification should be further investigated.

### Prevalence

About 27,000 persons were alive in Italy in 2010 with a past diagnosis of CNS tumours; of these, about 3,500 had an embryonal tumour of CNS in their clinical history, while the others had been diagnosed with any of the tumours of the CNS (astrocytic, oligodendroglial, ependymal, neuronal and mixed neuronal-glial, choroid plexus carcinoma, malignant meningioma). Astrocytic tumours were the most common among prevalent CNS cancers, followed by ependymal and oligodendroglial tumours.
The prevalence estimates well reflect the different incidence and survival of these tumours. Interestingly, very long-term survivors, those who survived more than 15 years after diagnosis, were on average 56% among prevalent cases of the heterogeneous group of tumours of the CNS, and 74% among cases of embryonal tumours of the CNS. A possible explanation for the proportion of long-term survivors is the high frequency of low-grade tumours which have a good prognosis.[2]
The estimates here presented are slightly lower than those previously published in the AIRTUM prevalence monograph, mainly because undefined tumours (such as ICD-O M8000 and M8001) are not included in our definition.

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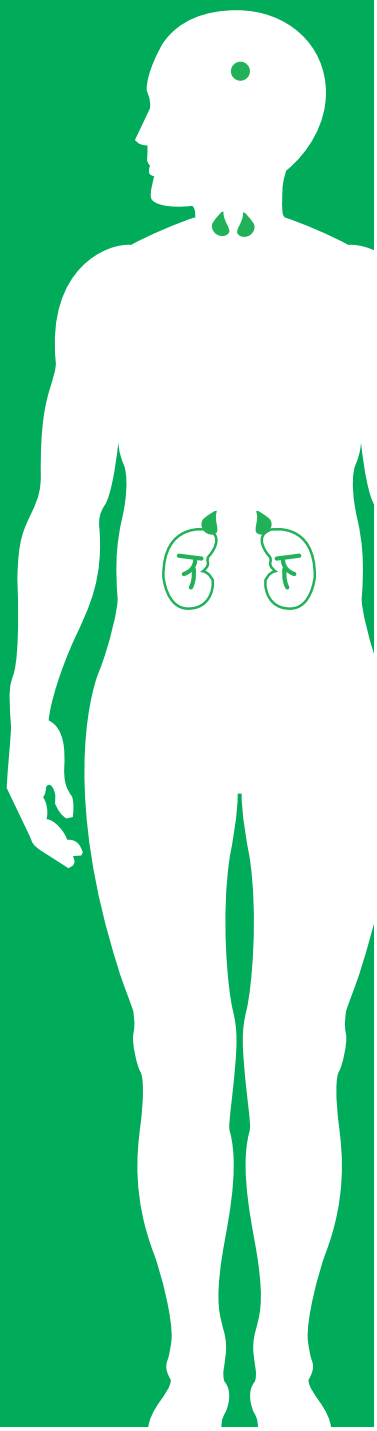
# TUMOURS OF THE ENDOCRINE ORGANS

**100%**
**OF ENDOCRINE ORGANS TUMOURS ARE RARE**

## INCIDENCE

**244**
ESTIMATED NEW CASES
ITALY, 2015

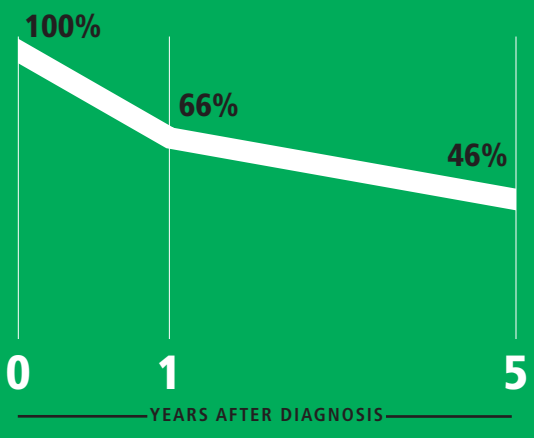
- **22** CARCINOMAS OF PITUITARY GLAND
- **33** CARCINOMAS OF PARATHYROID GLAND
- **189** CARCINOMAS OF ADRENAL CORTEX



## PREVALENCE

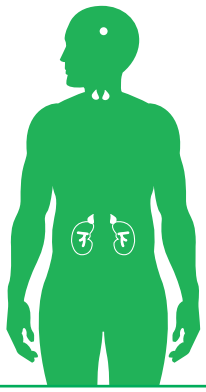
**2 222**
ESTIMATED PREVALENT CASES
ITALY, 2010

## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# TUMOURS OF THE ENDOCRINE ORGANS

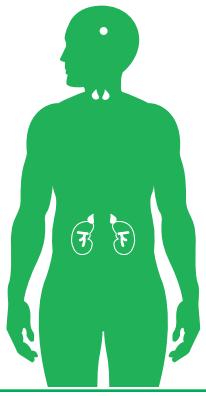


# INCIDENCE

**TUMOURS OF THE ENDOCRINE ORGANS.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

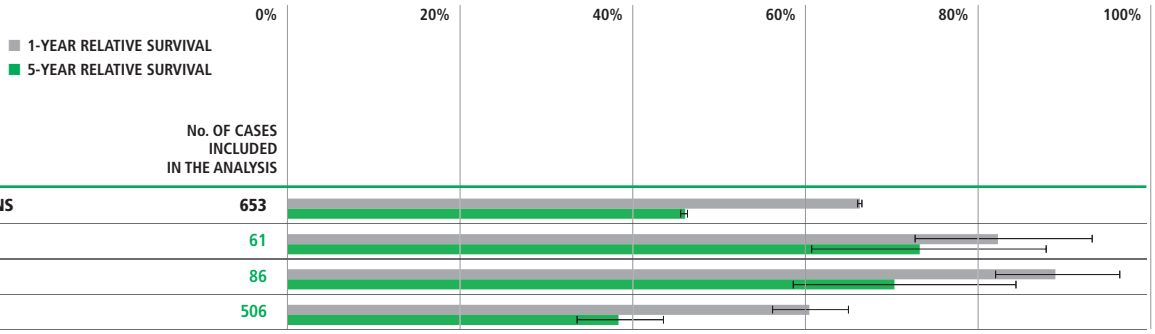
| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 |
| **TUMOURS OF THE ENDOCRINE ORGANS** | **0.37** | **0.35-0.40** | **830** | **100%** | **0.39** | **0.35-0.42** | **0.36** | **0.33-0.40** | **0.20** | **0.18-0.23** | **0.51** | **0.43-0.60** | **0.88** | **0.80-0.97** | **244** |
| CARCINOMAS OF PITUITARY GLAND | 0.03 | 0.03-0.04 | 76 | NA | 0.04 | 0.03-0.05 | 0.03 | 0.02-0.04 | 0.02 | 0.01-0.03 | 0.04 | 0.02-0.07 | 0.08 | 0.05-0.11 | 22 |
| CARCINOMAS OF PARATHYROID GLAND | 0.05 | 0.04-0.06 | 110 | NA | 0.05 | 0.04-0.06 | 0.05 | 0.04-0.07 | 0.02 | 0.02-0.03 | 0.08 | 0.05-0.13 | 0.12 | 0.09-0.16 | 33 |
| CARCINOMAS OF ADRENAL CORTEX | 0.29 | 0.27-0.31 | 644 | NA | 0.30 | 0.27-0.33 | 0.28 | 0.25-0.31 | 0.16 | 0.14-0.18 | 0.38 | 0.31-0.46 | 0.68 | 0.61-0.77 | 189 |

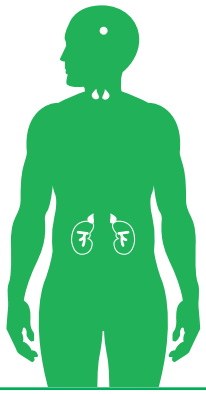
**NA:** not applicable



# SURVIVAL

**TUMOURS OF THE ENDOCRINE ORGANS.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



# PREVALENCE

**TUMOURS OF THE ENDOCRINE ORGANS.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **TUMOURS OF THE ENDOCRINE ORGANS** | **0.46** | **0.33-0.63** | **0.56** | **0.42-0.74** | **2.33** | **2.02-2.67** | **3.74** | **3.21-4.27** | **2 222** |
| CARCINOMAS OF PITUITARY GLAND | 0.05 | 0.01-0.12 | 0.21 | 0.12-0.33 | 0.62 | 0.47-0.81 | 1.07 | 0.77-1.36 | 627 |
| CARCINOMAS OF PARATHYROID GLAND | 0.08 | 0.03-0.17 | 0.11 | 0.06-0.21 | 0.47 | 0.34-0.64 | 0.77 | 0.53-1.01 | 448 |
| CARCINOMAS OF ADRENAL CORTEX | 0.33 | 0.22-0.48 | 0.24 | 0.15-0.37 | 1.24 | 1.02-1.50 | 1.91 | 1.54-2.27 | 1 147 |

The list of rare cancers proposed by the European RARECARE project (surveillance of rare cancers in Europe, www.rarecare.eu) considers thyroid cancer arising from the follicular epithelium rare, reporting an incidence rate lower than 6 per 100,000 in Europe. Even if rare at European level, thyroid carcinoma is not presented in the endocrine grouping of this monograph. This choice is due to the fact that the methodological assumptions used to estimate the epidemiological indicators for rare cancers (many of them extremely rare) are not applicable to thyroid cancer epidemiology in Italy (see «Materials and Methods», pp. 14-21).

This section deals in detail with tumours that arise from hormone-secreting endocrine glands, which are all rare:

- **carcinomas of pituitary gland**;
- **carcinomas of parathyroid gland**;
- **carcinomas of adrenal cortex**.

## WHAT DO WE KNOW ABOUT THESE CANCERS?

**Pituitary tumours** are indolent tumours representing approximately 15%-20% of intracranial neoplasms.[1] They can be characterised by pituitary dysfunction, neurological deficits (especially visual impairment), and/or invasion of the parasellar compartment and/or the sphenoid sinuses. Initially considered as sporadic tumours, some of them are associated with familial syndromes such as multiple endocrine neoplasia type 1, Carney complex, or familial isolated pituitary adenomas. Pituitary tumours can be typed based on their hormone-secreting properties into lactotropic (prolactin secreting, 35%), gonadotropic (follicle-stimulating hormone and luteinizing hormone, 35%), somatotropic (growth hormone, GH, 10%-15%), and other tumour types, including tumours with mixed secreting patterns and non-secreting adenomas. Primary pituitary carcinoma is a rare entity defined as any tumour of adenohypophyseal origin with demonstrated craniospinal and/or extracranial metastatic dissemination, fortunately very uncommon and accounting for only 0.1% of all pituitary tumours.[2] Both hormonally active (ACTH-, GH-, and PRL-producing) and hormonally inactive forms of pituitary carcinoma have been reported. Pituitary carcinoma can present in patients with preexisting pituitary adenomas with initial indistinguishable clinical course. The majority of **adrenal cancers a**rise sporadically but can develop as a part of a constellation of tumours in inherited familial cancer syndromes such as Li Fraumeni syndrome, Beckwith-Widerman syndrome, Gardner syndrome, and multiple endocrine neoplasia type 1, each syndrome is associated with unique germ-line mutation.[3] Steroid overproduction is present in over 60% of patients with adrenal cancers. Despite radical surgery with curative intent, the majority of patients with localised adrenal cancers will develop metastases within 6-24 months from resection.[4] **Parathyroid carcinoma** is a rare cause of primary hyperparathyroidism. It can occur either sporadically or in family members affected by hyperparathyroidism-jaw tumour syndrome or associated with multiple endocrine neoplasia.[5] Most parathyroid cancers secrete parathyroid hormone and cause hypercalcaemia. An increase in incidence (from 0.03 to 0.05) was observed in a population-based study in the USA in the period 1988-2003, probably due to increased serum calcium screening.[6]

Pituitary, adrenal, and parathyroid carcinomas are rare, and population-based studies are scarce. Thus, this population-based analysis, which uses data from the pool of the AIRTUM cancer registries, offers the first opportunity to describe the burden of these cancers in Italy.

## THE EPIDEMIOLOGICAL DATA IN ITALY

### Incidence

Incidence Rate per 100,000 (IR) of endocrine tumours is 0.37; 244 new cases of endocrine tumours are expected in 2015. The first tumour in order of frequency is adrenal cortex cancer. With 189 cases expected, it represents 78% of endocrine tumours considered, with an IR of 0.29 (incidence table, p. 99), slightly higher than the RARECARENet database (IR 0.22) (www.rarecarenet.eu) and equally distributed by sex. The IR progressively increases with age.

One hundred and ten cases of parathyroid cancers were detected, with an IR of 0.05 (see table p. 99), slightly higher compared to the European RARECARENet database (IR of 0.03) representing 13% of this group of rare tumours. Despite the few cases, the incidence seems to increase with age, with no differences between sexes. Since only pituitary carcinoma, based on a morphology code of the ICD-O with a malignant behaviour, has been included in the analysis, only 76 cases of pituitary tumours were detected, with an IR of 0.03 (see table p. 99) similar to that observed in the larger RARECARENet database.

### Survival

Relative survival (RS) of endocrine tumours is 66% at 1 year and 46% at 5 years. This value is influenced by the lower survival of adrenal cortex tumours compared to other endocrine tumours. Despite surgical, medical, and chemotherapeutic advances, patients with adrenal cancer show a poor prognosis, with an RS of 38% at 5 years (survival figure, p. 99) in line with European data of the RARECARENet database. This prognosis is most probably due to the high tendency to metastasise within 6-24 months from resection. Parathyroid cancer has an RS of 89% and 70% at 1 and 5 years, respectively (see figure p. 99). Morbidity and mortality for this cancer usually are caused by metabolic complications rather than tumour burden. Similar RS was observed for pituitary tumours (RS 82% at 1 year and 73% at 5 years) (see figure p. 99). These results are similar to those observed in the wider European RARECARENet database.

### Prevalence

Slightly more than 2,000 persons are estimated to be living in 2010 with a diagnosis of carcinoma of the endocrine organs (excluding thyroid cancer), of whom more than 50% have a diagnosis of adrenal cortex carcinoma (prevalence table, p. 99). The distribution of prevalent cases by time since diagnosis shows that cases where time since diagnosis is over 15 years are 42% for pituitary carcinoma, 38% for parathyroid carcinoma, and 35% for adrenal cortex carcinoma.

## REFERENCES

1. Melmed S. Pathogenesis of pituitary tumors. *Nat Rev Endocrinol* 2011;7(5):257-266.
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4. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007;356(23):2372-2380.
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# RARE HAEMATOLOGICAL DISEASES

**74%**
**OF HAEMATOLOGICAL DISEASES ARE RARE**

## INCIDENCE

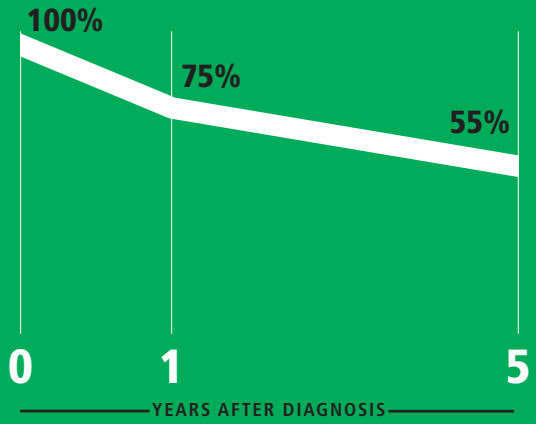
**27 084**
ESTIMATED NEW CASES
ITALY, 2015

| | | | |
|---|---|---|---|
| 17 464 | RARE LYMPHOID DISEASES | 48 | % OF RARE HAEMATOLOGICAL DISEASES OUT OF ALL HAEMATOLOGICAL DISEASE |
| 3 572 | ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS | 10 | |
| 3 610 | MYELOPROLIFERATIVE NEOPLASMS | 10 | |
| 2 371 | MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/ MYELOPROLIFERATIVE DISEASES | 6 | |
| 68 | HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS | 0.2 | |

## PREVALENCE

**225 872**
ESTIMATED PREVALENT CASES
ITALY, 2010

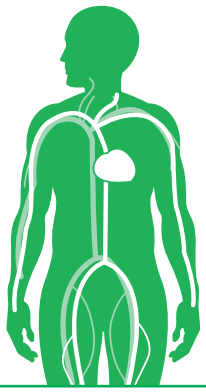
## SURVIVAL




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

# RARE HAEMATOLOGICAL DISEASES

# INCIDENCE



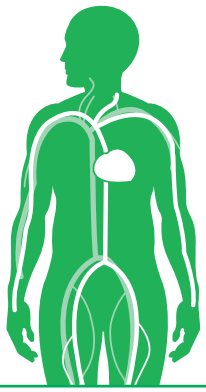
**RARE HAEMATOLOGICAL DISEASES.** Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

| | AIRTUM POOL (period of diagnosis 2000-2010) | | | | | | | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SEX | | | | AGE | | | | | | |
| | | | | | MALE | | FEMALE | | 0-54 yrs | | 55-64 yrs | | 65+ yrs | | |
| | RATE | 95% CI | OBSERVED CASES (No.) | RARE CANCERS BY SITE (%) | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | RATE | 95% CI | ESTIMATED NEW CASES 2015 No. |
| **RARE HAEMATOLOGICAL DISEASES** | **41.08** | **40.81-41.35** | **91 094** | **74%** | **45.43** | **45.03-45.84** | **37.00** | **36.65-37.36** | **16.17** | **15.97-16.38** | **53.07** | **52.21-53.94** | **118.92** | **117.9-119.94** | **27 084** |
| **RARE LYMPHOID DISEASES** | **26.78** | **26.56-27.00** | **59 384** | **48%** | **29.33** | **29.00-29.65** | **24.39** | **24.11-24.68** | **11.96** | **11.78-12.13** | **36.78** | **36.06-37.50** | **71.32** | **70.54-72.12** | **17 464** |
| Hodgkin lymphoma, classical | 3.50 | 3.43-3.58 | 7 769 | | 3.84 | 3.73-3.96 | 3.18 | 3.08-3.29 | 3.73 | 3.64-3.83 | 2.59 | 2.40-2.78 | 3.29 | 3.12-3.46 | 2 101 |
| Hodgkin lymphoma nodular lymphocyte predominance | 0.14 | 0.12-0.16 | 309 | | 0.18 | 0.16-0.21 | 0.10 | 0.08-0.12 | 0.14 | 0.12-0.16 | 0.18 | 0.13-0.24 | 0.12 | 0.09-0.16 | 85 |
| Precursor B/T lymphoblastic leukaemia/lymphoma (and Burkitt leukaemia/lymphoma) | 1.86 | 1.80-1.92 | 4 127 | | 2.23 | 2.14-2.32 | 1.52 | 1.45-1.59 | 1.91 | 1.84-1.98 | 1.31 | 1.17-1.45 | 2.05 | 1.92-2.19 | 1 168 |
| T cutaneous lymphoma (Sezary syndrome, Mycosis fungoides) | 1.07 | 1.02-1.11 | 2 363 | | 1.40 | 1.33-1.47 | 0.76 | 0.71-0.81 | 0.38 | 0.35-0.41 | 1.92 | 1.76-2.09 | 2.88 | 2.73-3.04 | 700 |
| Other T cell lymphomas and NK cell neoplasms | 0.87 | 0.83-0.91 | 1 922 | | 1.09 | 1.03-1.16 | 0.66 | 0.61-0.70 | 0.41 | 0.38-0.44 | 1.25 | 1.13-1.40 | 2.19 | 2.05-2.33 | 563 |
| Diffuse large B-cell lymphoma | 6.94 | 6.83-7.05 | 15 393 | | 7.24 | 7.08-7.40 | 6.67 | 6.52-6.82 | 2.44 | 2.37-2.52 | 9.31 | 8.95-9.68 | 20.87 | 20.45-21.31 | 4 568 |
| Follicular lymphoma | 2.85 | 2.78-2.92 | 6 320 | | 2.80 | 2.70-2.90 | 2.90 | 2.80-3.00 | 1.28 | 1.23-1.34 | 5.90 | 5.61-6.20 | 6.32 | 6.09-6.56 | 1 849 |
| Hairy cell leukaemia | 0.44 | 0.42-0.47 | 985 | | 0.72 | 0.67-0.77 | 0.19 | 0.16-0.21 | 0.24 | 0.21-0.26 | 0.86 | 0.76-0.98 | 0.89 | 0.80-0.98 | 292 |
| Plasmacytoma/Multiple Myeloma (and Heavy chain diseases) | 8.36 | 8.24-8.48 | 18 545 | | 8.75 | 8.58-8.93 | 8.00 | 7.83-8.16 | 1.27 | 1.22-1.33 | 12.11 | 11.70-12.53 | 30.31 | 29.80-30.83 | 5 643 |
| Mantle cell lymphoma | 0.72 | 0.68-0.75 | 1 588 | | 1.04 | 0.98-1.10 | 0.42 | 0.38-0.46 | 0.15 | 0.13-0.17 | 1.32 | 1.19-1.46 | 2.29 | 2.15-2.44 | 476 |
| Prolymphocytic leukaemia, B cell | 0.03 | 0.02-0.04 | 63 | | 0.04 | 0.03-0.05 | 0.02 | 0.01-0.03 | <0.01 | 0.00-0.01 | 0.03 | 0.01-0.05 | 0.11 | 0.08-0.15 | 20 |
| **ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS** | **5.34** | **5.24-5.44** | **11 837** | **10%** | **5.80** | **5.66-5.95** | **4.90** | **4.78-5.03** | **1.73** | **1.67-1.80** | **6.12** | **5.83-6.42** | **17.19** | **16.81-17.58** | **3 572** |
| Acute promyelocytic leukaemia (AML) with t(15;17) and variants | 0.23 | 0.21-0.25 | 513 | | 0.23 | 0.20-0.26 | 0.23 | 0.21-0.26 | 0.19 | 0.17-0.22 | 0.26 | 0.20-0.33 | 0.35 | 0.30-0.41 | 145 |
| Acute myeloid leukaemia | 4.79 | 4.70-4.88 | 10 620 | | 5.22 | 5.09-5.36 | 4.38 | 4.26-4.51 | 1.49 | 1.43-1.55 | 5.60 | 5.32-5.88 | 15.58 | 15.21-15.95 | 3 204 |
| **MYELOPROLIFERATIVE NEOPLASMS** | **5.47** | **5.37-5.56** | **12 119** | **10%** | **6.27** | **6.12-6.42** | **4.71** | **4.58-4.84** | **2.02** | **1.95-2.09** | **7.67** | **7.34-8.00** | **15.90** | **15.53-16.28** | **3 610** |
| Chronic myeloid leukaemia | 1.61 | 1.56-1.66 | 3 566 | | 1.87 | 1.79-1.95 | 1.36 | 1.30-1.43 | 0.65 | 0.61-0.69 | 2.09 | 1.92-2.27 | 4.59 | 4.39-4.79 | 1 075 |
| Other myeloproliferative neoplasms | 3.80 | 3.72-3.88 | 8 425 | | 4.34 | 4.21-4.47 | 3.29 | 3.19-3.40 | 1.32 | 1.27-1.38 | 5.50 | 5.22-5.79 | 11.22 | 10.91-11.53 | 2 499 |
| Mast cell tumours | 0.06 | 0.05-0.07 | 128 | | 0.06 | 0.05-0.08 | 0.05 | 0.04-0.07 | 0.04 | 0.03-0.06 | 0.08 | 0.05-0.12 | 0.10 | 0.07-0.13 | 36 |
| **MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES** | **3.39** | **3.31-3.46** | **7 511** | **6%** | **3.90** | **3.78-4.02** | **2.91** | **2.81-3.01** | **0.35** | **0.32-0.39** | **2.44** | **2.26-2.63** | **14.36** | **14.01-14.72** | **2 371** |
| Myelodysplastic syndrome with 5q syndrome | 0.02 | 0.01-0.03 | 41 | | 0.01 | 0.01-0.02 | 0.02 | 0.02-0.03 | <0.01 | 0.00-0.01 | 0.02 | 0.01-0.04 | 0.08 | 0.05-0.11 | 12 |
| Other myelodysplastic syndrome | 3.04 | 2.96-3.11 | 6 733 | | 3.45 | 3.34-3.57 | 2.64 | 2.55-2.74 | 0.32 | 0.29-0.35 | 2.18 | 2.01-2.36 | 12.86 | 12.53-13.20 | 2 129 |
| Chronic myelomonocytic leukaemia | 0.31 | 0.29-0.34 | 694 | | 0.41 | 0.37-0.45 | 0.22 | 0.19-0.25 | 0.03 | 0.02-0.04 | 0.22 | 0.17-0.28 | 1.35 | 1.24-1.46 | 216 |
| Atypical chronic myeloid leukaemia BCR/ABL negative | 0.02 | 0.01-0.02 | 39 | | 0.02 | 0.01-0.03 | 0.01 | 0.01-0.02 | <0.01 | 0.00-0.01 | 0.01 | 0.00-0.04 | 0.07 | 0.04-0.09 | 12 |
| **HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS** | **0.11** | **0.10-0.12** | **243** | **0.2%** | **0.13** | **0.11-0.16** | **0.09** | **0.07-0.11** | **0.11** | **0.09-0.13** | **0.07** | **0.04-0.10** | **0.14** | **0.11-0.18** | **68** |
| Histiocytic malignancies | 0.08 | 0.07-0.09 | 181 | | 0.10 | 0.08-0.12 | 0.06 | 0.05-0.08 | 0.10 | 0.08-0.11 | 0.03 | 0.02-0.06 | 0.07 | 0.04-0.09 | 50 |
| Lymph node accessory cell tumours | 0.03 | 0.02-0.04 | 62 | | 0.03 | 0.02-0.04 | 0.03 | 0.02-0.04 | 0.01 | 0.01-0.02 | 0.03 | 0.02-0.06 | 0.08 | 0.05-0.11 | 18 |

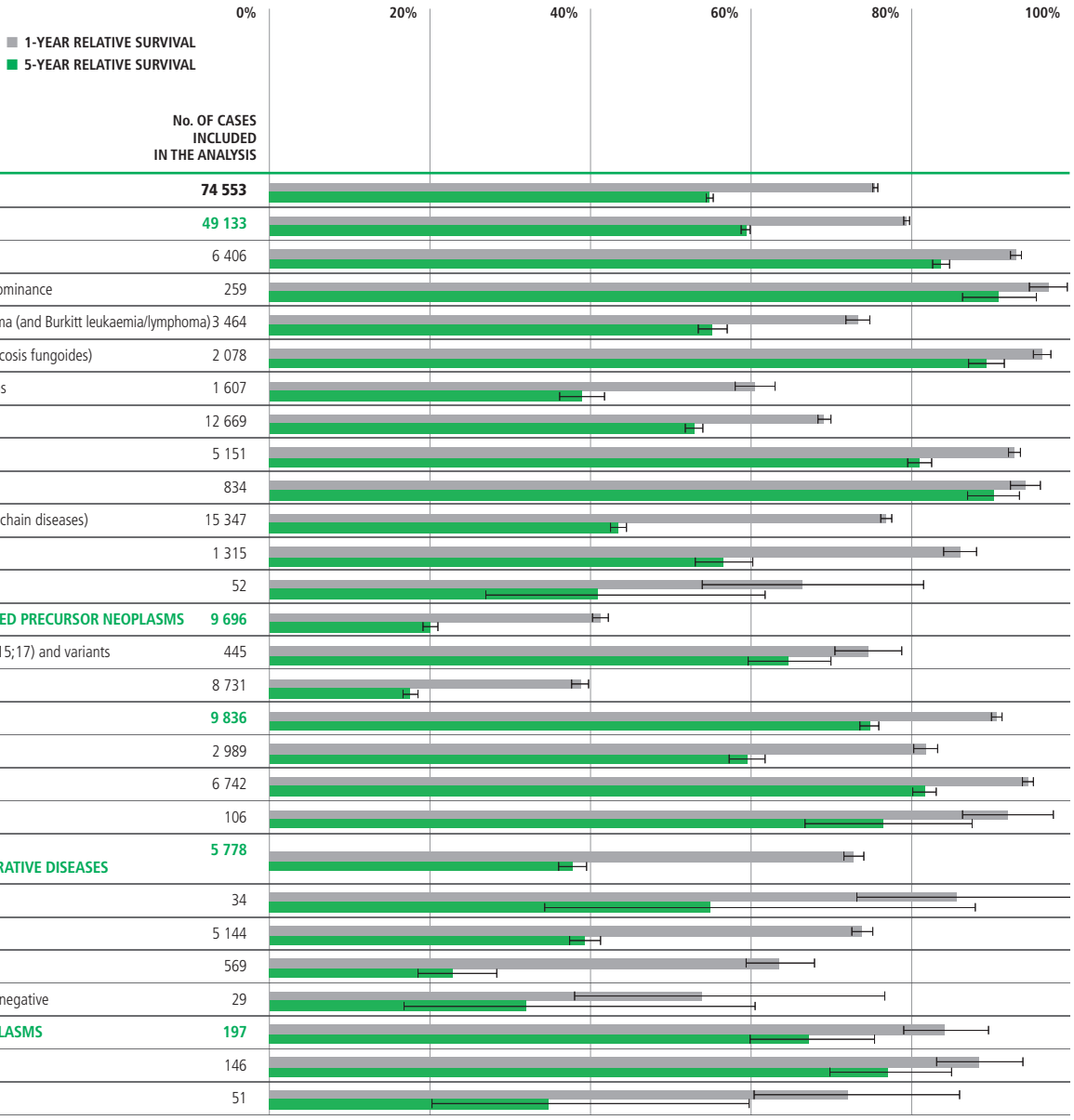
**NK:** natural killer

# RARE HAEMATOLOGICAL DISEASES

# SURVIVAL



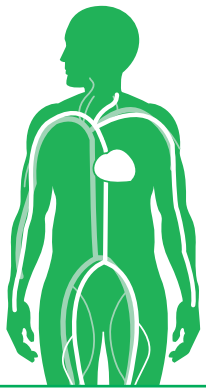
**RARE HAEMATOLOGICAL DISEASES.** One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.




| | No. OF CASES INCLUDED IN THE ANALYSIS |
|---|---|
| **RARE HAEMATOLOGICAL DISEASES** | **74 553** |
| **RARE LYMPHOID DISEASES** | **49 133** |
| Hodgkin lymphoma, classical | 6 406 |
| Hodgkin lymphoma nodular lymphocyte predominance | 259 |
| Precursor B/T lymphoblastic leukaemia/lymphoma (and Burkitt leukaemia/lymphoma) | 3 464 |
| T cutaneous lymphoma (Sezary syndrome, Mycosis fungoides) | 2 078 |
| Other T cell lymphomas and NK cell neoplasms | 1 607 |
| Diffuse large B-cell lymphoma | 12 669 |
| Follicular lymphoma | 5 151 |
| Hairy cell leukemia | 834 |
| Plasmacytoma/Multiple Myeloma (and Heavy chain diseases) | 15 347 |
| Mantle cell lymphoma | 1 315 |
| Prolymphocytic leukaemia, B cell | 52 |
| **ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS** | **9 696** |
| Acute promyelocytic leukaemia (AML) with t(15;17) and variants | 445 |
| Acute myeloid leukaemia | 8 731 |
| **MYELOPROLIFERATIVE NEOPLASMS** | **9 836** |
| Chronic myeloid leukaemia | 2 989 |
| Other myeloproliferative neoplasms | 6 742 |
| Mast cell tumours | 106 |
| **MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES** | **5 778** |
| Myelodysplastic syndrome with 5q syndrome | 34 |
| Other myelodysplastic syndrome | 5 144 |
| Chronic myelomonocytic leukaemia | 569 |
| Atypical chronic myeloid leukaemia BCR/ABL negative | 29 |
| **HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS** | **197** |
| Histiocytic malignancies | 146 |
| Lymph node accessory cell tumours | 51 |

**NK:** natural killer

# RARE HAEMATOLOGICAL DISEASES



# PREVALENCE

**RARE HAEMATOLOGICAL DISEASES.** Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

| | AIRTUM POOL | | | | | | | | ITALY |
|---|---|---|---|---|---|---|---|---|---|
| | OBSERVED PREVALENCE BY DURATION | | | | | | COMPLETE PREVALENCE | | |
| | ≤2 YEARS | | 2-5 YEARS | | ≤15 YEARS | | | | |
| | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | PROPORTION | 95% CI | ESTIMATED PREVALENT CASES 2010 |
| **RARE HAEMATOLOGICAL DISEASES** | **71.79** | **70.02-73.59** | **68.28** | **66.56-70.04** | **253.26** | **249.92-256.62** | **277.80** | **271.10-284.50** | **225 872** |
| **RARE LYMPHOID DISEASES** | **47.76** | **46.31-49.23** | **49.20** | **47.73-50.69** | **187.44** | **184.58-190.34** | **298.94** | **290.05-307.84** | **178 237** |
| Hodgkin lymphoma, classical | 6.83 | 6.29-7.40 | 8.99 | 8.37-9.64 | 37.95 | 36.66-39.26 | 78.56 | 75.58-81.54 | 45 356 |
| Hodgkin lymphoma nodular lymphocyte predominance | 0.26 | 0.17-0.40 | 0.33 | 0.22-0.48 | 1.25 | 1.03-1.51 | 3.32 | 2.35-4.30 | 1 974 |
| Precursor B/T lymphoblastic leukaemia/lymphoma (and Burkitt leukaemia/lymphoma) | 2.66 | 2.33-3.03 | 2.71 | 2.38-3.08 | 12.19 | 11.46-12.94 | 56.49 | 48.73-64.26 | 33 843 |
| T cutaneous lymphoma (Sezary syndrome, Mycosis fungoides) | 2.62 | 2.29-2.98 | 3.44 | 3.06-3.86 | 13.35 | 12.6-14.15 | 18.57 | 17.43-19.70 | 11 173 |
| Other T cell lymphomas and NK cell neoplasms | 1.01 | 0.81-1.25 | 1.02 | 0.82-1.25 | 3.64 | 3.25-4.07 | 4.61 | 4.10-5.13 | 2 817 |
| Diffuse large B-cell lymphoma | 10.61 | 9.94-11.32 | 10.78 | 10.10-11.49 | 41.36 | 40.02-42.73 | 48.29 | 46.71-49.88 | 29 550 |
| Follicular lymphoma | 6.54 | 6.02-7.10 | 6.01 | 5.51-6.55 | 23.61 | 22.6-24.65 | 27.28 | 26.06-28.51 | 16 815 |
| Hairy cell leukaemia | 0.98 | 0.78-1.21 | 1.33 | 1.10-1.60 | 5.05 | 4.59-5.54 | 7.59 | 6.73-8.46 | 4 637 |
| Plasmacytoma/Multiple Myeloma (and Heavy chain diseases) | 14.70 | 13.91-15.53 | 13.20 | 12.45-13.98 | 43.70 | 42.32-45.11 | 47.76 | 46.23-49.30 | 28 229 |
| Mantle cell lymphoma | 1.51 | 1.26-1.79 | 1.36 | 1.12-1.62 | 5.46 | 4.98-5.97 | 6.25 | 5.68-6.81 | 3 731 |
| Prolymphocytic leukaemia, B cell | 0.05 | 0.01-0.12 | 0.08 | 0.03-0.17 | 0.16 | 0.09-0.27 | 0.19 | 0.09-0.29 | 112 |
| **ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS** | **4.47** | **4.03-4.93** | **2.73** | **2.40-3.10** | **12.48** | **11.75-13.25** | **18.94** | **17.79-20.09** | **11 146** |
| Acute promyelocytic leukaemia (AML) with t(15;17) and variants | 0.37 | 0.25-0.52 | 0.43 | 0.30-0.59 | 1.62 | 1.36-1.91 | 1.79 | 1.49-2.09 | 1 039 |
| Acute myeloid leukaemia | 3.82 | 3.42-4.26 | 2.15 | 1.85-2.48 | 10.05 | 9.39-10.74 | 16.53 | 15.40-17.67 | 10 481 |
| **MYELOPROLIFERATIVE NEOPLASMS** | **12.21** | **11.49-12.97** | **12.06** | **11.34-12.81** | **38.95** | **37.65-40.28** | **45.30** | **43.64-46.96** | **26 243** |
| Chronic myeloid leukaemia | 2.42 | 2.10-2.77 | 3.00 | 2.65-3.39 | 9.98 | 9.33-10.67 | 10.76 | 10.04-11.49 | 6 221 |
| Other myeloproliferative neoplasms | 9.68 | 9.04-10.35 | 8.86 | 8.24-9.50 | 28.49 | 27.38-29.63 | 33.88 | 32.45-35.32 | 19 620 |
| Mast cell tumours | 0.11 | 0.06-0.21 | 0.21 | 0.12-0.33 | 0.48 | 0.35-0.65 | 0.97 | 0.64-1.29 | 579 |
| **MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES** | **7.17** | **6.62-7.76** | **4.17** | **3.76-4.63** | **13.90** | **13.12-14.70** | **15.87** | **14.96-16.78** | **9 213** |
| Myelodysplastic syndrome with 5q syndrome | 0.09 | 0.04-0.18 | 0.05 | 0.01-0.12 | 0.15 | 0.08-0.26 | 0.17 | 0.08-0.27 | 102 |
| Other myelodysplastic syndrome | 6.52 | 5.99-7.08 | 3.83 | 3.43-4.26 | 12.67 | 11.93-13.44 | 13.52 | 12.72-14.32 | 7 965 |
| Chronic myelomonocytic leukaemia | 0.54 | 0.40-0.72 | 0.30 | 0.20-0.44 | 1.03 | 0.83-1.27 | 1.37 | 1.07-1.67 | 803 |
| Atypical chronic myeloid leukaemia BCR/ABL negative | 0.02 | 0.00-0.08 | 0.00 | 0.00-0.04 | 0.05 | 0.01-0.12 | 0.05 | 0.00-0.10 | 28 |
| **HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS** | **0.22** | **0.13-0.34** | **0.13** | **0.06-0.23** | **0.77** | **0.60-0.98** | **1.68** | **1.19-2.17** | **1 033** |
| Histiocytic malignancies | 0.11 | 0.06-0.21 | 0.11 | 0.06-0.21 | 0.64 | 0.49-0.84 | 1.45 | 0.99-1.92 | 895 |
| Lymph node accessory cell tumours | 0.10 | 0.05-0.20 | 0.01 | 0.00-0.06 | 0.13 | 0.06-0.23 | 0.23 | 0.09-0.37 | 138 |

**NK:** natural killer

The classification of lymphoproliferative disorders includes various entities divided according to cytohistological features, immunephenotype, molecular characteristics, and clinical relevance. Overall, about 74% of haematological cancers are rare (incidence table, p. 102). This group includes:

- **rare lymphoid diseases** (classic Hodgkin lymphoma, Hodgkin lymphoma with nodular lymphocyte predominance, precursor B/T lymphoblastic leukaemia/lymphoma, Burkitt's leukaemia/lymphoma, T cutaneous lymphoma – Sezary syndrome, Mycosis fungoides, other T-cell lymphomas and NK-cell neoplasms, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukaemia, plasmacytoma/multiple myeloma and heavy chain diseases, mantle cell lymphoma, B-cell prolymphocytic leukaemia);
- **acute myeloid leukaemia** (acute promyelocytic leukaemia with t(15;17) translocation and variants, acute myeloid leukaemia);
- **myeloproliferative neoplasms** (chronic myeloid leukaemia, other myeloproliferative neoplasms, mast cell tumours);
- **myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases** (myelodysplastic syndrome with 5q syndrome, other myelodysplastic syndrome, chronic myelomonocytic leukaemia, atypical chronic myeloid leukaemia BCR/ABL negative);
- **histiocytic and dendritic cell neoplasms** (histiocytic malignancies, accessory cell tumours).

It is worth mentioning that variations in classification between ICD-O-2 and ICD-O-3 mainly concern these diseases and especially the group of myeloproliferative neoplasms (MPNs) and the group of myelodysplastic/myeloproliferative diseases (MDS/MPDs). Many of the tumours included in these 2 groups changed behaviour (becoming malignant invasive) with the ICD-O-3, which was introduced in the year 2000. Thus, cancer registries (CRs) started to register these entities only from 2000 on and at different paces. In addition, information sources used by CRs to identify cancer cases do not properly capture all cases of haematological diseases. All this translates into an underestimation in our data of these diseases.

However, the proportion of haematological diseases with «not otherwise specified» (NOS) morphology across Italian CRs was below 30%, which is the cut-off used by international studies to exclude CRs from analyses because of low quality.[1]

In addition to the proportion of NOS morphologies, we also looked at the incidence trends of MPNs and MDS/MPD across the different Italian CRs. In this exploratory analysis of the incidence trend, two groups of CRs were identified: the first included CRs with lower than average (4 per 100,000) age-standardised incidence rates for MPN during the 2000-2010 period, whereas the second included CRs with higher than average rates. The first group had a very low incidence rate, which increased after 2000 without reaching, in 2010, the incidence rate of the other AIRTUM CRs, for both MPN and MDS/MPD. The incidence rate in the second group of CRs increased up to 2010 to almost double the rate of the CRs of the first group for both MPNs and MDS/MPDs. It is very likely that in the first group there are CRs which tend to not properly record all cases of MPNs and/or MDS/MPDs. Nevertheless, the incidence rate obtained considering only the second group of CRs is substantially comparable to the one obtained combining together the two groups of CRs. Thus, all CRs were considered in order to include the largest possible number of cases in the analysis of these tumours, which, for the first time, are described in Italy in such morphological detail. This is an opportunity to provide estimates to discuss with clinicians and CRs how to improve registration.

## RARE LYMPHOID DISEASES

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Lymphoid diseases comprise a heterogeneous group of disorders originating from clonal proliferation of B or T lymphocytes and covering both Hodgkin and non-Hodgkin disease. These are considered in this group, clinical management is rapidly evolved and various treatments (in terms of drugs employed and intensity of approaches) are now applied according to different entities and characteristics of patients: the new targeted therapy inhibits the proto-oncogenes which signal cells to proliferate, differentiate, and survive, and whose overactivity results in malignancy.[2]

About one-third of non-Hodgkin lymphomas (NHL) arise from sites other than lymph nodes, spleen, or bone marrow, and even from sites which normally contain no native lymphoid tissue. In principle, as for primary nodal disease, treatment strategies depend on the patient's clinical conditions, the extent and/or location of the disease, and the histological type.[3] However, in the list of rare haematological diseases proposed by RARECARE,[4] extranodal lymphomas are not separated from the others.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Rare lymphoid diseases account for 65% of all rare haematological diseases (see table p. 102). About a third of rare lymphoid diseases (31%) are plasma cell tumours, followed by diffuse large B-cell lymphoma (26%), classic Hodgkin lymphoma (13%), and follicular lymphoma (11%). The other lymphoid diseases represent a minority of cases ranging from 1% to 7% of all rare lymphoid diseases. The rarest is prolymphocytic leukaemia, B-cell (see table p. 102). Most rare lymphoid diseases are diagnosed in people aged 50 years and older, with a few exceptions. Classic Hodgkin lymphoma has the highest incidence in the 15-29 year age group and precursor B/T lymphoblastic leukaemia/lymphoma has the highest incidence in children (0-14 years) (data not shown). The former represent 64% of all rare lymphoid diseases in adolescents and young adults (15-29 years) and the latter account for 77% of all rare lymphoid diseases in children (data not shown).

The highest male to female ratio (M/F ratio) is observed for hairy cell leukaemia and mantle cell lymphoma (M/F ratio: 3.8 and 2.5, respectively). About 17,000 new cases of rare lymphoid diseases are expected in Italy in 2015 (see table p. 102). Among young adults, about 600 cases of rare lymphoid diseases are expected, of which 500 are classic Hodgkin lymphoma. Among children, about 330 cases of rare lymphoid diseases are expected in 2015, of which 250 are precursor B/T lymphoblastic leukaemias/lymphomas (data not shown).

The incidence rate (IR) of rare lymphoid diseases in Italy is much higher than the IR observed in the European RARECAREnet database (www.rarecarenet.eu) (IR 26.8 per 100,000 in Italy vs.

18.1 per 100,000 in Europe), because in Italy the IR of diffuse large B-cell lymphoma and multiple myeloma is higher than in Europe. Thus, these two diseases are rare in Europe but not in Italy (see «The burden of rare cancers in Italy», pp. 22-27).

### Survival

Rare lymphoid diseases have a good survival rate 1 year after diagnosis (79%), which decreases after 5 years from diagnosis (59%) (survival figure, p. 103). However, 5-year relative survival (RS) differs across diseases, and is 80%-90% for classic Hodgkin lymphoma, follicular lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, T cutaneous lymphoma, and hairy cell leukaemia (HCL) (see figure p. 103) and around 40% for other T-cell lymphomas and NK-cell neoplasms, plasmacytoma/multiple myeloma and prolymphocytic leukaemia, B cell. The lower survival observed in the latter diseases could be due to the fact that they mainly arise in the elderly (>70 years), thus in people who are likely to have comorbidities and are more difficult to treat.

These results are similar to those observed in Europe, where a significant increase of survival over time (from 1997 to 2008) for all lymphoid malignancies, with the greatest increases for follicular lymphoma and diffuse large B-cell lymphoma was also reported.[5] The survival increase for follicular lymphoma and diffuse large B-cell leukaemia are probably a result of the adoption of RITUXIMAB, which is safe and effective in older as well as younger patients.[1,2] Improved supportive care with better control of comorbidities, especially for older patients, might also have contributed to improve survival for lymphoid malignancies in general.[5]

Five-year RS for rare lymphoid diseases is 86% and 85% among children and young adults, respectively (data not shown). In children, 5-year RS is 89% for precursor B/T lymphoblastic leukaemias/lymphomas; among young adults, 5-year RS is 94% for classic Hodgkin lymphoma (data not shown).

### Prevalence

Around 178,000 persons were estimated to be living with a previous diagnosis of rare lymphoid diseases in Italy in 2010; 37% of these cases had survived more than 15 years from diagnosis. Most prevalent cases are represented by patients with a previous diagnosis of classic Hodgkin lymphoma (25%) and precursor B/T lymphoblastic leukaemia/lymphoma (19%), diffuse large B-cell lymphoma (17%), and plasmacytoma/multiple myeloma (16%). This is due to the high survival for classic Hodgkin lymphoma and relatively high IR for the other entities, which have a 5-year RS rate ranging from 50% to 40%.

## ACUTE MYELOID LEUKAEMIA

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Acute myeloid leukaemia (AML) is a heterogeneous clonal disorder (differentiation arrest or malignant proliferation) of haemopoietic progenitor cells, in particular myeloid precursors in the bone marrow and blood.[6] The new 2008 WHO classification[7] divides them, according to their cellular and molecular characteristics, into myelocytic, myelogenous, or non-lymphocytic disorders. Furthermore, they are classified as primary (or de novo) or secondary, if they arise after an MDS or MDS/MPN, or a blast transformation in a previously diagnosed MPN, or as consequence of exposure to toxic substances and/or chemotherapy.

However, AML has long been recognised as a nosological entity, thus the criteria for disease definition are stable over time. In the past twenty years, there has been little improvement in chemotherapeutic regimens with the exception of the treatment of acute promyelocytic leukaemia (APL), in which all trans-retinoic acid (ATRA) is used.[8] Thus, within the RARECARE[4] project it was decided to identify two major groups of AML on the basis of the different way in which they are treated.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

AML and related precursor neoplasms account for 13% of rare haematological diseases. AML mainly occurs in the over 65 population (see table p. 102), the IR is 5 per 100,000 per year in those aged 50-55 and 7 per 100,000 per year in those aged 60-64 (data not shown). The IR is very low <1 per 100,000 in children (0-14 years) and increases slightly from 1 per 100,000 (in those aged 20-24 years) to 2 per 100,000 (in those aged 40-44 years) confirming that AML is typical of the elderly (data not shown).

APL with t(15;17) translocation and variants accounts for 4% of all AML. Its IR increases with age, and is very low in children (IR 0.1 per 100,000; data not shown) and highest in the elderly (see table p. 102). However, APL is typical of children and young adults, representing in the 0-29 year age class 14% of all AML, compared to only 2% of all AML in those aged >65 years (data not shown).

The M/F ratio is 1.2, and approximately 3,600 cases of AML and related precursor neoplasms are estimated in Italy in 2015 (see table p. 102).

The IR of AML in Italy is slightly higher than that observed in the European RARECAREnet database (IR 5.3 per 100,000 in Italy vs. 3.8 per 100,000 in Europe).

#### Survival

Survival is different for the two observed entities. APL has a better prognosis at 1 year and 5 years after diagnosis (74% and 64%, respectively) compared to AML (39% and 18%, respectively) (see figure p. 103). The relatively good prognosis of APL is mainly attributable to the use of trans retinoic acid (ATRA) and is consistent with previous findings[8] and the new results observed in Europe.[5]

Unfortunately, in the past twenty years, there has been little improvement in chemotherapeutic regimens and hence in the overall survival for patients with AML (other than APL). The major improvements in AML treatment during the last two decades have not come from the introduction of new therapeutic agents, but rather from improved use of well-known drugs. However, the limit of acceptable toxicity for standard chemotherapeutic drugs used in AML therapy has been reached and new therapeutic strategies are therefore needed.[8]

#### Prevalence

Around 11,000 persons were estimated to be living with a previous diagnosis of AML and related precursor neoplasms in Italy in 2010; this is due to the relatively high IR of AML rather than to RS, which is low for AML.

## MYELOPROLIFERATIVE NEOPLASMS

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Myeloproliferative neoplasms (MPNs) comprise clonal blood disorders, such as chronic myeloid leukaemia (CML), polycythaemia vera, essential thrombocythaemia, primary myelofibrosis, and mast cell tumours and are characterised by increased production of terminally differentiated myeloid cells. These disorders are classified according to rearrangements or mutations of genes (i.e. Ph-chromosome-positive, the BCR-ABL1 fusion gene, in CML, and JAK2-, CALR-, MPL-, and KIT-mutation-positive in the other neoplasms).[9,10]

The management of these tumours with targeted treatments is based on clinical, biologic, cytogenetic, and molecular characteristics. The prognosis of CML has dramatically improved since the availability of IMATINIB in current practice.

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

MPNs represent 13% of all rare haematological diseases. These pathologies are mainly diagnosed in the over 65 population (see table p. 102). The majority of these diseases is represented by the group of «other myeloproliferative neoplasms», which include primary myelofibrosis, essential thrombocythaemia, polycythaemia vera, which together account for 75% of the «other myeloproliferative neoplasms» group (data not shown).

CML represents the second most common MPN (see table p. 102).

The M/F ratio is 1.3, with no differences among the different diseases. New cases of MPNs are estimated to be around 3,500 in Italy in 2015 (see table p. 102). Selecting only CRs with the higher incidence rates (see definition of group two in the introduction to the present chapter), the number of estimated new cancer cases would be of about 4,500 in Italy in 2015.

The IR of these diseases is, in any case, higher in Italy than in the European RARECAREnet database (IR 5.5 per 100,000 in Italy vs. 3.0 per 100,000 in Europe). Probably, the main reason for the low rates in Europe is the not yet standardised and complete registration in Europe of MPNs other than CML, as they were only recognised as malignant in the ICD-O-3 classification. The discovery of the JAK2-V617F mutation, which is a clue in the diagnosis of primary myelofibrosis essential thrombocythaemia and polycythaemia vera, will make it easier than in the past to diagnose these diseases. This will likely increase the systematic registration of essential thrombocythaemia and polycythaemia vera, and will probably lead to an increase of the reported incidence.

Low incidence rates in Europe for MPNs with a relatively indolent behaviour might also be due to the fact that most CRs use information of pathology labs and hospital discharge records as their main notification source. Information from outpatient departments is not always systematically notified and thus a large proportion of patients with polycythaemia vera and essential thrombocythaemia, which often lack pathological confirmation and are outpatients only, are not registered by those CRs. This can explain also the difference between the IR observed in the two groups of CRs in Italy (see definition of group one and two in «A guide to the cancer-specific data sheets», pp. 28-31).

#### Survival

MPNs have a good prognosis at 1 and 5 years after diagnosis (90% and 75%, respectively), with differences across the specific disease subtype. The highest 5-year RS was observed for mast cell tumours and other myeloproliferative neoplasms (76% and 81%, respectively) (see figure p. 103). The latter group includes entities with high survival, such as essential thrombocythaemia (5-year RS 94%) and polycythaemia vera (5-year RS 92%), as well as entities with poor survival, such as primary myelofibrosis (5-year RS 54%) (data not shown).

The 5-year RS of patients with CML was 59% (see figure p. 103).The treatment of CML has been significantly modified since the discovery of IMATINIB, a targeted molecule that inhibits the tyrosine kinase activity of the neo protein resulting from the BCR ABL fusion gene. The prognosis of CML has dramatically improved since the availability of IMATINIB in current practice. In Europe, an increase in survival was observed, from 32% in the period 1997-1999 to 54% in the period 2006-2008.[5] Thus, these data confirm, for the first time even in Italy, the great impact that the introduction of IMATINIB has had at the population level.

#### Prevalence

Around 26,000 persons were estimated to be living with a previous diagnosis of MPNs in Italy in 2010; 14% of these cases had survived more than 15 years from diagnosis.

## MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/ MYELOPROLIFERATIVE DISEASES

### WHAT DO WE KNOW ABOUT THESE CANCERS?

Myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases (MDS/MPD) comprise a heterogeneous group of disorders originating from clonal hematopoietic stem cells. These are characterised by ineffective haematopoiesis, peripheral cytopoenias, and a variable propensity for leukaemic transformation.[11] The classification is based on genetic mutations: for example, chronic myelomonocytic leukaemia (CMML) is associated with diverse pathways that include mutations of signal transduction, DNA methylation, transcriptional regulation, chromatin modification, and the RNA splicing machinery.[12] Though the general approach for the treatment is tailored to symptoms of patients, some therapeutic approaches, including lenalidomide, azacitidine, erythropoiesis stimulating agents and iron chelation have been demonstrated to alter the natural history of these disease in selected MDS patients.[13]

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

MDS/MPDs represent 8% of all rare haematological diseases (see table p. 102). The majority of these tumours are represented by the group of «other myelodysplastic syndromes», which includes, in decreasing order: refractory anaemia (18%), refractory anaemia with excess of blasts (12%), refractory cytopoenia with multilineage dysplasia (4%), refractory anaemia with sideroblasts (3%), myelodysplastic syndrome NOS (64%) (data not shown). The other specific disease subtypes are very rare. This group of diseases has a high IR in the elderly,

however, chronic myelomonocytic leukaemia is much more common in children than in the elderly: it represents 26% of all MDS/MPDs in children compared to 9% in those aged >65 years (data not shown). The highest M/F ratio is observed for CML (1.9) while myelodysplastic syndrome with 5q syndrome is more common among females than males. Around 2,500 cases of MDS/MPD are expected in 2015 in Italy (see table p. 102). Selecting only CRs with higher incidence rates (see definition of group two in the introduction to the present chapter), the number of estimated cancer cases in Italy would be of about 3,000 in 2015. The IRs observed in Italy are slightly higher than those reported by the European RARECAREnet database (IR 3.4 per 100,000 in Italy vs. 2.5 per 100,000 in Europe). As for myeloproliferative neoplasms, even for this group of diseases the lower IR in Europe could be due to heterogeneity in the registration of these entities across European CRs.

### Survival

In general, these disorders do not have a good prognosis: 1-year RS is 73%, but 5-year RS decreases to 38%. Five-year RS is highest for myelodysplastic syndrome with 5q syndrome (55%) and lowest for chronic myelomonocytic leukaemia (23%) (see figure p. 103). Major changes in treatment are attributable to the introduction of new drugs such as lenalidomide, azacytidine, and decitabine. However, their effect on survival in the general population has not been observed yet. At the European level, the 5-year RS is higher (48%) than in Italy, but no major changes were observed from 2003-2005 to 2006-2008.[5]

### Prevalence

Around 9,000 persons were estimated to be living with a previous diagnosis of MDS/MPD in Italy in 2010; 12% of these cases had survived more than 15 years from diagnosis.

## HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

### WHAT DO WE KNOW ABOUT THESE CANCERS?

These disorders include Langerhans cell histiocytosis, histiocytic sarcoma, follicular dendritic cell sarcoma, interdigitating cell sarcoma, indeterminate cell sarcoma, and fibroblastic reticular cell tumours. Histiocytic and dendritic cell neoplasms are very rare and should be diagnosed with a combination of morphology review and a battery of immunohistochemistry to rule out mimics such as carcinoma, lymphoma, and neuroendocrine tumours, and to better sub-classify these hard-to-diagnose lesions.[14] The treatment for localised disease is surgical resection and the role of adjuvant therapy is unclear. In patients with multiple areas of involvement, multimodality treatment at tertiary care centres is likely needed.[15]

### THE EPIDEMIOLOGICAL DATA IN ITALY

#### Incidence

Histiocytic and dendritic cell neoplasms represent only 0.3% of all rare haematological diseases (see table p. 102). Histiocytic malignancies have the highest IR in children and in particular in those aged <4 years. They represent 99% of histiocytic and dendritic cell neoplasms in children compared to 45% in those aged >65 years. On the contrary, accessory cell tumours have the highest IR in the elderly (>65 years) and are extremely rare in children (IR 0.1 per 100,000) (data not shown). The M/F ratio is 1.6 for histiocytic malignancies, while no differences exist between males and females for accessory cell tumours. About 70 cases of histiocytic and dendritic cell neoplasm cases are estimated in 2015 in Italy (see table p. 102). In the European RARECAREnet database, the IR is lower (IR 0.1 per 100,000 in Italy vs. 0.05 per 100,000 in Europe).

#### Survival

Overall, histiocytic and dendritic cell neoplasms have a good 1-year RS (84%), which decreases after 5 years from diagnosis (67%). However, differences exist between the specific disease subtype. Five-year RS is highest for histiocytic malignancies (77%) and lowest for lymph node accessory cell tumours (35%) (see figure p. 103). This could be partially due to the fact that the latter are typical of the elderly, and poor survival in elderly patients is generally attributed to the inability to give potentially curative treatments because patients are frail or have comorbidities. Late diagnosis and under-evaluation of disease symptoms could also play a part. Finally, most clinical trials do not include older patients or those with low performance status, so treatment protocols are not optimised for the elderly.

#### Prevalence

Around 1,000 persons were estimated to be living with a previous diagnosis of histiocytic and dendritic cell neoplasms in Italy in 2010; 54% of these cases had survived more than 15 years from diagnosis and were represented by histiocytic malignancies because of both high incidence and high 5-year RS compared to lymph node accessory cell tumours.

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# COMMENTS
## FROM OTHER SCIENTIFIC ASSOCIATIONS AND PATIENTS' ORGANISATIONS

# COMMENTI
## DA ALTRE ASSOCIAZIONI SCIENTIFICHE E DI PAZIENTI

FAVO

# The role of cancer patient organisations as advocates for people with rare types of cancer

## Il ruolo delle organizzazioni di pazienti oncologici in difesa di chi è affetto da tumore raro

Federazione italiana delle associazioni di volontariato in oncologia (FAVO)

Italian Federation of Volunteer-Based Cancer Organisations (FAVO) considers the data presented in this monograph to be very valuable and important to outline the burden of rare cancers in Italy, which weigh heavily on the national health budget, and provide a fundamental prerequisite to adequately support people who have to face an uncommon cancer diagnosis and treatment.

In 2010, 360,000 persons were diagnosed with cancer in Italy. Of these, 89,000 (25%) were diagnosed with a rare type of cancer. The monograph adds that the majority of rare cancers (139 out of 198) are very rare (incidence rate <0.5 per 100,000) and affect only 7,100 individuals, or about 2% of the total number of people with cancer. This is important, because low incidence is a major obstacle to conducting clinical trials to develop effective treatments.

This monograph includes another important result. Five cancers considered rare on the basis of the European incidence rate are not rare in Italy (diffuse large B-cell lymphoma, multiple myeloma, hepatocellular carcinoma or HCC, larynx and thyroid cancer). These 5 cancers affect around 30,000 individuals in Italy and do not seem to be as critical as the other types, thereby presenting a countertrend compared to European figures.

Rare cancers imply late diagnosis and hence late treatment, limited access to appropriate treatments, including compassionate use of drugs, reduced number of centres with specialised experience and expertise, lack of information on the disease and difficulties to carry out clinical trials on the efficacy of a new treatment.

FAVO provides information on the available centres with specialised experience and expertise in rare cancers both in Italy and in Europe, and produces and disseminates information on diagnosis and treatment through ad-hoc designed materials (for more information, please call the toll-free number 800-903789, write to info@favo.it, or visit the website: www.favo.it). FAVO has also played a major role in the performance of joint research projects supported by the Italian Ministry of Health and carried out in collaboration with the Fondazione IRCCS, Istituto Nazionale dei Tumori of Milan (Rare Cancers in Italy, Surveillance and evaluation of access to diagnosis and treatment – RITA2 project, Interaction Framework between patient advocacy groups and sarcoma cancer centres as a model for rare cancers).

FAVO has partnered with the European Cancer Patient Coalition (ECPC) within the RARECAREnet (Information Network on Rare Cancers) research project financed by the European Commission and coordinated by the Fondazione IRCCS, Istituto Nazionale dei Tumori of Milan. As part of this project, ECPC drafted a list of 144 rare cancer patient organisations in Europe with the aim to build a good network to support patients with rare cancers. The list, which is available on the RARECAREnet website (http://www.rarecarenet.eu/rarecarenet/index.php/patient-organisations), provides details such as name, country, contact details, and website of each organisation. ECPC also collected information materials on most rare cancers identified by RARECAREnet experts, thereby creating an online library (available on the RARECAREnet website) that patients can query to find information on diagnosis, treatment, and follow-up of any rare type of cancer. To help patients with rare cancers to deal with the numerous disease-related issues, FAVO has joined the Rare Disease Inter-Parliamentary Group chaired by Parliament member Mrs. Binetti, and used their connections with scientific societies, academia, scientific institutions, etc. to form a group of stakeholders. The result of this joint effort was a Rare Cancer Paper that Mrs. Binetti discussed in Parliament through a specific motion, soon followed by numerous others. All motions were approved unanimously by the Chamber of Deputies with the Government's consent.

The approved motions call on the Italian Government to:

- encourage initiatives aimed at ensuring continuity and institutionalisation of the Rare Cancer Network operation (for further information, please refer to «The Italian Rare Cancer Network», p. 116) and its inclusion in the National Health System;
- formalise a rare cancer list;
- initiate a pathway leading to the definition of rare cancer centre accreditation criteria in order to centralise treatment locally and serve as an interface between treatment centres within the specific joint networks to achieve maximum effectiveness;
- set up a rare cancer working group under the Ministry of Health with the participation of cancer registries and cancer patient organisations;
- facilitate rare cancer patient access to compassionate use of drugs through amendment of Ministerial Decree May 8, 2003 (*Therapeutic use of a drug undergoing clinical trial*);
- invest on clinical research on rare cancers and their inclusion in public health programs;
- make sure that representatives from rare cancer patient organisations with recognised experience and expertise are involved in all rare cancer forums;
- facilitate patient referral to the Network centres in the early treatment phases through a widespread information system in which cancer patient organisations play a leading role;
- facilitate access to off-label drugs through the Italian Agency for Drugs's (AIFA) research fund, even by involving patients' caring physicians, to ensure ongoing, effective care, even though, so far, certain, definitive solutions are lacking.

For rare cancer patients, the activation of cross-border health care is extremely important. To this end, the Cross-Border Directive set as a priority for rare disease and rare cancers the creation of European Reference Networks (ERNs), to connect centres with specialised experience and expertise in specific diseases from the various Member States. ERNs can help treat patients with rare diseases for whose treatment it would be impossible to establish new treatment centres in all European Member States. ERNs can facilitate patient mobility among the Member States, above all to allow them to have access to particularly complex or specific health services for the treatment of rare diseases, including rare cancers.

AIOM

# Necessary steps to cope with rare cancers in Italy

## Passi necessari per affrontare i tumori rari in Italia

Associazione italiana di oncologia medica (AIOM)

Rare cancers are neoplasms with an annual incidence of less than 6 cases per 100,000 inhabitants; altogether, they account for as many as 25% of all cancer cases.[1,2]

Rare tumours pose particular problems for health system organisation, assistance, research, and new drug approval and reimbursement.[2,3]

Following current methodologies, clinical trials need a high number of patients to reach statistical significance, and it is not easy to collect such a number for uncommon tumours.

As a consequence, clinical evidence is more complicated to reach in rare than in frequent cancers. The final result is a high level of uncertainty in the whole process of decision making.[2-4]

Lack of evidence, low levels of recommendations, poor expertise of pathologists and clinicians lead, in general, to worse treatment results and worse survival in patients with rare cancers, compared to those recorded for common tumours.[1-4]

However, there is a great variance in incidence, natural history, and treatment outcomes among the groups of rare cancers.[5]

For instance, the highest 5-year survival level is recorded in testicular tumours, whereas, at the other extreme, mesothelioma has the lowest; both are considered rare cancers.[5-7]

Late diagnosis, incomplete or wrong pathological reports, and suboptimal treatment are frequent in uncommon tumours.[2-4]

For about 15 years, efforts have been made to improve knowledge and outcomes in rare cancers.[1-4]

As with more frequent types of cancer, decision making should be addressed rationally. Clinical studies must provide physicians, patients, and families with informative results which can be useful in the choice of the right therapy.[2,3,5,6]

A structure comprised of referral centres (hubs) with a higher expertise in a specific rare cancer, leading minor centres (spokes) grouped in a reference network, is at present the most accepted solution in health organisation.[1-5]

Earlier and more precise identification and diagnosis of an uncommon tumour and consequent decision making are essential to cure a higher percentage of patients, increase the number of long-term survivors, and lower the costs of management.[2-4]

A review of the pathologic diagnosis performed in hub centres is the first, fundamental step in the treatment of a rare tumour.[2-4,9]

Concordance between initial diagnosis and referral centre review is required.[9]

The exchange of experience, with ongoing communication between the hub and spokes, is crucial.[2,3,11]

However, the «rare tumour» label groups many entities, different for histology, anatomic presentation, natural history, and prognosis.[5]

The best example comes from soft tissue sarcomas (STS), one of the most studied groups of rare tumours. They can arise from fat, muscles, tendons, vessels, peripheral nervous system, and visceral organs. Almost all anatomic sites can be involved and more than 50 different histological types are recognised.[8]

Such a complexity requires a high level of expertise from a variety of specialists: pathologists for a correct diagnosis, surgeons performing interventions, orthopaedists for STS of the extremities and girdles, gynaecologists for uterine sarcomas, abdominal surgeons for retroperitoneal sarcomas, thoracic surgeons for lung and chest sarcomas, and otolaryngologists for head and neck sarcomas.[2,3,9]

Radiotherapy and medical treatment also require a particular expertise.

Since rare cancers include more than 200 entities, it is easy to understand that nobody can be a global expert in all these tumours.[1,2]

Searching for a referral centre, very often the patient has to move from the area of residence to a distant specialised hospital, in order to get the highest level of care. This solution increases personal and family costs.

In the hub/spoke system, on the other hand, the patient has to move to the referral centre only for brief phases of treatment, requiring high expertise. Ordinary therapies can be offered at the closest spoke hospital connected with the hub.[2-4]

How many referral centres should be planned in Italy to cope with all rare cancers?

Grouping the uncommon cancer by anatomic site, it is conceivable that a centre every 15-20 million inhabitants could be planned.[2-4]

In any case, the rarity of these tumours and the uncertainty in diagnosis and treatment do not modify the process of decision making applied in more frequent tumours.[2]

A multidisciplinary approach is the preferred model of health organisation in uncommon tumours,[2-4,9] with certain limitations: if the multidisciplinary group is unbalanced with expertise levels varying between the components, results can be less than optimal.[2-4]

Adequate training of all members of the group, steady communication with referral centres, and a periodical review of final results are necessary. Implementation and sharing of approved guidelines and constant monitoring of outcomes are fundamental to increase the group's experience and skills.[2-4]

Precise pathological diagnosis, well-defined staging of disease, and accurate clinical evaluation of the patient can lead to precise planning

of treatment. The complete evaluation of a treatment's risks and benefits must be shared with patients and their family and patient preference must be taken into account in the final decisions.[2-4,10]

Rare tumours have a specific profile in clinical studies, too. Because of the low number of patients, low levels of evidence are normally reached. When large and randomised trials are not feasible, evidence can be derived from single case reports, uncontrolled trials, and observational studies.[2,11]

Observational studies on selected patient subgroups can make it possible to collect important pieces of information on natural history and clinical characteristics in tumours which sometimes have only a pathological description.[2,8,11] National and international collaborations should be pursued.[2,11]

Another solution is to use non-frequentist or Bayesian statistical approaches.[11,12] Each piece of data must be recorded to increase knowledge: to this purpose, a wide and well-equipped data network is crucial in rare cancer cooperation.[11]

Quality control programs between hub and spokes should be planned in order to ensure data quality. Research networks must improve the knowledge and level of care of rare cancers.[2,5,9,11]

Collaborative studies involving hub and spokes can prove important to improve the quality of diagnosis and treatment.[11]

In rare cancers, planning clinical studies on new agents is strongly encouraged and pharmacological companies receive support to develop orphan drugs.[11]

Patients should be informed about ongoing trials and close cooperation with patient advocacies is mandatory.[2,3,11]

Sometimes, off-label application of a new treatment, if ethically correct, could be considered as a solution in order to shorten the time of approval of an innovative therapy.[11]

On the other hand, regulatory agencies, national health systems, and insurance companies have to guarantee equality among patients with common and rare tumours.

In rare cancers, less strict rules on compassionate use, approval, and reimbursement of new drugs is recommended, taking into consideration the higher level of uncertainty in rare cancers.[2]

The role of scientific societies such as the Italian Association of Medical Oncology (AIOM) is to support modern, high-quality cancer treatment, encouraging in rare cancers a multidisciplinary and multispecialty approach. The care of patients must be carefully planned and coordinated from the outset with all specialists meeting together.

Another important role of AIOM is to act as a stakeholder to evaluate the treatment of rare cancers in order to cooperate with the Italian Agency for Drugs (AIFA) and reduce procedures and timing in introducing new active drugs.

The assessment of orphan drugs must be encouraged to facilitate pricing and payback for a new treatment.

Furthermore, AIOM must support the role and function of the scientific societies created to study rare tumours, actively cooperating with national and international organisations such as the Italian Network for Rare Tumours (RTR) or European Society for Medical Oncology (ESMO) – Rare Cancer in Europe.

But the highest commitment of AIOM is to improve the educational level of oncologists by promoting, editing, and implementing national guidelines on rare tumours.

AIOM has recently produced six National Guidelines on Rare Cancers on:

- neuroendocrine tumours;
- CNS tumours;
- soft tissue sarcomas, GIST and gynaecologic sarcomas;
- oesophageal cancer;
- bile duct and gallbladder cancer;
- testicular tumours.

The next step will be the completion of guidelines on more rare tumours, such as mesothelioma, thymoma, salivary gland tumours, small intestine and appendicular tumours, vulvar and penile carcinomas.

Close cooperation with other Italian scientific societies, such as the Associations of radiotherapists and pathologists, and various surgical societies, is necessary.

The final goal is to transform the present AIOM guidelines into national, multidisciplinary, shared guidelines, approved by the Ministry of Health, to be used academically in Italian schools of medicine and specialisation.

Finally, the guidelines should be translated into English, to facilitate diffusion in other countries.

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SIE

# Registering rare haematological tumours: it is time for a breakthrough!

## La registrazione dei tumori ematologici rari: è tempo di una svolta!

Società italiana di ematologia (SIE)

Most haematological malignancies (HMs) are rare cancers, and their appropriate characterisation often requires an expert haematologist, a committed pathologist, and the integration of consolidated clinical, morphological, and phenotypic data with the rapidly progressing molecular knowledge. It is conceivable that the forthcoming new World Health Organization's classification will provide further insights in this setting, assigning even more importance to the molecular characterisation of these diseases. However, as the availability of molecular techniques and, more importantly, their standardisation, is not homogeneously applied throughout the country, finding an appropriate balance between accuracy of diagnosis and completeness of case recording will be a major issue for cancer registries (CRs). Indeed, for some HMs, as in the case of fusion genes PML/RAR in acute promyelocytic leukaemia (APL), BCR/ABL in chronic myeloid leukaemia (CML), and adult acute lymphoblastic leukaemia (ALL), FIP1L1-PDGFRA in hypereosinophilic syndromes, and mutations of JAK2/MPL/CALR in myeloproliferative neoplasms (MPNs), molecular biology is already mandatory for diagnosis according to the 2016 WHO criteria. In other situations, for instance mutations of NPM1 and FLT3 for acute myeloid leukaemia (AML), BRAF for hairy cell leukaemia (HCL), MYD88 for Waldenstrom's macroglobulinaemia (WM), and c-KIT for mast-cell disorders, these exams represent, when available, the strongest support for a correct diagnosis and/or a useful tool to stratify patients into different risk groups or to select the most appropriate treatment. Centralising biological samples for molecular analysis at referral laboratories (according to the model employed in other Europen countries) could be a possible solution. In Italy, a national network for CML (Labnet) is currently active and others are developing for MPNs and AML.

Thus, rare haematological cancers should, ideally, be diagnosed in onco-haematologic centres with recognised clinical skills and adequate diagnostic facilities. Diagnosis provided by centres with less expertise and not specifically involved in HMs (e.g., transfusion services and units of general medicine or geriatrics) should be considered with caution, and every effort to have appropriate confirmation should be pursued. As a consequence, reported incidence of some rare HMs might change in the future because of more stringent diagnostic criteria, and this should be taken into account when comparisons are made with previous data.
Another important issue will be the availability of novel agents, many of which, in the last years, have gained (or will soon acquire) a place in the real-world treatment of several HMs, for instance new proteasome inhibitors and IMIDs for multiple myeloma (MM); PI3K and Bruton-kinase inhibitors for mantle and follicular lymphoma; arsenic trioxide for APL; brentuximab-vedotin and anti-PD1 agents for Hodgkin's disease (HD); brentuximab-vedotin for anaplastic lymphoma; JAK inhibitors for PMF and other MPNs; hypomethylating agents for elderly AML; azacitidine and lenalidomide for myelodysplastic syndromes (MDS). In this setting, the most brilliant example is likely to be CML, where recently updated OS curves of patients enrolled in clinical trials show an >90% long-term survival. This is likely due to the availability of novel TK-inhibitors, which have substantially improved the percentage and quality of molecular response in these patients. We expect that such an improvement in survival may be observed in a short time not only in clinical studies, but also in real life. Prevalence of this disease (and that of other rare HMs potentially benefitting from novel therapies in terms of survival) will likely increase accordingly.
Finally, in order to avoid duplications, particular attention should by paid to the possible evolution from an initial HM into other, more aggressive ones, such as AML after MDS or MPN; primary myelofibrosis (PMF) after essential thrombocythemia (ET) or polycythemia vera (PV); aggressive lymphoma after indolent lymphoma; MM after MGUS/asymptomatic myeloma; plasma cell leukaemia after MM; WM after MGUS.
Looking to the near future, some additional considerations are here reported in relationship to specific rare HMs.

**MPN.** Data on PMF, ET, and PV should be separately reported. In this setting, bone marrow biopsy and driver mutation assessment are fundamental and require expertise in the evaluation. It should also be considered that mast cell disorders include a variety of neoplasms with different characteristics, ranging from indolent disorders to very aggressive forms; this would warrant that they should probably be better defined. More comprehensive data on chronic eosinophilic neoplasms should also be specifically collected.

**MDS.** A diagnosis of MDS should, ideally, always be performed by an expert haematologist on both marrow aspirate and peripheral blood smears. Though recommended by European guidelines, bone marrow biopsy is not always performed on a routine basis; however, it may be useful and necessary in selected cases. Perls's staining (to identify ring sideroblasts) and karyotype (which has a relevant prognostic value and selects patients eligible for azacitidine – high risk – or lenalidomide – del5q – therapy) should be considered mandatory in most cases and possibly registered, while flow cytometry is not useful for MDS in current clinical practice. It should also be outlined that overall survival of MDS may range from a few months to many years, based on available prognostic

models. Therefore, a more detailed analysis with respect to risk needs to be implemented. Furthermore, while awaiting new WHO criteria, "true" MDS (too simply defined here as «other myelodysplastic syndromes»: they represent the large majority!) should be clearly separated from "mixed" MDS/MPD, as these are disorders with overlapping characteristics based on different genomic abnormalities. Finally, 5q-syndrome is a well defined MDS associated with recognised clinical and morphological features, deletion of the long arm of chromosome 5 (del5q) as single cytogenetic abnormality, low-risk profile, and response to lenalidomide. CR operators should bear in mind, however, that del5q may occur in many other subtypes of MDS (including higher risk MDS), which must not be confused with the 5q- syndrome identified by WHO as a specific entity.

**AML.** As in MDS, a diagnosis of AML should be urgently performed by an expert haematologist on both marrow aspirate and peripheral blood smears and possibly integrated by flow cytometry. Cytogenetic and molecular data are also critical for risk assessment and guide treatment decision making. With the exception of APL, overall survival in AML is generally disappointing, with less than 20% of patients becoming long-survivors. However, when the analysis is performed by age, it should be noted that long-term survival in younger (15-60 year-old) patients, in whom intensive treatments, including allogeneic stem cell transplantation, can be delivered, is currently 35%-40%. In addition, selected groups of patients with favourable cytogenetic and molecular features may have an even better outcome.

**OTHER LEUKAEMIAS.** Adult ALL represents another rare HM requiring particular attention, while it would also be of some interest to collect data on blastic plasmacytoid dendritic cell leukaemia, a very uncommon entity currently included by WHO among AMLs.

**LYMPHOMAS.** Each diagnosis of lymphoma should always derive from an adequate surgical biopsy (preferably an entire lymph node) with appropriate histologic, immune-histochemical and, when required, cytogenetic and molecular evaluation. Core-needle biopsy may be useful in selected situations, while relying on simple fine-needle biopsy to make a diagnosis of lymphoma is not recommended. Lymphoma evaluation should include approaches for clear differentiation between B and T-cell neoplasms (Burkitt's lymphoma/leukaemia should also be analysed separately from T-lymphoblastic/leukaemia), as well as a further identification of aggressive vs. indolent forms. Within aggressive lymphomas, specific subtypes with clinical and biological peculiar characteristics should also be considered; for instance, variants of diffuse large B-cell lymphomas (DLBCL), such as primary mediastinal, leg-type, activated vs. germinal centre, and c-myc positive DLBCL. Among indolent lymphomas, lympho-plasmocytic (WM, if an IgM component is present) and splenic, nodal, and extra-nodal marginal zone lymphomas should be detailed.
Among T-cell lymphomas, anaplastic ALK+ lymphoma should be differentiated from ALK-subtypes. In addition, it should be considered that other T-cell lymphomas (in particular lymphoblastic, angio-immunoblastic, and peripheral T-cell-NOS), as well as NK neoplasms, also have distinctive features, treatments, and survival. Again, they should be analysed separately.

**MM.** Based on available criteria, symptomatic myelomas, which require treatment, should be well distinguished from asymptomatic/smouldering myelomas, which do not require therapy and have a different outcome; likewise, localised plasmacytomas (bone or extramedullary), as well as primary and secondary forms of plasma cell leukaemia, should be separately detailed. Primary AL amyloidosis should also be considered.
SIE has recently activated an easily accessible IT platform, which provides specialists with timely updated national guidelines for several HMs. In addition, SIE and AIRTUM are closely collaborating in order to define (and refine) the most useful criteria for registering all HMs within cancer registries in Italy, aiming to improve quality and completeness of data and provide a breakthrough in recording. Training of dedicated personnel, identification of new, non-conventional and more appropriate sources (e.g., pharmacies for specific drugs and haematology units for well-documented diagnoses) and integration of central and regional specific haematological expertise within the registering teams will represent the new backbone for the development of these activities.
Last, but not least, following the virtuous example of other registries (e.g., SEER in the US), more accurate registrations of rare HMs could also provide a unique scientific opportunity. Such a qualitative change requires attention to additional data, such as the role of specific clinical and biological prognostic factors, environmental and professional exposures, the role of viral or bacterial infections, and therapies delivered. By depicting as complete as possible a scenario of these tumours in Italy, we aim at carrying out solid population-based studies with numbers not otherwise attainable outside a cancer registry.

SICO

# Defining criteria to build a national excellence network

## Definire i criteri per costruire una rete nazionale di eccellenza

Società italiana di chirurgia oncologica (SICO)

Surgery is the mainstay of therapy in solid rare cancer care. RARECAREnet project data have shown that 65% of adult solid rare tumours (which represent 60% of all rare tumours) can be treated by surgery alone, compared to 35% which require radiotherapy and 28% which can be treated with chemotherapy. If we consider the preferred first line therapeutic strategy by stage, 82% of patients with localised disease can be treated by surgery.

The great surgical challenge concerning rare tumours is the ubiquitous diffusion in the human body: for this reason a "rare cancer surgeon", i.e. a surgeon expert in all rare cancers, cannot exist. Moreover, a fair amount of rare cancers arise in "common" sites, leading the surgeon, though expert in that particular organ or district, to act as for frequent tumours, in a climate of uncertainty. The final result can be overtreatment, undertreatment or a harmful intervention which can dramatically change the patient's prognosis and quality of life.

Frequent cancers, which can be cured by surgery, are frequently treated according to validated guidelines or diagnostic-therapeutic pathways which can be in some way standardised. Guidelines have shown to improve outcomes even in some rare cancers: a continuous, repeated referral to guidelines might have a highly valuable educational impact, enhancing awareness of a standardised work-up among inexperienced clinicians. Unfortunately, guidelines covering the entire clinical pathway from diagnosis to treatment, including relevant referrals for the whole range of rare cancer families, are not always available and/or are difficult to access.

The key issue for rare tumours is a correct preoperative diagnosis and appropriate therapeutic planning within a multidisciplinary environment. The expert surgeon's role in a multidisciplinary team is crucial, because the surgeon can assess the quality and feasibility of the planned surgical act, taking into account the biological aggressiveness of the disease, and matching the possible surgical outcome with different therapeutic alternatives.

Rare tumours require a deep knowledge of their natural history and biological characteristics. Such knowledge can be available only in centres in which high volumes of rare cancers are observed and treated. This is the only way to overcome uncertainty and develop the best possible, tailor-made treatments. One of the main obstacles to this strategy lies in the difficulty in defining accreditation criteria for centres of this kind, which focus on the peculiar aspects of rare cancers.

In Italy, the Italian Society of Surgical Oncology (SICO) is working with the main oncological scientific societies to pinpoint and define the criteria upon which a national excellence network can be built. The first step, which is currently being worked on with the Italian government, is to define a toolkit of indicators to enable:

- identification and accreditation of reference centres for rare tumours to which patients can be referred for an appropriate surgery, a second opinion concerning the pathological diagnosis, or preoperative treatment planning;
- definition of the fundamentals of a national excellence network in which reference centres act as hubs for referral, education, and knowledge, facilitating the integration of existing working groups;
- adequate empowerment and informing of patients and general practitioners, as well as primary care hospitals;
- prospective collection of data on a nationwide basis concerning quality of care and outcomes.

# The Italian Rare Cancer Network

## La rete italiana dei tumori rari

Rete Tumori Rari

Italy has a population of over 60 million. The total number of new cancer cases each year is about 360,000; of these, 89,000 – more than 25% – are rare. If the group of rare cancers is split up into all paediatric cancer cases, all haematological cancers except lymphomas (which are not rare, unless they are further split into subgroups), and rare adult solid cancers, the latter account for about 60,000 new cases each year. The Italian health system is region-based, with 20 regions. The new cases of rare adult solid cancers in each region range from slightly more than 100 to almost 10,000, i.e. there is a difference by a factor of 100 in the number of new cases seen region by region. The smallest region parallels a small city, the largest ones are tantamount to some European countries.

It is useful to single out rare adult solid cancers because Italian paediatric cancer patients have a number of centres available that are highly specialised in their care and have pooled efforts effectively over the last decades. Collaboration between these centres has led to "large" clinical studies, in a research context which has always been marked by a kind of overlap between research and healthcare. This means that quality of care for paediatric cancer is assured by a system of dedicated centres of reference that are used to collaborating with each other. A similar situation occurs for haematological neoplasms, since clinical haematology has always had a strong academic tradition in Italy. Again, there are several high-level reference centres, which, likewise, have been able to collaborate on clinical research in recent years. Unfortunately, the same cannot be said for rare adult solid cancers, at least if one considers them collectively, even though there are reference centres for each of the rare cancer "families". Although these institutions, too, have developed collaborations for research purposes, each group of rare cancers has its own research network and we lack a framework accommodating all of them to reach critical mass. Even more importantly, these efforts have not affected healthcare.

This is why, in 1997, the Rete Tumori Rari (Italian Rare Cancer Network) was set up, with the aim of covering rare adult solid cancers. The overall number of this type of cancers has been mentioned above, and this AIRTUM monograph provides detailed figures about them. Due to the main clinical interest of the coordinating group at the Fondazione IRCCS Istituto Nazionale Tumori of Milan, sarcomas were the Network's first and main focus, but over the years other groups of rare adult solid cancers have been incorporated. The core work of the Italian Rare Cancer Network is to share clinical cases between distant institutions, namely between a cancer facility handling a rare cancer case and a centre of reference specialising in treatment of that cancer. This happens at the national level, given the numbers reported by the AIRTUM monograph, which clearly show that in most regions the number of cases for each group of rare cancers is definitely low, too low to allow development of centres of expertise. It goes without saying that this results in a significant degree of health migration linked to rare cancers. This occurs despite the fact that the Italian healthcare system has high-quality cancer facilities spread across the entire country, which would certainly be able to handle rare cancer cases, if they were properly connected with centres of reference. This was the idea which led to the creation of the Italian Rare Cancer Network several years ago and which has proved to work effectively in a number of cases which currently averages one thousand each year. Of course, with about 60,000 new rare adult solid cancers each year in Italy, the Network would have a tangible impact on a population basis only if this number could be increased by a factor of 10. Indeed, several cancer facilities regularly sharing cases over the Network have been able in a way to specialise on rare adult solid cancers, in the sense that they are able to deal with some rare cancer cases by actively sharing information with centres of reference. They cannot develop the expertise of a reference centre, but have developed the ability to interact with reference centres effectively.

The Italian Rare Cancer Network is a bottom-up effort that, as such, has proved to be effective on thousands of individual patients. The challenge is now to make it grow to reach the numbers required to exert a population impact, first by covering most rare adult solid cancer groups and secondly by reaching out to a higher number of patients in each region. The first aim is currently being pursued by increasing the reference centres available in the Network, the second by stepping up the Network's organisational model, in collaboration with the Italian Health Ministry and the Conference of Regions. This is a work in progress, which involved incorporation of the Network into the national Healthcare objectives in 2012, with the goal to eventually incorporate it into the National Healthcare System. The main challenge is that the transformation of a bottom-up process into a framework endorsed by the national and regional healthcare authorities naturally implies an active transfer of resources, primarily to the facilities providing their expertise, as well as, to a lesser extent, the institutions requesting teleconsultation. A health research project will try to formally assess the Network's model, including its economic aspects and its current and potential impact on the healthcare system, while concomitantly improving it. At the same time, a working group at the Italian Ministry of Health, including representatives of each region, will try to work out the best ways to finally incorporate the Italian Rare Cancer Network into the National Health System, with the goal of improving the effectiveness of rare cancer care in Italy on a population basis and significantly reduce healthcare migration.

# THE NETWORK OF THE AIRTUM CANCERS REGISTRIES

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Si ringraziano per la collaborazione i medici delle strutture ospedaliere pubbliche e private convenzionate e il dottor Francesco Bellù che, nonostante il pensionamento, continua volontariamente la sua preziosa attività per il Registro.

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Si ringraziano le direzioni sanitarie e i dirigenti sanitari delle strutture pubbliche e private coinvolte, nonché gli uffici anagrafici comunali per la preziosa collaborazione fornita. Un ringraziamento va a tutti coloro, in particolare alla direzione aziendale e alla Fondazione Edo ed Elvo Tempia, che hanno creduto e sostenuto il registro fin dall'avvio collaborando alle iniziative di AIRTUM e dell'epidemiologia piemontese.

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Si ringraziano Regione Lombardia, gli Ospedali intra ed extraprovinciali, i Servizi di anatomia patologica e gli operatori dell'Istituto nazionale per lo ricerca sul cancro (INT) di Milano per il costante sostegno.

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Si ringraziano per la collaborazione e il sostegno ricevuti la Regione Emilia-Romagna, l'Azienda ospedaliera universitaria di Ferrara, l'Azienda USL di Ferrara e tutti i colleghi che a vario titolo hanno contribuito all'attività del Registro tumori.

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Si ringraziano le aziende sanitarie ospedaliere, le ASL liguri (in particolare quelle della Provincia di Genova) e tutti i dirigenti sanitari (direzioni sanitarie, reparti di cura, anatomie patologiche, radioterapie eccetera) che hanno interagito con l'RTRL per agevolare la rilevazione degli operatori. Si ringraziano il dottor Sergio Vigna, referente regionale c/o Agenzia regionale sanitaria Liguria, la dottoressa Gabriella Paolo, Assessorato alla sanità Regione Liguria, la dottoressa Elena Ricci, responsabile dell'Ufficio statistico regionale, per aver messo a disposizione i principali sistemi informativi regionali; un ringraziamento alle amministrazioni dei Comuni liguri per la collaborazione nel follow-up dei casi.

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Si ringraziano Regione Lombardia, la Direzione strategica aziendale, le strutture ospedaliere pubbliche e private, i Servizi di anatomia patologica e gli operatori sanitari per la collaborazione all'attività del Registro tumori.

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**Si ringraziano il professor Enrico Maria Silini, direttore dell'Istituto di anatomia patologica, Università di Parma, il dottor Alberto Tardini, del laboratorio CERB di Parma, il dottor Giuseppe Ugolotti, laboratorio di citologia azienda USL Parma, la dottoressa Dina Gnappi dell'Ufficio mobilità sanitaria, Azienda unità sanitaria locale Parma.**

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**Si ringraziano Regione Lombardia, l'ASL di Varese, gli ospedali, le case di cura, i medici di medicina generale e i Comuni della Provincia di Varese per la preziosa collaborazione.**

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**Si ringrazia il personale delle strutture ospedaliere piemontesi e in particolare del Reparto di oncoematologia pediatrica dell'Ospedale infantile Regina Margherita Sant'Anna di Torino per la preziosa collaborazione all'attività del Registro tumori.**

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**Si ringrazia la Regione Emilia-Romagna per il contributo finanziario.**

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**Si ringraziano pazienti e colleghi per la convinta collaborazione e Regione Liguria per il contributo finanziario e organizzativo.**

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