# 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

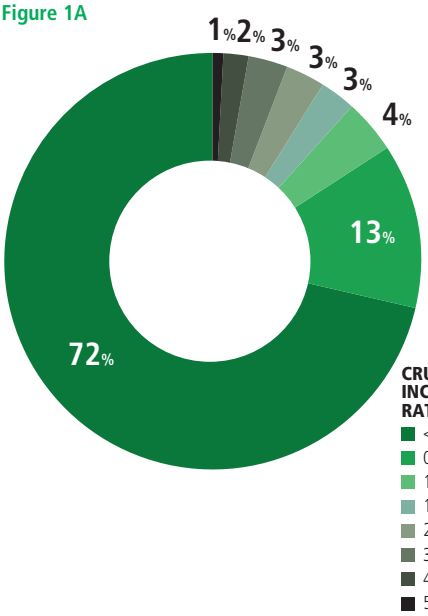


Figure 1B

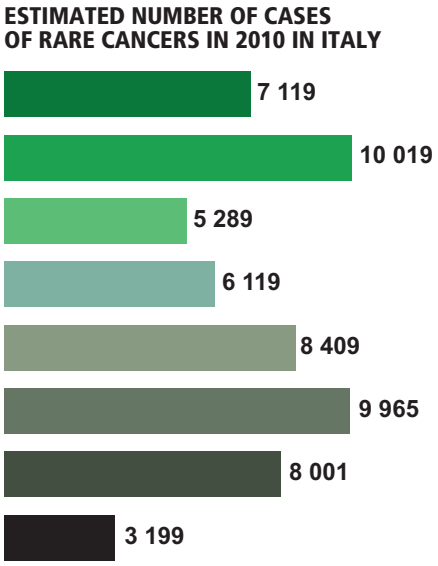


**Figure 1.** Proportion of rare cancers (**A**) and estimated number of new cases of rare cancers (**B**) in Italy in 2010 by crude incidence rate. Crude incidence rate for 193 out of the 198 rare cancers of the RARECAREnet list grouped together and obtained from the Pool of 39 AIRTUM cancer registries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

Figure 2

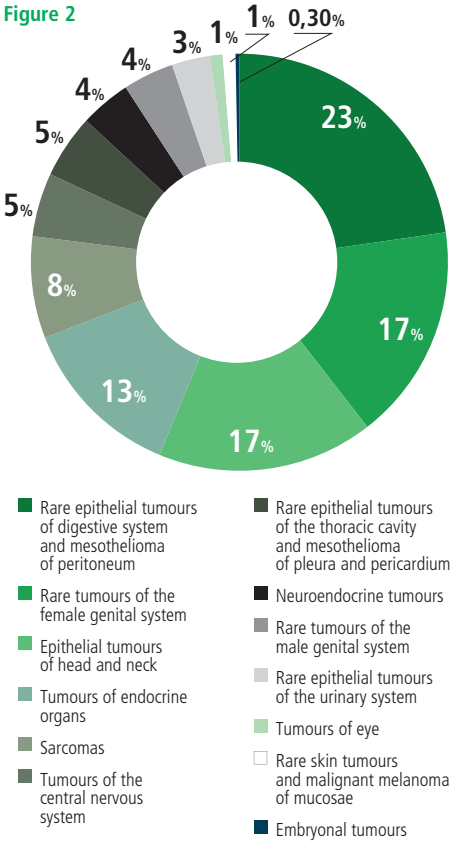


**Figure 2.** Distribution of the 13 groups of rare solid cancers presented in this monograph among all solid rare cancers. AIRTUM Pool of 39 cancer registries (period of diagnosis 2000-2010).

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

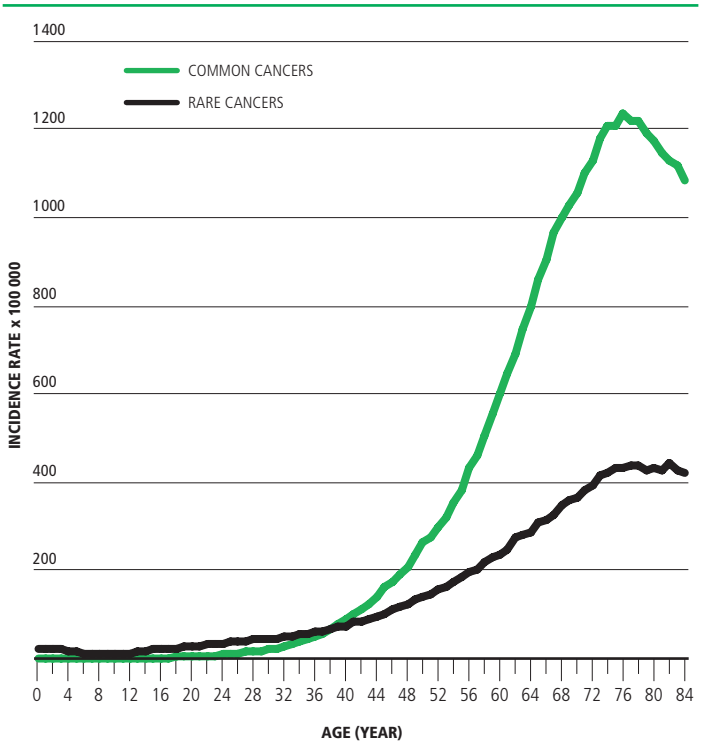


**Figure 3.** Age-specific incidence rates for rare and common cancers (solid + haematological tumours) of the RARECAREnet list in Italy, period of diagnosis 2000-2010. AIRTUM Pool of 39 cancer registries.

| 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

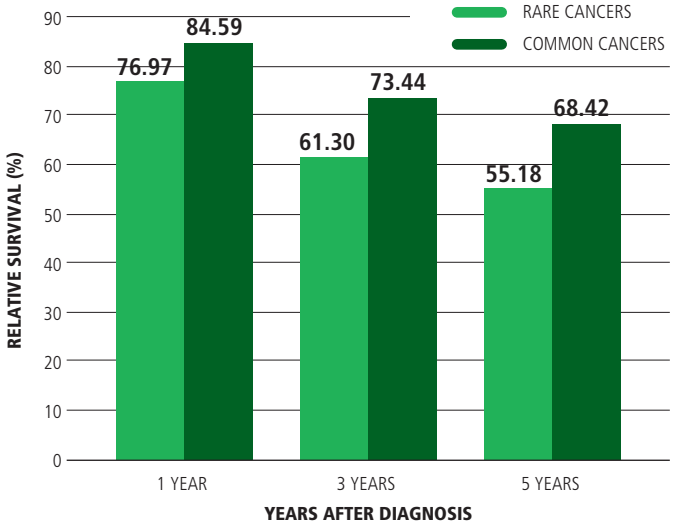


**Figure 4.** Relative survival (%) for rare and common cancers of the RARECAREnet list in Italy by time since diagnosis (1, 3, and 5 years). Cases diagnosed in 2000-2008, and followed up to 31st December 2009. AIRTUM Pool of 37 cancer registries.

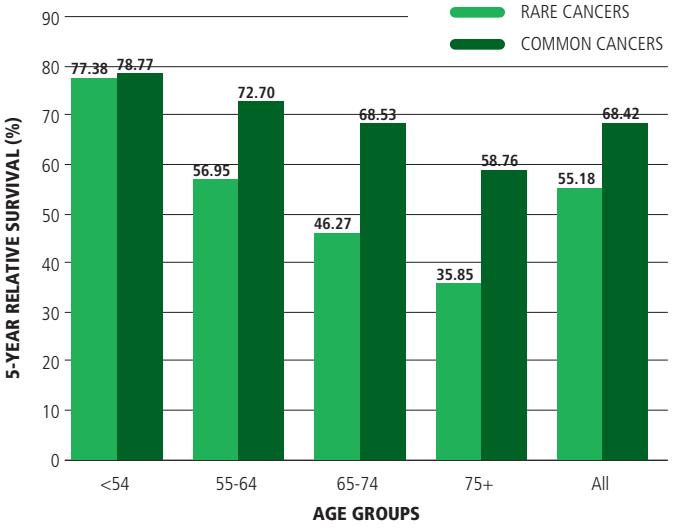


**Figure 5.** Five-year relative survival (%) for rare and common cancers of the RARECAREnet list in Italy by age group. Cases diagnosed in 2000-2008, and followed up to 31st December 2009. AIRTUM Pool of 37 cancer registries.

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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