Rare thoracic cancers, including peritoneum mesothelioma

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Abstract Rare thoracic cancers include those of the trachea, thymus and mesothelioma (including peritoneum mesothelioma). The aim of this study was to describe the incidence, prevalence and survival of rare thoracic tumours using a large database, which includes cancer patients diagnosed from 1978 to 2002, registered in 89 population-based cancer registries (CRs) and followed-up to 31st December 2003. Over 17,688 cases of rare thoracic cancers were selected based on the list of the RACECARE project. Mesothelioma was the most common tumour (19 per million per year) followed by epithelial tumours of the trachea and thymus (1.3 and 1.7, respectively). The age standardised incidence rates of epithelial tumours of the trachea was double in Eastern and Southern Europe versus the other European regions: 2 per million per year. Epithelial tumours of the thymus had the lowest incidence in Northern and Eastern Europe and UK and Ireland 1 and somewhat higher.
1. Introduction

Rare thoracic cancers are located in the chest and include those of the trachea, of the thymus and mesothelioma. Apart from mesothelioma, little information is available on their patterns of incidence and survival. This is largely because in the routine statistics and publications 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 heart, mediastinum and pleura and called ‘Other thoracic organs’.1

Moreover, the three tumour types have a different aetiology. As with lung cancer, cancer of the trachea is associated with active and passive smoking (environmental exposure). Survival is comparable with the survival of lung cancer, thus very low. The causation of mesothelioma by asbestos has been established for more than 50 years.2 The use of this dangerous carcinogen peaked between 1970 and 1990. Still the worldwide production has not declined significantly, resulting in an ongoing rise in incidence and mortality. In most industrialised countries more than 90% of all (pleural) mesotheliomas are related to asbestos exposure. Tumours of the thymus have a largely unknown aetiology with a complex biology. The most frequent tumours of the thymus are the thymomas. Survival of thymomas is mainly related to the stage at diagnosis, histological type and completeness of resection.3,4

In the present study, population-based data from different European cancer registries (CRs) participating in the RARECARE project, were used to estimate the burden of rare thoracic cancers. This database gives us the unique opportunity to study these rarities. The RARECARE project produced a list of tumours based on both cancer morphologies and topographies according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3).5 using an incidence rate less than 6/100,000 as a threshold for rarity.

The aim of this study was to describe the incidence, prevalence and survival of the epithelial cancers of the trachea, thymus, and mesothelioma. Malignant mesothelioma most commonly arises in the pleura but can also arise in the peritoneum. To give a complete overview of the burden of mesothelioma we included the mesothelioma located on the peritoneum as well in our study. Furthermore, for the first time ever complete prevalence estimates will be reported for these specific types of rare tumours.

2. Patients and methods

2.1. Tumour grouping

The rare thoracic cancers described in this article include the epithelial tumours of the trachea, epithelial tumours of the thymus and malignant mesothelioma, including both mesotheliomas in the pleura and in the peritoneum. The present analyses are based on the list of cancers provided by RARECARE. The list is based on the ICD-O-35 and is organised in two hierarchical tiers (Table 1). Tier 2 includes cancer entities considered similar from the point of view of clinical management and research. Tier 2 cancer entities were grouped into general categories (tier 1 of the list) considered to involve the same clinical expertise and patient referral structure. For rare epithelial thoracic cancers described in this paper, there are three ‘tier 1’: epithelial tumours of the trachea (C33), thymus (C37) and mesothelioma (ICD-O-3 morphology codes 9050–9053).

For epithelial cancer of the trachea three ‘tier 2’ entities were identified: squamous cell carcinoma (ICD-O morphology codes 8004, 8020–8022, 8031–8032, 8050–8076, 8078, 8082–8084, 8560, 8980); adenocarcinoma (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); and salivary gland type tumours (8200, 8430, 8982; thus including adenoid cystic carcinoma, mucoepidermoid carcinoma and myoepithelial carcinoma).

For epithelial cancer of thymus five ‘tier 2’ entities were identified: malignant thymoma (8580–8586; thus including not otherwise specified (NOS, 8580), type AB (8582), type A (8581), type B (8583, 8584, 8585), type C (8586)); squamous cell carcinoma (8051–8076, 8078, 8083–8084); undifferentiated carcinoma (8020–8022); lympho-epithelial carcinoma (8082) and adenocarcinoma (the same as for trachea).

For mesothelioma, two ‘tier 2’ entities were recognised: mesothelioma of pleura and pericardium (C38), mesothelioma of peritoneum (C39).
2.2. Cancer Registry (CR) selection and population coverage

RARECARE gathered data from the EUROCARE-4 study which were based on cancer patients diagnosed from 1978 to 2002, archived in 89 population-based CRs and with vital status information available up to at least 31st December 2003. The mean population covered was about 162,000,000 corresponding to 39% of the population of the 21 countries participating in RARECARE and 32% of the population of the European Union members. 6 For 11 countries, CRs covered the entire national population (Austria, Iceland, Ireland, Malta, Norway, Slovakia, Slovenia, Sweden, Northern Ireland, Scotland and Wales). The other 10 countries were represented by regional CRs, each being divided into the respective national populations. CRs covering the whole population of the EU or the national population of one country were denoted as national CRs (e.g. England, Scotland, Wales, Belgium, Germany, Italy, France, Spain, Portugal, the Netherlands, Norway, Denmark, Ireland, Sweden, Austria, and Italy). The other 64 CRs were classified as regional CRs.

2.2.1. Data selection for incidence analysis

Incidence rates were estimated on 17,688 cases after exclusion of CRs which did not classify cancers according to the ICD-O-3 and specialised registries (Table 1). Thus, the incidence analyses were restricted to 64 CRs. Over the period 1995 to 2002 age-standardised incidence rates per 1,000,000 were computed to adjust for different age distribution of the compared population, using the European standard population (male and female). The age-adjusted incidence rates were calculated by sex and by the five European regions.

2.2.2. Data selection for relative survival analysis

Relative survival was estimated according to the Hakulinen method. Period survival indicators for the years 2000–2002 were also estimated using the Brenner algorithm. For six CRs out of the 70 European CRs, data were not available for analyses for this period and could not be included for analyses. The prevalence per 1,000,000 was estimated at the index date of 1st January 2003. Only data from 22 registries covering the whole 15-year period were used for prevalence estimation. The counting method based on death certificate only for patients diagnosed in 1995–2002 was used for survival analysis.
cancer registries incidence and follow-up data was applied to cancer registries data from 1988 to 2002. The completeness index method was used to estimate complete prevalence and involved adding the estimated number of surviving cases diagnosed with rare cancer prior to 1988 to those counted in 1988–2002.10

The expected number of new cases per year and of prevalent cases in Europe (EU27) was estimated multiplying the crude incidence and prevalence estimates to the 2008 European population (497,455,033) provided by EUROSTAT.11 The number of prevalent cases was estimated using the EU population in 2008, thus prevalent cases are at 2008.

In providing rare thoracic tumours burden estimates, we assumed that the population covered by our CRs was representative of the population of the EU27 as a whole. Further details on methods and representativeness of RARECARE data are reported in the paper of Gatta et al.12

2.3. Data quality analysis

The main data quality indicators for the cases included were defined in the EURO CARE study13 for the rare thoracic tumours they are presented in Table 1. Overall, 2.4% of the cases were registered based on the death certificate only (DCO) ranging from 1.6% (epithelial tumour of the thymus) to 3.6% (epithelial tumours of the trachea). About 89% of the cases included in the analysis were microscopically verified, although the proportion varied among cancer entities from 86% of the epithelial tumours of the trachea to 92% of the thymus. Of the ‘adenocarcinomas and variant of thymus’ (subgroup of the epithelial tumours of the thymus) 6.3% was censored before 5 years. Twelve percent of the epithelial tracheal tumours were diagnosed with an unspecified morphology (ICD-O 8000 and 8001). This was 5.4% for the epithelial thymic tumours. Cases without a specific morphology (8000–8001) were included in the tier 1 entity only while they were not included in the tier 2 entities. Morphology NOS was not included in the definition of the tier 1 of the malignant mesothelioma, however they are very low (5%). Overall, the % of NOS in pleura was 5% and it ranged from 2 in UK to 18% in Eastern Europe being somewhat high also in Southern Europe (11%).

3. Results

3.1. Incidence

Table 2 shows the crude incidence rate in Europe, rates by sex and age-group and the number of new cases diagnosed in Europe (EU27) every year. Among the thoracic cancers, mesothelioma was the most common tumours with a crude rate of 19 per million per year. Within this group mesothelioma were predominantly

<table>
<thead>
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<th>EU overall</th>
<th>Sex</th>
<th>Age</th>
<th>Estimated number of cases arising in EU per year</th>
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<td></td>
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<td>Female</td>
<td>0–24 years</td>
<td>25–64 years</td>
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<td>SE</td>
<td>Rate</td>
<td>SE</td>
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</table>

~ Statistic could not be calculated.
located in the pleura and pericardium (16 per 1,000,000) epithelial tumours of the trachea and thymus had a crude rate of 1.3 and 1.7 per million per year. For the epithelial tumours of the thymus, malignant thymomas were most common (1.4 per million per year). For trachea, squamous cell carcinomas were predominant (0.8 per million per year).

The incidence rate for thymus cancers was the same in men as in women. For tracheal tumours the rate was higher in men (1.9) than in women (0.8). For mesothelioma the incidence rate was about three times higher in men than in women, 32 and 6.8 per million per year overall, respectively. For mesothelioma located in the peritoneum and in the tunica vaginalis, the male to female ratio was 2.

For all the rare epithelial thoracic tumours, incidence was highest in the oldest age group of patients (65 years old and older): within this age-group, the highest rates were reported for mesothelioma (77). For the other tumours the rates in patients older than 65 years was less than 5 (4.7 for trachea and 4.2 for thymus). In the age group 25–64 the highest incidence rate was found in mesothelioma (13) followed by epithelial tumours of the thymus (1.8) and trachea (1.1). Among children and young adults (<25 years of age) epithelial tumour of the thymus occurred more frequently than the other rare thoracic cancers (0.13 per million per year).

Although being classified as a rare case, 11,000 new cases of rare thoracic cancers have been diagnosed in Europe in 2008: 700 epithelial tumours of the trachea, 800 tumours of the thymus and 9500 mesotheliomas. Table 3 shows age standardised incidence rates for the three different cancer types.

The age standardised incidence rates of epithelial tumours of the trachea was 1 or slightly less per million per year in Northern Europe, Central Europe and UK and Ireland. In Eastern and Southern Europe it was double that in the other European regions: 2 per million per year.

The incidence of epithelial tumours of the thymus had lowest incidence in Northern and Eastern Europe and UK and Ireland (1) and somewhat higher incidence in Central and Southern Europe (2).

In malignant mesothelioma differences in incidence were seen, having highest incidence in UK and Ireland (23) and lowest in Eastern Europe (4.2). Central and Southern Europe had both an incidence rate of 13 and Northern Europe of 11 per 1,000,000, which resulted in an overall incidence rate in the EU of 16 per 100,000. This difference in incidence between EU regions was based on the difference in incidence in mesothelioma of the pleura and pericardium, which was 18 per 1,000,000 in the UK and Ireland and 3.3 in Eastern Europe. Also the incidence of the mesothelioma of the peritoneum tunica vaginalis was lowest in the Eastern region (0.7) and highest in Southern Europe (1.3).
3.2. Survival

Table 4 presents period survival for the years 2000–2002 for the first tier entities of the thoracic cancers. Both observed and relative survival with the estimated standard error of relative survival, are shown at 1- and 5-years after diagnosis by sex, age and EU geographic regions.

Fig. 1 shows 5-year relative survival of first and second tier entities of the thoracic cancers. The following comments focus on relative survival, which is adjusted by competitive mortality and is therefore more comparable between cancers and populations.

Within rare thoracic cancers the tumours of the thymus had the best prognosis (1-year survival 85%, 66% at 5 year). No difference in survival between men and women were revealed. Patients older than 65 years had a 5-year relative survival of 60% compared to 78% of the youngest age group (0–24 years of age). Highest 5-year survival was seen in Eastern European region (75%) versus lowest survival in the UK and Northern Ireland (53%) however, in Eastern Europe the proportion of younger cases (<64 years) was higher (77%) than those in UK and Ireland (61%). The 5-year survival for malignant thymoma was somewhat higher than for squamous cell carcinoma of the thymus (69% versus 58%, respectively) (Fig. 1).

Prognosis for both epithelial tumours of the trachea as for mesothelioma after 1 year was about 37%. Survival after 5 years was lowest for the mesothelioma 5% compared to 14% of patients with tumours of the trachea.

No difference in 5-year relative survival in between men and women with tumours of the trachea were revealed. Patients older than 65 years had the worse prognosis: 1-year survival was 27% compared to 48%
in the age group 25–64 years old. This difference was seen in the 5-year relative survival (10% and 16%, respectively). Northern and Central European regions had the highest 1-year survival (52% and 63%, respectively). The Eastern, Southern and UK and Ireland regions had a lower 1-year survival between 31% and 24%.

For the epithelial tumours of the trachea high survival was found in salivary gland type tumours of the trachea, being 57% compared to 10% and 6% of the squamous cell carcinoma and adenocarcinoma variants of trachea, respectively (Fig. 1).

Men with mesothelioma had somewhat lower survival than women (5-year survival 3.6% versus 7.9%). Patients older than 65 years of age had worse 1-year survival compared to patients between 25 and 64 years of age (29% versus 47%). This large difference levelled of by years resulting in a 5-year survival of 3% in the 65+ group versus 8% in the age group 25–64. However, these differences could be partly due to the highest proportion of mesothelioma of peritoneum and tunica vaginalis, localisation with relatively good prognosis, in the youngest (10%) than in oldest (8%) age groups.

Within Europe lowest survival was seen in the UK and Ireland region (31% 1-year relative survival) followed by Eastern Europe (34% 1-year survival), which was mainly due to the low survival of pleural mesothelioma (28%). Southern Europe had highest 1-year survival of 47%. On the contrary the relative 5-year survival was highest in the Eastern Europe region (12%). UK and Ireland had worse 5-year survival (3%). However, in Eastern Europe the proportion of younger cases (<64 years) was higher (54%) than in UK and Ireland (33%). Survival of the Southern Europe region was 8%.

Five year relative survival of patients with malignant mesothelioma located in the peritoneum was twice as high compared to patients with the mesothelioma located in the pleura and pericardium (10% and 5% respectively, Fig. 1). In men the 5-year survival of pleural mesothelioma was 4% versus 6% in peritoneum mesothelioma. For women these percentages were 7% and 17%, respectively.
3.3. Prevalence

Table 5 shows observed prevalence proportion at 2, 5 and 15-years and the estimated complete prevalence in Europe (index date 1st January 2003). Mesothelioma was the most prevalent rare cancer (12,000 cases), followed by those of the thymus (7000) and trachea (1400). Also, mesothelioma was the group with the highest prevalence at 2 years since diagnosis (68% cases were prevalent within 2 years since diagnosis) and the lowest proportion of long survivors (6% alive after 15 years from diagnosis). Differently, the corresponding figures for the epithelial tumours of thymus were 20% and 30%, thus a larger proportion of long survivors with a diagnosis of epithelial tumour of thymus. For trachea, 2-year prevalence was 30% and only 13% was the prevalence of long survivors, who were living with a diagnosis made 15 or more years before the index date.

The low proportion of long survivors for mesothelioma and the epithelial tumour of trachea were related to bad prognosis of these cancers (Table 5). The number of prevalent cases of epithelial cancer of trachea was 2 times higher than the number of new cases. It was 8 times higher for epithelial cancer of thymus and 1.2 times higher for mesothelioma.

4. Discussion

Our study showed an estimated number of rare thoracic cancers of about 11,000 cases per year in the EU. This is mainly based on the numbers of the malignant mesotheliomas of which 85% were located in the pleura. Tumours of the thymus and tumours of the trachea were less frequent with an expected number of about 700–800 cases per year in the EU. The majority of the rare thoracic tumours were diagnosed in patients older than 65 years. This was confirmed by a population based study conducted in the Netherlands, reporting median age at diagnoses of 69 years for men and women combined. Striking was the high incidence of mesothelioma in the UK and Ireland and the low incidence in Eastern Europe, which was due to the incidence of pleural mesothelioma. Moreover, among rare thoracic cancers, mesothelioma was also the most prevalent. Survival was highest for thymic tumours and lowest for mesothelioma. In all tumours, patients with older age revealed a lower survival. The UK and Ireland revealed lowest survival for all tumour types. Survival of mesothelioma was highest in Eastern Europe. This is probable influenced by the very small number of cases in this region. Another reason could be difficulties in reaching a correct diagnosis, therefore inclusion of non-neoplastic lesions. Actually, in the Eastern registries the proportion of DCO and autopic mesothelioma cases was 14% versus <5% in the other regions.

Interpretation of the results should be done in the light of the quality of the data, which has been described in this study by several quality indicators. A considerable number of the trachea and epithelial tumours of the thymus cancers could not be classified into a morphology group and thus were classified as ‘NOS’. This suggests difficulties in pathological diagnosis, which could be reduced by turning to account pathology panels. Based on the quality indicators in Table 1, data were considered to be of high quality. However, one of the specific tasks of the RARECARE project was to study the data quality in rare cancer registration. Specifically for mesothelioma, of which NOS is not included in the definition, we revised the pathology reports of a sample of 678 long survivors (alive 2 or more years after the
and some nationwide studies. It has been described in some countries, for instance in France and Great Britain.21,22

In addition, the magnitude of recent trends in younger men was generally lower than those and a significant increase was detectable solely in England and France. In the case of extensive use of crocidolite (UK and Australia for example), the proportion of asbestos related mesotheliomas in women is also high as well. The latency period has a mean of 30–40 years after exposure. From past exposure the peak in death cases in the UK is estimated to be in 2015–2020, with more than 2000 per year.17 In Western-Europe it has been postulated that a quarter of a million people will die from asbestos induced mesothelioma in the next 35 years with highest risk in men born around 1945–1950.18 In women the relation with exposure to asbestos was less clear and often provoked through the occupation of their husbands or the environment.19,20 Between 1978 and 1987, rates in men significantly increased in all countries (except for Denmark). In the following 10 years, there was a deceleration in trend, and a significant increase was detectable solely in England and France. In addition, the magnitude of recent trends in younger men was generally lower than those estimated for older men, in both national and regional cancer registry settings. While mesothelioma incidence rates are still rising in Europe, a deceleration has started in some countries, for instance in France and Great Britain.21,22

Most of the knowledge of tracheal cancer has been based on case reports, single institution experiences and some nationwide studies.25,26 It has been described that up to 86% of all patients with tracheal cancer have a history of smoking, particularly those with squamous cell carcinoma (93%) which is also the most common subtype. Therefore, similar to lung cancer, smoking represents the main risk factor for this malignant disease. Lower incidence of smoking-related tracheal cancer in Northern and Central Europe, as well as in UK can be therefore explained by early implementation of smoke-free policies in these regions.27,28 The incidence of other histological types of tracheal cancer (adenocarcinoma and salivary gland type tumours) did not display remarkable regional differences with the exception of adenocarcinoma that was slightly higher in Southern Europe. Reasons for this are not fully understood, although the role of smoking has been, similar to lung cancer, suggested.

In the present study, overall 5-year survival of tracheal cancer patients was 14% and comparable to the 5-year survival described in previously published nationwide studies.25,26 This is, however, in a clear contrast to some population based reports from the USA, where an overall 5-year survival of 27% has been documented.29 This difference is expected to be related to the inclusion of a relative large amount of adenoid cystic carcinomas, in this study which is a tumour with a good prognosis (see Fig. 1). Like others, no differences between men and women but clear differences between histological subtypes were revealed.25,26 The large inter European region variation observed for tracheal cancer is due to geographical histological type composition of tracheal cancers: actually the less lethal entities, the salivary gland type tumours, were more common in the Northern (16%). Also age may in part explain geographical difference: however in this case patients were younger in the Eastern countries than in the other parts of Europe.

Survival of cancer patients is mainly influenced by the tumour stage at diagnosis and the use of effective treatment choices. Despite the straightforward symptoms of central airway obstruction and mucosal irritation, the definitive diagnosis of tracheal cancer is commonly delayed (from 0–3 to 12 months).26,30

Tracheal tumours can be treated preferably by surgery (irrespective of histological type of cancer), which is ignored in Europe leading to a low proportion (6–25%) of patients.25,26,31,32 In the USA this proportion was much higher (71–74%), which correlated with longer survival times.30,31 Therefore, the small number of patients with this type of cancer leading to a small awareness under physicians and perhaps delays in patient presentation, lack of clear guidelines and undertreatment might have had a huge impact on scarce treatment results in regions involved in the RARECARE project. Centralisation of care to tertiary oncology centres is strongly recommended, which increases awareness and decreases the undertreatment.26,32

Regarding thymic cancers, our results are similar to those reported by the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) reporting for thymomas an incidence of 0.13 per 1,00,000 person-years similar in male and female; and with a peak in the seventh decade of life.33 Thymomas
had a relatively good prognosis (5-year survival in our study: 69%) and, in fact, they are considered as indolent cancers with a lymphogenous metastasis rate of 1.8% and an even rarer haematogenous metastasis rate.\textsuperscript{34}

Although studies evaluating prognostic determinants have been hindered by the use of different histologic classifications and by their retrospective nature three factors consistently emerge to shape prognostics: stage of disease, completeness of resection and tumour histology.\textsuperscript{35}

Other poor prognostic indicators include recurrent disease, unresectable tumour, symptoms at presentation (myasthenia gravis), invasion of great vessels, which are not however an independent factor for thymoma-related mortality.\textsuperscript{36} Inter-relation between the different prognostic factors (Masaoka staging, myasthenia gravis, WHO histology) are of great importance.\textsuperscript{37} Surgical resection is the recommended treatment for early stage thymic epithelial malignancies, where complete resection increases survival.\textsuperscript{38} A 20\% recurrence rate has been described for stage I patients with peritumoural adherences found at surgery (Masaoka stage II),\textsuperscript{39} whereas patients who received RT in this situation had not recurrences.\textsuperscript{40} Differences in survival could be influenced by the low number in Eastern Europe (n = 35). Also differences in the role of adjuvant treatments (mainly radiotherapy, more rarely chemotherapy) in UK compared to other European countries could be a reason. Moreover, due to the heterogeneity within thymic carcinoma and differences with thymomas targeted treatments will have to be different.\textsuperscript{41}

For the first time prevalence is available for these rare thoracic cancers. Taken into account the fact that the European orphan drug regulation for rare diseases incentives is based on prevalence, our data are of major importance. Taking the latency time and the risk factors into account it is of great importance to have de Cancer Registry data at this moment as they represent a base line to monitor the influence of prevention programs, early detection and patient care. It is to be expected that incidences of these cancer types are going to decline, due to regulations. The cancer registries can play an important role in monitoring the effect of these regulations on asbestos use and smoking related policies (the no smoking policies in public places and restaurants and cafes).

**Conflict of interest statement**

None declared.

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**Appendix A**

The RARECARE Working Group consists of Austria: N Zielonk (Austrian National Cancer Registry); Belgium: E Van Eycken (Belgian Cancer Registry); D Schrijvers (Antwerp Hospital Network); H Sundseth (European Cancer Patient Coalition); France: G Hedelin (Bas-Rhin Cancer Registry); AM Bouvier (Côte d’Or Digestive Cancer Registry); AS Woronoff (Doubts Cancer Registry); A Buemi (Haut-Rhin Cancer Registry); B Tretarre (Hérault Cancer Registry); M Colonna (Isère Cancer Registry); S Bara (Manche Cancer Registry); O Ganry (Somme Cancer Registry); P Grosclaude (Tarn Cancer Registry); Germany: B Holleczek (Saarland Cancer Registry); Iceland: L Tryggvadottir (Icelandic Cancer Registry); Ireland: S Deady (National Cancer Registry of Ireland); Italy: F Bellù (Alto Adige Cancer Registry); S Ferretti (Ferrara Cancer Registry); D Serraino (Friuli Venezia Giulia Cancer Registry); M Vercelli (Liguria Cancer Registry c/o IST/UNIGE, Genoa); S Vitarelli (Macerata Province Cancer Registry); M Fedora (Modena Cancer Registry); M Fusco (Napoli Cancer Registry); M Michiara (Parma Cancer Registry); A Giacomini (Piedmont Cancer Registry, Province of Biella); R Tumino (Cancer Registry and Histopathology Unit, “M.P. Arezzo” Civic Hospital, Ragusa); L Mangone (Department of Research Azienda Ospedaliera Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia); F Falci (Romagna Cancer Registry); G Senatore (Salerno Cancer Registry), M Budroni (Sassari Cancer Registry); S Piffer (Trento Cancer Registry); A Caldarella (Tuscan Cancer Registry); F La Rosa (Umbria Cancer Registry); P Contiero (Varese Cancer Registry); P Zambon (Veneto Cancer Registry); PG Casali, G Gatta, A Gronchi, L Licitra, M Ruzza, S Sowe, A Trama (Fondazione IRCCS Istituto Nazionale dei Tumori); R Capecaccia, R De Angelis, S Mallone, A Taverna (Centro Nazionale di Epidemiologia, Istituto Superiore di Sanità); AP Dei Tos (Local Health Unit No. 9, Region of Veneto); Malta: K England (Malta National Cancer Registry); Norway: G Ursin (Cancer Registry of Norway); Poland: J Rachtan (Cracow Cancer Registry); S Gozdz, (Kielce Cancer Registry); M Zwierko (Warsaw Cancer Registry); M Bielska-Lasota (National Institute of Public Health – National Institute of Hygiene, Warsaw); J Slowinski (Department of Neurosurgery in Sosnowiec, Medical University of Silesia); Portugal: A Miranda (Southern Portugal Cancer Registry); Slovakia: Ch. Safaei Diba (National Cancer Registry of Slovakia); Slovenia: M Primic-Zakelj (Cancer Registry of Slovenia); Spain: A Mateos (Albacete Cancer Registry); I Izarzugaza (Basque Country Cancer Registry); A Torrella-Ramos (Castillon Cancer Registry); R Marcos-Gragera (Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Department of Health and Catalan Institute of Oncol-
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