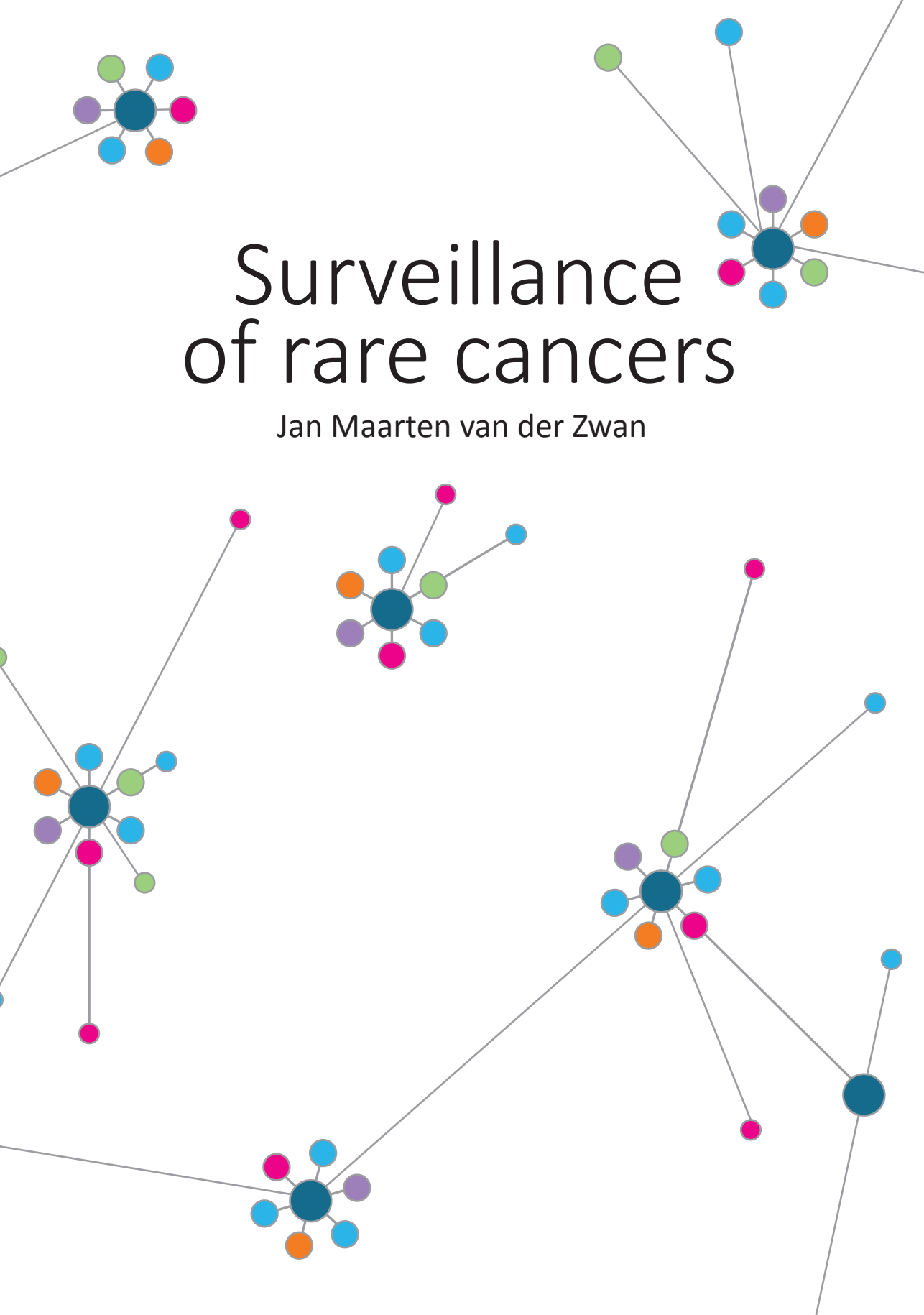
Surveillance of rare cancers

Jan Maarten van der Zwan



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OF
RARE CANCERS

Jan Maarten van der Zwan

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RARECARE
Surveillance of Rare Cancers in Europe

SURVEILLANCE OF RARE CANCERS

PROEFSCHRIFT

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Contents

Chapter 1

General introduction

Rare cancers

The widespread incidence and effects of cancer[1] have led to a growing development in cancer prevention in the form of screening and research programs and cancer registries. These initiatives have resulted in improvement of cancer detection, diagnostics, treatment, follow-up and research. However, this improvement has not applied to all cancer patients to the same extent. Patients with rare cancers sometimes benefit from developments directed at specific high volume cancers; for example the breast cancer screening program contributed to early diagnoses for women suffering from the rare Paget's disease of the breast.[2,3] But in general, because the number of patients with rare cancers is low there is insufficient focus on accurate and timely diagnosis, effective treatment modalities and evidence based guidelines. The result is that these patients often do not receive optimal healthcare services. Due to lack of (clinical) experience with rare cancers the correct diagnosis is often delayed. The patient will first consult a general practitioner, who will often not recognise early symptoms and not immediately consider the possibility of a rare cancer. Moreover, when a patient has been diagnosed with a rare cancer not all hospitals have specialized multidisciplinary teams (MDTs) with clinical consultants; as a result, discussion of the diagnosis and effective treatment are not standard and patients are often not referred in time to a centre of expertise. Furthermore, it is difficult to find funds for research to study rare cancers. It is also difficult to perform clinical trials for rare cancers because of the lack of adequate sample sizes.[3] For this reason rare cancers are often called 'orphan diseases'; rare cancer patients are 'orphans' of research, market interest and effective public health policies.[4]

To counteract this problem and reach the volume needed to study rare cancers, large scale collaboration between clinicians and researchers is mandatory. The establishment of worldwide and European collaboration between cancer registries started in 1966 with the forming of the International Association of Cancer Registries (IACR), and the European Network of Cancer Registries (ENCR) in 1989 was the first step to join forces making it possible to study rare cancers using large datasets.[5] The project called 'Surveillance of Rare Cancers in Europe' (RARECARE) collected data on cancers from 21 European countries using 89 population based cancer registries (CR). This collaboration has made it possible to develop this thesis, presenting an overview of the incidence, prevalence and survival of rare cancers.[6]

Although rare diseases, including rare cancers, represent a serious health problem for the European Union (EU)[7] the extent of this problem was previously not clear. No generally accepted definition and specific list of rare cancers existed. Monitoring rare cancers on an (inter)national level demands the availability of both a definition and a list of cancers, including information on incidence, prevalence and survival. To support this surveillance the RARECARE project[6] was put in place with the aims to;

- provide an operational definition of rare cancers, and a list of cancers that meet this definition
- estimate the burden of rare cancers in Europe
- improve the quality of data on rare cancers
- develop strategies and mechanisms to diffuse information among all the stakeholders
- involved in Europe-wide surveillance and treatment of rare cancers

This thesis aims to estimate the burden of rare cancers in general and of some specific tumours in particular. We here define the burden of rare cancers in terms of their incidence, prevalence and rates of survival. The first aim is to apply the RARECARE project's proposed definition of rare cancers to the European and Dutch populations to estimate the burden of rare cancers in Europe and the Netherlands **(Part I)**. The second aim is to estimate the burden of disease for rare thoracic cancers, including peritoneum mesotheliomas, carcinomas of the endocrine organs and rare neuroendocrine cancers, by describing incidence, prevalence and survival in Europe. Moreover, a study of European patients suffering from invasive extra-mammary Paget's disease (EMPD) provides an example of more in-depth analysis of incidence, survival and risk for second primary cancer after EMPD **(Part II)**.

Part I Definition of rare cancer

Until recently no general definition of rare cancer existed, in contrast to the over 290 different existing definitions for rare diseases.[8] Any definition should be applicable to the context in which it is used.[8] For example the European Agency for the Evaluation of Medical Products (EMA) defines a disease as rare when it has a prevalence of ≤50 patients per 100,000 persons.[9] The EMA uses this definition in the context of their responsibility to provide scientific evaluation, supervision and safety monitoring of medicines in the European Union. From the clinical perspective it is questionable whether prevalence is the correct measure to define rare cancers. Since prevalence is based on the number of newly diagnosed cases in relation to life expectancy, some cancers with a favourable prognosis do not fulfil the prevalence based definition of a rare disease as affecting ≤50 patients per 100,000 persons, and face clinical difficulties because of their low number of newly diagnosed cases per year. Mainly for this reason, the group of experts participating in the RARECARE project arrived at a consensus to use incidence, rather than prevalence, to define rare cancers.[10] Incidence is calculated by the number of new cases per year as observed in the population at risk. A threshold was set at fewer than 6 per 100,000 person-years. The choice for incidence instead of prevalence is supported by a study of Greenlee, and confirmed by the RARECARE project.[11-13]

To assure uniform use of this incidence-based definition for rare cancers a generally accepted list differentiating all possible cancer entities is mandatory. Many organ-related (so-called topography) and cell-type related (so-called morphology) combinations are options for

categorizing cancers. However, lack of a rationale for using the list of cancers will lead to different interpretations of the proposed definition. For this reason the RARECARE group provided a rationale involving a three-tier hierarchically structured list based on various topography and morphology combinations[6] as found in the International Classification of Disease for Oncology third edition (ICD-O-3)[14];

Tier 1) families of tumours
This tier involves ICD-O-3 topography and morphology combinations which reflect the main families of tumours as identified from a consensus-based clinical perspective. This grouping should be useful mainly for patient referral purposes. A family of cancer generally follows its own referral pattern.

Tier 2) clinically meaningful tumour
This tier involves ICD-O-3 topography and morphology combinations reflecting the relevance of the tumour from the clinical perspective, particularly from the therapeutic decision-making perspective. This partitioning should be useful mainly for clinical purposes, such as research.

Tier 3) tumour entities
This tier involves all possible ICD-O-3 topography and morphology combinations of malignant cancer as listed in the WHO blue books.[15] For rare cancers this usually involves a small selection of topography codes with a wide range of morphology codes (e.g. Tables 1 & 2) or vice versa (e.g. Table 3).

Example: the group of 'Endocrine tumours' is considered to be a tier 1 family of tumours as they follow a specific referral pattern as seen from the clinical perspective. Within this group the tier 2 clinically meaningful tumours are defined as; 'Carcinomas of the pituitary gland', 'Carcinomas of the thyroid gland', 'Carcinomas of the parathyroid gland' and 'Carcinomas of the adrenal gland'. Specific knowledge of these tumours is needed for clinical decision-making. tier 3 is a further differentiation based on the WHO blue book[16]; it describes the different pathological types of possible topography and morphology combinations, as for example 'medullary carcinoma of the thyroid gland'.

In addition to the structured three-tier list, an incidence threshold for rarity was determined. This threshold includes as rare all cancers belonging to the first (family of cancers) and second tier (clinically meaningful) cancers whose incidence is less than 6 per 100,000 person-years.[6] The RARECARE list of cancers includes 59 tier 1 families of cancers, 201 tier 2 clinical meaningful cancers and 579 tier 3 tumour entities.

Part II Tumour-specific outcome and burden of disease

In part II of this thesis the tumour-specific burden of rare cancers is estimated by selecting the tier 1 'families of tumours' that fit the definition of rare cancers. The burden is defined as the incidence, prevalence and survival per tier 1 'families of tumours' and tier 2 'clinically meaningful tumours'. All tier 1 'families of tumours' that conform to the definition of rare cancers were divided among the participating research groups of the RARECARE project to be described and published. The tier 1 rare thoracic cancers, including peritoneum mesotheliomas, carcinomas of endocrine organs and neuroendocrine tumours, were assigned by the RARECARE project to the Dutch research group and are therefore included in this thesis. As an example of a possible in-depth study using cancer registry data we discuss in greater detail the incidence, relative survival and risk to develop a second primary tumour after being diagnosed with EMPD.

Aims of this thesis

The focus of the first part of this thesis is to:

1. Give an overview of the burden using the RARECARE list of cancers and identify the cancers that meet the definition for rare cancers in Europe. **(chapter 2)**
2. Apply the RARECARE list and definition of rare cancers to the Netherlands population using the Netherlands Cancer Registry (NCR), and determine the usefulness of this definition and to quantify rare cancers on a country specific level. **(chapter 3)**

In **chapter 2** we discuss the incidence, prevalence and survival of rare cancers in Europe. The RARECARE threshold for rarity is applied to the proposed RARECARE list of cancers, stating that tier 1 and tier 2 cancers with an incidence of <6 new cases per 100,000 person-years is a rare cancer. By using the RARECARE database, including 89 population-based cancer registries in 21 countries between 1988 and 2002, we cover 32% of the European Union (EU27) population. Incidence rates are estimated as the number of new cases occurring from 1995 to 2002, divided by the total person-years in the general population (male and female) over the same period in each CR area. To estimate prevalence, we used data from the cancer registries (CRs) which were able to provide cases for the relatively long period from 1988 to 2002; only 22 CRs fulfilled this condition. We used data from all 76 CRs (including specialised registries) to reach survival estimates. To estimate survival for patients diagnosed in 1995–1999 we needed a follow-up until at least the end of 2003 to allow for estimation of 5-year survival.

In **chapter 3**, to determine the usefulness of the RARECARE list and its definition of rare cancers, we applied it to the Dutch population. We selected NCR data between 2004 and 2008 to generate an overview of cancers that measured up to the new definition. We compared the Dutch RARECARE results with those in Europe **(chapter 2)** to get better insight into differences and ambiguities. We selected the period 2004–2008 because for this period the most complete

data were available. We defined the ICD-O-3 topography and morphology combinations as stipulated for tier 1 'families of tumours' and presented the tier 2 'clinical meaningful tumours'. We presented more detailed gender specific incidence data using the European Standardized Rate (ESR).

In the second part of this thesis the aim is to give an overview of the disease burden, calculating incidence, prevalence and survival for:
1. Rare thoracic cancers, including peritoneum mesotheliomas
2. Carcinomas of endocrine organs
3. Rare neuroendocrine tumours

For the EMPD disease the incidence, survival and the risk for developing a second primary after EMPD are presented in more detail.

In **chapter 4** we present the burden of rare thoracic cancers, including peritoneum mesotheliomas. For incidence analyses we include 17,688 cases from 64 different cancer registries over the period 1995-2002. Using the RARECARE database we analysed carcinomas of endocrine organs, based on 33,594 cases **(chapter 5)**, and neuroendocrine tumours (NET), based on 20,994 cases **(chapter 6)**. As presented in table 3 of this introduction we describe NETs excluding NETs of the lung because their European incidence rate is estimated at 7.3 per 100,000 person-years, and therefore not considered rare.[17] For all three chapters we estimated relative survival according to the Hakulinen method.[18] We estimated period survival indicators for the years 2000–2002 by using the Brenner algorithm.[19] Forty six of the 76 European CRs do have data available for these analyses. We estimated 2, 5 and 15 year prevalence per 100,000 and 1,000,000 persons, using January 1, 2003 as index date. For this estimation we used data from 22 registries, covering the whole 15-year period. We applied the counting method[20] to CRs data between 1988 and 2002. We used the completeness index method to estimate complete prevalence, adding the estimated number of surviving cases diagnosed with rare cancer prior to 1988 to those counted from 1988 to 2002.[21] In all three chapters **(chapters 4 to 7)** we evaluated differences among European regions, dividing the participating RARECARE CRs into 5 different European regions; 1) Northern Europe (Iceland, Norway, Sweden), 2) United Kingdom and Ireland (England, Scotland, Wales, Northern Ireland, Republic of Ireland), 3) Central Europe (Belgium, Austria, France, Germany, the Netherlands, Switzerland), 4) Eastern Europe (Poland, Slovakia), 5) Southern Europe (Italy, Malta, Portugal, Slovenia, Spain).

In **chapter 7** we study the incidence, relative survival and risk for second primary tumours for patients diagnosed with invasive EMPD, also using RARECARE data. We selected patients with EMPD, using topography and morphology combinations from 1995 to 2002. Incidence was expressed in European standardized rates (ESR). Relative survival was calculated for the period 1995-1999, with a follow-up until 31st December 2003. Standardized incidence ratios (SIR)

of second primary tumours were calculated to reveal possible increased risk for secondary primary tumours after EMPD.

Chapter 8 provides a summary of the main findings and conclusions of this thesis, followed by a general discussion focusing on the definition of rare tumours and the future implications of our findings.

Tumour selection

We present the tier and cancer entity name, together with the exact ICD-O-3[14] topography and morphology combinations[6], per family of cancer as described in **chapters 4 to 6**.

Rare thoracic cancers including peritoneum mesotheliomas

Rare thoracic cancers are located in the chest and include those of the trachea (C33), of the thymus (C37) and peritoneal mesothelioma (C48). In table 1 the topography codes represent the localisations included for chapter 4 on rare thoracic tumours, including peritoneal mesotheliomas. The codes C38 and C63.7 represent the pleura and pericardium, and the peritoneum and tunica vaginalis. The morphology codes included represent the cell tissues related to the specific localisations. For example code 8580 stands for thymomas that can develop only in the thymus, and group 9050-9053 stands for the mesotheliomas.[14] More general morphology codes like the 8000-8001 codes (neoplasms and unspecified tumour cells) are also included.

Tier and cancer entity	Topography codes included	Morphology codes included
1. Epithelial tumour of the trachea	**C33**	**8000-8001,8004,8010-8011,8044,8020-8022,8031-8032,8050- 076,8078,8082-8084,8140-8141,8143-8144,8147,8190, 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**
2. Squamous cell carcinoma with variants of trachea	C33	8004,8020-8022,8031-8032,8050-8076,8078 8082-8084,8560,8980
2. Adenocarcinoma with variants of trachea	C33	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
2. Salivary gland type tumours of trachea	C33	8200,8430,8982
1. Epithelial tumour of the thymus	**C37**	**8000-8001,8010-8011,8020-8022,8032,8050-8076,8078,8082-8084,8140-8141, 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, 8480-8482,8490,8504, 8510,8512,8514,8525,8542,8550-8551,8560,8562-8576,8580-8586**
2. Malignant thymoma	C37	8580-8586
2. Squamous cell carcinoma of thymus	C37	8051-8076,8078,8083-8084
2. Undifferentiated carcinoma of thymus	C37	8020-8022
2. Lymphoepithelial carcinoma of thymus	C37	8082

2. Adenocarcinoma with variants of thymus	C37	8050,8140-8141,8143,8144,8147,8190,8200-8201, 8210-8011,8221,8230,8231, 8255,8260-8263,8290, 8310,8315,8320, 8323,8333,8380-8384,8430,8440-8441,8480-8482,8490,8504,8510,8512,8514,8525, 8542,8550-8551,8560,8562-8576
1. Malignant mesothelioma	**All cancer sites**	**9050-9053**
2. Mesothelioma of pleura and pericardium	C38	9050-9053
2. Mesothelioma of peritoneum and tunica vaginalis	C48,C63.7	9050-9053

Table 1: Inclusion of Rare thoracic cancers including Mesotheliomas based on ICD-O-3 topography and morphology combinations

Carcinomas of endocrine organs

For endocrine tumours of the thyroid gland we excluded the medullar, mixed medullary-follicular and mixed medullary-papillary tumours of the thyroid gland, since these tumours, being rare neuroendocrine tumours, are described in the chapter on Neuroendocrine tumours. For the endocrine tumours of the adrenal gland we included for analyses both the cortex and the medulla of the adrenal gland; we also included the adrenocortical carcinomas and the malignant phaeochromocytoma (table 2). The topography codes represent the different localisations of carcinomas of the endocrine organs. For example the C73.9 is the ICD-O-3 code for thyroid gland and C74 for the adrenal gland. The morphology codes represent the specific type of cell tissue included. For example, codes 8003-8004 are the ICD-O-3 codes for giant cell- and spindle cell-types of tumours. More specifically, code 8381 is the code for endometrioid adenofibroma and 8700 that for pheochromocytoma.[14]

Tier and cancer entity	Topography codes included	Morphology codes included
1. Carcinomas of endocrine organs	**C73-C75.1**	**8000-8001,8003-8004,8010-8012,8014-8035,8050-8084,8140, 8147,8190,8201, 8211,8230-8231,8255, 8260-8263,8270,8272, 280-8281,8290,8310,8320, 8323,8330-8333,8334-8350,8370, 8430,8440,8480, 8481,8490,8504,8510 ,8512,8514, 8525, 8542,8550-8551,8560,8562,8570-8573,8575-8576,8588-889,8700**
2. Carcinomas of pituitary gland	C75.1	8000-8001,8010,8140-8381
2. Carcinomas of thyroid gland	C73.9	8000-8001,8003-8004,8010,8012,8014-8035,8050-8084,8140, 8201,8230,8260, 8290,8310,8330-8333, 8334-8344,8350,8430, 8480,8481,8490,8588-8589
2. Carcinomas of parathyroid gland	C75.0.	8000-8001,8010-8012,8014-8035,8050-8076,8140, 8147,8190, 8211,8230-8231,8255,8260-8263,8290, 8310,8320,8323,8430, 8440,8480,8481,8490,8504, 8510,8512,8514,8525,8542,8550-8551,8560,8562, 8570-8573,8575-8576,8980
2. Carcinoma of adrenal gland	C74	8000-8001,8010-8012,8014-8035,8050-8076,8140, 8147,8190, 8211,8230-8231,8255,8260-8263,8290, 8310,8320,8323,8370, 8430,8440,8480,8481,8490, 8504,8510,8512,514,8525,8542,8550-8551,8560, 8562,8570-8573,8575-8576,8700

Table 2: Inclusion of endocrine tumours based on ICD-O-3 topography and morphology combinations cluding

Neuroendocrine tumours

In table 3 the topography codes represent the different localisations included for neuroendocrine tumours. For example, C44 is the ICD-O-3 code for the skin. The code C34 represents the lung, being excluded within the selection of rare neuroendocrine tumours. As neuroendocrine tumours can occur in almost all organs[22], they are mainly differentiated from other tumour types by the morphology codes included. For example, code 8013 is the ICD-O-3 code for large cell neuroendocrine carcinoma; other specific codes included are 8151, 8152 and 8153, representing insulinomas, glucagonomas and gastrinomas, respectively.[14]

Tier and cancer entity	Topography codes included	Morphology codes included
1. Neuroendocrine tumours	**All cancer sites except C34**	**8013, 8041-8045,8150-8157,8240-8247,8249,8345-8347,8510**
2. Well differentiated endocrinetumours, carcinoid	All cancer sites except C15-C26, C34,C44	8240-8246
2. Well differentiated endocrine tumours, atypical carcinoid	All cancer sites except C15-C26, C34, C44	8249
2. Poorly differentiated endocrine carcinoma (lung small cell carcinoma and carcinoma of the skin excluded)	All cancer sites except C34,C44,C73	8013,8041-8045
2. Mixed endocrine-exocrine carcinoma	All cancer sites except C34,C44	8154
2. Endocrine carcinoma of thyroid gland	C73	8041,8510,8345-8347
2. Well differentiated non functioning endocrine carcinoma of pancreas and digestive tract	C15-26	8240-8246,8249,8150
2. Well differentiated functioning endocrine carcinoma of pancreas and digestive tract	C15-26	8151-8153,8155-8157
2. Endocrine carcinoma of skin	C44	8041-8044,8240-8247

Table 3: Inclusion of neuroendocrine tumours based on ICD-O-3 topography and morphology combinations

The invasive extra-mammary Paget's disease (EMPD) is described in **chapter 7**. For analyses we included morphological code 8542. For this chapter we only excluded tumours located in the breast (ICD-O-3 C50). For the second primary tumour after EMPD no morphology and topography restrictions were done.

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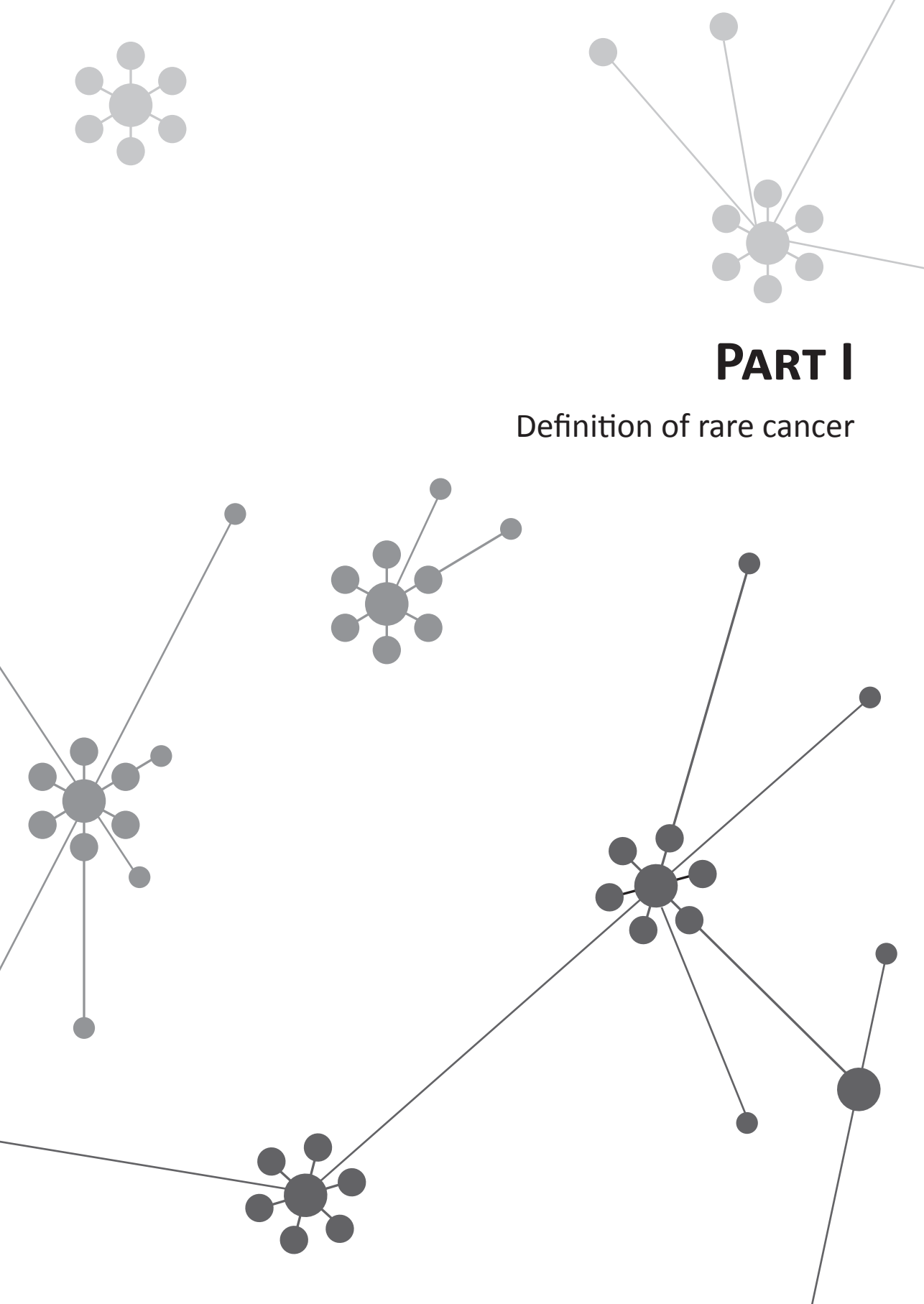

Part I

Definition of rare cancer

Chapter 2

Rare cancers are not so rare:

The rare cancer burden in Europe

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Eur J of Cancer 2011; 47: 2493-2511.

Abstract

Purpose:
Epidemiologic information on rare cancers is scarce. The project Surveillance of Rare Cancers in Europe (RARECARE) provides estimates of the incidence, prevalence and survival of rare cancers in Europe based on a new and comprehensive list of these diseases.

Materials and methods:
RARECARE analysed population-based cancer registry (CR) data on European patients diagnosed from 1988 to 2002, with vital status information available up to 31st December 2003 (latest date for which most CRs had verified data). The mean population covered was about 162,000,000. Cancer incidence and survival rates for 1995–2002 and prevalence at 1st January 2003 were estimated.

Results:
Based on the RARECARE definition (incidence <6/100,000/year), the estimated annual incidence rate of all rare cancers in Europe was about 108 per 100,000, corresponding to 541,000 new diagnoses annually or 22% of all cancer diagnoses. Five-year relative survival was on average worse for rare cancers (47%) than common cancers (65%). About 4,300,000 patients are living today in the European Union with a diagnosis of a rare cancer, 24% of the total cancer prevalence.

Conclusion:
Our estimates of the rare cancer burden in Europe provide the first indication of the size of the public health problem due to these diseases and constitute a useful base for further research. Centres of excellence for rare cancers or groups of rare cancers could provide the necessary organisational structure and critical mass for carrying out clinical trials and developing alternative approaches to clinical experimentation for these cancers.

Introduction

There is no internationally agreed definition of rare cancers. In Europe rare diseases are often defined as those with a prevalence of <50/100,000.[1] In the US, the Orphan Drug Act defined rare diseases as those affecting <200,000 persons.[2] However, a recent analysis of rare cancers in the US employed the definition of <15 incident cases per 100,000 person-years.[3]

A major problem with rare cancers is that their overall burden on society has not been adequately estimated, although they are thought to constitute a major public health problem.[4–6] Rare cancers are often inadequately diagnosed and treated[4] in relation both to lack of knowledge and lack of clinical expertise. Improving the quality of care for these cancers is a public health priority. One way of doing this would be to use a similar approach to that used for rare childhood cancers: concentrate treatment at specialised centres, and recruit most patients diagnosed to clinical trials.[5] However this requires a huge organisational effort; and for the rarest cancers it will always be impossible to recruit sufficient patients to perform standard clinical trials. Thus new approaches to obtaining evidence on treatment efficacy need to be developed.[6] The project Surveillance of Rare Cancers in Europe (RARECARE) collected data on cancers from 89 population-based cancer registries (CRs) in 21 European countries, making it possible to study the epidemiology of these cancers as a whole in a large and heterogeneous population. Working from this database and the literature, a RARECARE working group produced a new list of cancers and developed a new definition of rare cancers (http://www.rarecare.eu). This paper delineates the burden of these cancers in Europe, providing estimates of the incidence, prevalence and survival of rare cancers diagnosed from 1988 to 2002, based on the RARECARE definition and list.

Materials and methods

RARECARE gathered data on cancer patients diagnosed from 1978 to 2002 and archived in population-based CRs, all of which had vital status information available up to at least 31st December 2003. For 11 countries, the CRs covered the entire national population (Austria, Iceland, Ireland, Malta, Norway, Slovakia, Slovenia, Sweden, Northern Ireland, Scotland and Wales); the other countries do not have national cancer registration and were represented by regional CRs covering variable proportions of their national populations. The mean population covered, over the period 1995–1999, was about 162,000,000 corresponding to 39% of the population of countries participating in RARECARE and 32% of the European Union (EU27) population. Systematic data checks were performed to detect errors, inconsistencies or unusual combinations of site, morphology, sex and age at diagnosis.[7,8] Only a negligible proportion (0.14%) of cases had major errors and had to be excluded.[7] RARECARE collected data from 89 CRs; however the present paper considered data from 76 CRs, excluding CRs which did not classify cancers according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3),[9] and also those which collected data on childhood cancers only.

Incidence

The incidence analysis only considered cases incident in the more recent 1995–2002 period. Specialised CRs and some non-specialised CRs, with information available only for some anatomical sites were excluded. This criterion implied restricting the incidence analyses to 4,048,903 cases from 64 CRs. Incidence rates were estimated as the number of new cases occurring in 1995–2002 divided by the total personyears in the general population (male and female) in each CR area, over the same period. The expected number of new cases per year in EU27 in 2008 was also estimated, assuming that incidence rates in Europe were same as those in the RARECARE sample.

Prevalence

CRs that started up recently do not have records of longerterm cancer survivors diagnosed before start up, resulting in underestimation of prevalence. To estimate prevalence, we therefore used data from CRs able to provide cases for the relatively long period 1988–2002; only 22 CRs fulfilled this condition. We calculated the number of prevalent cancers in 2008 and prevalence per 100,000 at the index date of 1st January 2003. The counting method[10] based on CR incidence and follow-up data, was applied to CR data from 1988–2002. The completeness index method[11] was used to estimate the complete prevalence and involved adding the estimated surviving cases diagnosed prior to 1988 to those counted in 1988–2002. The total number of prevalent cases in the EU27 in 2008 was estimated assuming the same prevalence as in the RARECARE sample. Overall, 4,302,067 cancer cases were used to produce the prevalence estimates.

Survival

Data from all 76 CRs (including specialised registries) were used to produce survival estimates. We used the cohort approach[12] to estimate survival for patients diagnosed in 1995–1999 and followed-up until at least the end of 2003, enabling estimation of 5-year survival. A total 2,708,344 cases were used for the analysis. We estimated relative survival,[12] the ratio of observed survival to the expected survival in the general population of the same age and sex, to correct for deaths from causes other than the cancer under investigation.

List of cancers and definition of rare cancers

The present analyses are based on the new list of cancer types provided by RARECARE. The list was produced by a group of pathologists, haematologists, clinicians and epidemiologists and emerged after a consultation process during which the developing list and its rationale were available at http://www.rarecare.eu. The list, endorsed by major European cancer organisations, is organised into three tiers as exemplified in Table 1. The bottom tier corresponds to the WHO names of individual cancer entities (http://www.iarc.fr/en/publications/pdfs-online/pat-gen/) and their corresponding ICD-O-3[9] codes. Bottom tier entities were grouped into categories (middle tier) considered to require similar clinical management and research. Middle tier

entities were grouped into general categories (top tier) considered to involve the same clinical expertise and patient referral structure.

TIER	NAME
Top	**EPITHELIAL TUMOURS OF ANAL CANAL**
Middle	Squamous cell carcinoma and variants of anal canal
Bottom	Verrucous carcinoma
Bottom	Undifferentiated carcinoma
Bottom	Basaloid carcinoma
Middle	Adenocarcinoma and variants of anal canal
Bottom	Mucinous adenocarcinoma
Middle	Paget disease of anal canal

Table 1: The three-tier structure of the RARECARE list of cancers illustrated for epithelial cancers of the anal canal.

RARECARE defined rare cancers as those with an incidence of <6/100,000/year, corresponding to <30,000 new cases/year in Europe. A total of 186 cancers were rare according to this definition. The list of the rare and common cancers defined by RARECARE is available at the RARECARE website and in Table 2 which shows the top and middle tiers only. Table 2 also shows the estimates of crude annual incidence, complete prevalence and 5-year survival, together with the expected number of new cases per year and prevalent cases in the EU27 in 2008.

Results

Table 3 shows quality indicators for the data on rare and common cancers diagnosed from 1995 to 2002 and archived by the 76 CRs considered in the study. The overall proportion of death-certificate only (DCO) cases was 3%, with only six CRs having more than 5% DCOs. The overall proportion of cases discovered at autopsy was 0.5%. A high proportion of cases (86% overall) was verified microscopically (MV). Follow-up was complete for most CRs, with follow-up censored before 5 years for only 1.2% of cases overall, with only two CRs having high proportions of cases not followed-up after 2002. Two other data quality indicators, pertinent to the accuracy of diagnoses and completeness of incidence for rare cancers, are the proportion of cases with not otherwise specified (NOS) morphology codes (M8000–8001) and the proportion of cases with poorly defined topography (codes C260, C268, C269, C390, C398, C399, C559, C579, C639, C689, C729, C759–C765, C767–C768). The former was 8.2% overall and varied markedly across CRs. The latter did not exceed 2% and was <1% overall and for almost all CRs.

Incidence

RARECARE estimated that about 2,511,000 persons were diagnosed with cancer in the EU27 each year from 1995 to 2002 (Table 4). The annual EU27 incidence rate of all rare cancers was about 108 per 100,000 per year corresponding to 541,000 new diagnoses annually or 22% of all cancer diagnoses. Fig. 1a shows the distribution of cancer types, as defined by RARECARE, according to incidence rate. Fig. 1b shows the estimated number of new cancer diagnoses in the EU27 each year, again according to incidence rate. About 74% of rare cancers had an annual incidence rate of <0.5/100,000/year. However, this plethora of cancers accounted for only 70,000 (3%) of the 2.5 million cancers diagnosed each year. Another 17 cancer types, with incidence 0.5–1/100,000/year, accounted for 49,000 new diagnoses each year in EU27, while the 31 cancer types with incidence >1–6/100,000/year, accounted for 422,000 new cases/year. Seventeen common cancers accounted for the remaining cases.

Fig. 2 shows age-specific incidence rates by age class for rare and common cancers. Patients with rare cancers were on average younger than those with common cancers. Essentially all childhood cancers and most cancers (sarcomas and lymphomas) in persons up to 39 years were rare. From age 40 on, the common cancers (breast, prostate, colon, rectum and lung) became increasingly prominent. Average age at diagnosis was 60 years for rare cancers and 67 for common cancers.

Table 4 shows incidence and prevalence rates of rare and common cancers by site. Rare cancers constituted 72% of incident haematological malignancies, 55% of incident female genital tract cancers, 21% of incident respiratory cancers and 15% of incident digestive tract cancers. Rare cancers were <10% of incident cancers at other sites. The proportions of rare and common cancers (columns 6 and 10) do not sum to 100% for each cancer site, since some cancers could not be classified as rare or common because of unspecified morphology. The proportion of unclassifiable cancers varied with site, being highest (30%) for respiratory tract cancers and lowest (2%) for skin cancers.

Prevalence

We estimated that 4,300,000 people were alive in the EU27 with a previous diagnosis of a rare cancer, 24% of the total cancer prevalence. Almost all cancers considered rare according to RARECARE are also rare according to the commonly adopted prevalence criterion in Europe[1] of <50/100,000. Only squamous cell carcinoma of the uterine cervix and thyroid carcinoma are rare according to the incidence (RARECARE) criterion and ‘common’ according to the prevalence criterion. Six cancers are common according to the incidence criterion and rare according to the prevalence criterion. These are stomach adenocarcinoma, pancreatic adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, poorly differentiated endocrine carcinomas of lung and the group other non-Hodgkin mature B cell lymphomas. The explanation is that these are poor prognosis cancers which hence have low prevalence, even though incidence is relatively high.

Relative survival

Rare cancers had, on average, worse relative survival than common cancers. For patients with rare cancers diagnosed in 1995–1999, 1, 3 and 5-year relative survival was 68%, 52% and 47%, respectively; the corresponding figures for patients with common cancers were 80%, 69% and 65% (Fig. 3). Fig. 3 shows that survival 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, and suggesting that later stage at diagnosis is not a factor in the poorer survival for rare cancers.

Fig. 4 shows 5-year relative survival for rare and common cancers by age class. For patients 0–39 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 –17% at 40–59 years to –30% at 75–99 years. In the oldest age group, survival for rare cancers was almost half that of common cancers. From Fig. 4 it is evident that 5-year survival was similarly high for both rare and common cancers in children and young adults (up to 39 years) but that 5-year survival for rare cancers fell increasingly behind that of common cancers as age of diagnosis increased. Most cancers in children and young adults were rare (Fig. 2) 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 so effective as for the rare paediatric cancers.

Five-year relative survival was ≥50% for most rare cancers (Table 2) but was poor (<20%) for cancers of liver, gallbladder and trachea, as well as mesothelioma, acute myeloid leukaemia and glioma. Survival was also poor for some rare cancers belonging to common categories (squamous cell cancer of kidney, and some rare histotypes of lung, pancreatic, oesophagus and stomach cancers). Highest 5-year survival (>90%) was for testicular cancers (except epithelial testicular cancers), pancreatoblastoma, retinoblastoma, Paget's disease of vulva and vagina, soft tissue skin cancers, special types of breast adenocarcinoma and middle ear adenocarcinoma.

Discussion

Data quality

The data were derived from the largest available database on rare cancers itself obtained from European CRs. The major indicators of data quality (Table 3) indicate a high quality dataset.[7]

For rare cancers, the most likely quality problem is lack of specificity of morphology codes making it impossible to assign such cases to a specific (rare) cancer entity, resulting in underestimation of the true incidence and prevalence of such entities (although they still contribute to overall incidence and prevalence estimates). Nine percent of RARECARE cases had missing morphology specification (codes M8000 or M8001) and could be assigned to a 'top tier' (Table 1) cancer category but not to middle (more specific) tiers. This is well illustrated for

Rare (R) or common (C) (middle tier only)	Tier	Top tier (upper case) and middle tier (lower case) tumour categories	Crude incidence per 100,000 per year	Standard error incidence	Expected new cases per year	Observed 5-year survival (%)	Relative 5-year survival (%)	Standard error relative survival (%)	Complete prevalence per 100,000	Standard error complete prevalence	Prevalent Cases
	1	EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES	0.44	0.01	2198	39.3	48.3	1.3	2.92	0.08	14,492
R	2	Squamous cell carcinoma with variants of nasal cavity and sinuses	0.31	0.01	1545	40.2	49.2	1.5	2.1	0.07	10,416
R	2	Lymphoepithelial carcinoma of nasal cavity and sinuses	0	0	12	28.6	31	13.1	0.01	0.01	72
R	2	Undifferentiated carcinoma of nasal cavity and sinuses	0.02	0	86	27.5	32.4	6	0.13	0.02	665
R	2	Intestinal type adenocarcinoma of nasal cavity and sinuses	0	0	12	43	50.1	14.6	0.02	0.01	123
	1	EPITHELIAL TUMOURS OF NASOPHARYNX	0.44	0.01	2205	44.1	49.1	1.1	2.94	0.09	14,637
R	2	Squamous cell carcinoma with variants of nasopharynx	0.33	0.01	1626	44.4	49.2	1.3	2.2	0.07	10,966
R	2	Papillary adenocarcinoma of nasopharynx	0	0	4	57.1	58.8	23.8	0.01	0	29
	1	EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY-GLAND TYPE TUMOURS	1.31	0.01	6501	54.2	64.8	0.7	13.08	0.18	65,063
R	2	Epithelial tumours of major salivary glands	0.73	0.01	3624	53.7	64.6	1	7.9	0.14	39,290
R	2	Salivary gland type tumours of head and neck	0.43	0.01	2134	60.3	69.1	1.2	4.53	0.11	22,553
	1	EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX	6.26	0.03	31,138	46.9	54.8	0.3	39.98	0.33	198,863
R	2	Squamous cell carcinoma with variants of hypopharynx	1.19	0.01	5905	21.6	24.6	0.6	3.47	0.09	17,293
R	2	Squamous cell carcinoma with variants of larynx	4.64	0.02	23,082	54.5	63.7	0.4	34.39	0.28	171,098
	1	EPITHELIAL TUMOURS OF OROPHARYNX	2.75	0.02	13,667	33.1	37.1	0.4	13.04	0.18	64,877
R	2	Squamous cell carcinoma with variants of oropharynx	2.58	0.02	12,858	33.3	37.2	0.5	12.52	0.18	62,254
	1	EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP	4.79	0.02	23,828	49	59.1	0.4	34.07	0.35	169,507
R	2	Squamous cell carcinoma with variants of oral cavity	3.28	0.02	16,337	41.3	48.2	0.4	19.34	0.25	96,196
R	2	Squamous cell carcinoma with variants of lip	1.22	0.01	6093	70.1	91.7	0.7	12.79	0.18	63,621
	1	EPITHELIAL TUMOURS OF OESOPHAGUS	7.51	0.03	37,379	8.4	10.6	0.2	12.11	0.16	60,221
R	2	Squamous cell carcinoma with variants of oesophagus	3.4	0.02	16,927	8.7	10.7	0.3	5.42	0.1	26,953
R	2	Adenocarcinoma with variants of oesophagus	2.85	0.02	14,182	9.1	11.7	0.3	5.55	0.1	27,625
R	2	Salivary gland type tumours of oesophagus	0.01	0	29	8.1	9.6	5.3	0.01	0	36
R	2	Undifferentiated carcinoma of oesophagus	0.07	0	367	5.6	7.3	1.5	0.08	0.01	390
	1	EPITHELIAL TUMOURS OF STOMACH	18.62	0.05	92,649	16.4	21.6	0.2	49.17	0.32	244,582
C	2	Adenocarcinoma with variants of stomach	15.23	0.04	75,772	17.8	23.1	0.2	45.9	0.31	228,325

R	2	Squamous cell carcinoma with variants of stomach	0.13	0	646	11.3	14.2	1.5	0.24	0.02	1193
R	2	Salivary gland-type tumours of stomach	0.01	0	25	16.9	20.6	7.8	0.02	0.01	118
R	2	Undifferentiated carcinoma of stomach	0.17	0	838	10.1	13.2	1.3	0.33	0.02	1633
	1	EPITHELIAL TUMOURS OF SMALL INTESTINE	0.72	0.01	3595	20.4	25.3	0.8	2.67	0.08	13,276
R	2	Adenocarcinoma with variants of small intestine	0.57	0.01	2823	21.1	25.8	0.9	2.21	0.07	10,983
R	2	Squamous cell carcinoma with variants of small intestine	0.01	0	30	18.2	21.4	7.9	0.03	0.01	125
	1	EPITHELIAL TUMOURS OF COLON	42.64	0.07	212,093	41.3	53.2	0.1	251.08	1.08	1,248,973
C	2	Adenocarcinoma with variants of colon	37.21	0.07	185,092	44.5	56.3	0.1	241.06	0.99	1,199,156
R	2	Squamous cell carcinoma with variants of colon	0.02	0	104	25	31.9	5.2	0.09	0.01	440
	1	EPITHELIAL TUMOURS OF RECTUM	17.11	0.05	85,133	41.6	52.5	0.2	110.89	0.73	551,594
C	2	Adenocarcinoma with variants of rectum	15.52	0.04	77,205	43.5	54.3	0.2	105.49	0.68	524,771
R	2	Squamous cell carcinoma with variants of rectum	0.07	0	368	41.4	50.4	3	0.67	0.04	3323
R	2	Basaloid carcinoma of rectum	0.01	0	74	42.6	51.1	6.6	0.06	0.01	307
	1	EPITHELIAL TUMOURS OF ANAL CANAL	1.09	0.01	5427	45.2	55.4	0.8	8.16	0.14	40,589
R	2	Squamous cell carcinoma with variants of anal canal	0.73	0.01	3634	51.6	61.4	1	6.84	0.13	29,266
R	2	Adenocarcinoma with variants of anal canal	0.26	0.01	1276	32.3	42	1.7	1.07	0.05	5333
R	2	Paget's disease of anal canal	0	0	20	47.8	59.9	13	0.02	0.01	4750
	1	EPITHELIAL TUMOURS OF PANCREAS	11.79	0.04	58,639	2.9	3.7	0.1	8.3	0.12	41,268
C	2	Adenocarcinoma with variants of pancreas	7.59	0.03	37,758	2.7	3.4	0.1	6.27	0.11	31,178
R	2	Squamous cell carcinoma with variants of pancreas	0.03	0	129	8	9.7	2.9	0.05	0.01	242
R	2	Acinar cell carcinoma of pancreas	0.02	0	108	18.4	21.4	4.3	0.06	0.01	281
R	2	Mucinous cystadenocarcinoma of pancreas	0.01	0	40	32.7	36.5	8.9	0.04	0.01	200
R	2	Intraductal papillary mucinous carcinoma invasive of pancreas	0	0	3	NE	NE	NE	0.01	0	29
R	2	Solid pseudopapillary carcinoma of pancreas	0	0	4	66.7	70.7	28.9	0	0	18
R	2	Serous cystadenocarcinoma of pancreas	0	0	1	100	102.2	0	0	0	0
R	2	Carcinoma with osteoclast-like giant cells	0	NE	NE	NE	NE	NE	0	NE	0
	1	EPITHELIAL TUMOURS OF LIVER AND INTRA-HEPATIC BILE TRACT (IBT)	6.19	0.03	30,802	7	8.7	0.2	5.62	0.1	27,957
R	2	Hepatocellular carcinoma of liver and IBT	3.09	0.02	15352	9.6	11.6	0.3	3.66	0.08	18186
R	2	Cholangiocarcinoma of IBT	0.84	0.01	4167	4.3	5.5	0.4	0.74	0.03	3675

(continued on next page)

Rare (R) or common (C) (middle tier only)	Tier	Top tier (upper case) and middle tier (lower case) tumour categories	Crude incidence per 100,000 per year	Standard error incidence	Expected new cases per year	Observed 5-year survival (%)	Relative 5-year survival (%)	Standard error relative survival (%)	Complete prevalence per 100,000	Standard error complete prevalence	Prevalent Cases
R	2	Adenocarcinoma with variants of liver and IBT	0.21	0.01	1027	4.4	5.3	0.8	0.19	0.02	951
R	2	Undifferentiated carcinoma of liver and IBT	0.02	0	81	3	3.6	2.5	0.01	0	45
R	2	Squamous cell carcinoma with variants of liver and IBT	0.01	0	57	7.7	9.6	4.6	0.02	0.01	80
R	2	Bile duct cystadenocarcinoma of IBT	0	0	9	11.1	12.1	11.4	0	0	11
	1	EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT (EBT)	4.37	0.02	21,763	9.7	12.6	0.3	6.83	0.11	33,974
R	2	Adenocarcinoma with variants of gallbladder and EBT	2.62	0.02	13,038	12.1	15	0.3	5.37	0.1	26,702
R	2	Squamous cell carcinoma of gallbladder and EBT	0.04	0	180	9.8	12.3	2.7	0.05	0.01	227
	1	EPITHELIAL TUMOUR OF TRACHEA	0.13	0	670	10.1	12.1	1.4	0.28	0.02	1396
R	2	Squamous cell carcinoma with variants of trachea	0.08	0	408	7.2	8.5	1.4	0.12	0.01	602
R	2	Adenocarcinoma with variants of trachea	0.01	0	67	6.6	7.6	3.3	0.02	0.01	119
R	2	Salivary gland type tumours of trachea	0.01	0	48	50.9	55.2	7.7	0.11	0.02	523
	1	EPITHELIAL TUMOUR OF LUNG	55.93	0.08	278,226	8.5	10.6	0.1	85	0.44	422,831
C	2	Squamous cell carcinoma with variants of lung	13.49	0.04	67,125	10.9	13.4	0.1	25.35	0.23	126,097
C	2	Adenocarcinoma with variants of lung	10.29	0.04	51,193	11.8	13.9	0.2	22.14	0.22	110,140
R	2	Large cell carcinoma of lung	4.01	0.02	19,936	10.2	12.3	0.3	6.83	0.12	33,969
R	2	Well differentiated endocrine carcinoma of lung	0.63	0.01	3148	53	58.7	1	6.96	0.18	34,627
C	2	Poorly differentiated endocrine carcinoma of lung	7.68	0.03	38,221	3.9	4.6	0.1	8.43	0.13	41,925
R	2	Bronchiolo-alveolar carcinoma of lung	0.68	0.01	3383	26.5	31.1	0.9	2.42	0.07	12,066
R	2	Salivary gland type tumours of lung	0.04	0	220	38.5	43.4	3.6	0.3	0.03	1505
R	2	Sarcomatoid carcinoma of lung	0.14	0	697	13.4	15.9	1.5	0.32	0.02	1621
R	2	Undifferentiated carcinoma of lung	0.98	0.01	4887	5.6	6.6	0.4	1.27	0.05	6328
	1	EPITHELIAL TUMOURS OF THYMUS	0.17	0	829	52.6	57.7	1.9	1.4	0.06	6962
R	2	Malignant thymoma	0.14	0	680	55.7	60.9	2	1.22	0.06	6055
R	2	Squamous cell carcinoma of thymus	0	0	23	40	44.6	10.9	0.02	0.01	119
R	2	Undifferentiated carcinoma of thymus	0	0	12	16.7	18.2	11.8	0	0	16
R	2	Lymphoepithelial carcinoma of thymus	0	0	4	66.7	67.6	27.6	0.01	0.01	60

R	2	Adenocarcinoma with variants of thymus	0	0	10	31	32.8	15.5	0.01	0	40
	1	EPITHELIAL TUMOURS OF BREAST	63.85	0.09	317,621	71.4	80.6	0.1	697.23	6.27	3,468,450
C	2	Invasive ductal carcinoma of breast	40.32	0.07	200,559	75.9	83.5	0.1	441.33	4.02	2,195,417
C	2	Invasive lobular carcinoma of breast	7.18	0.03	35,742	77.5	86	0.2	78.54	1.01	390,709
R	2	Mammary Paget's disease of breast	0.51	0.01	2544	71.3	83	1	6.1	0.14	30,348
R	2	Special types of adenocarcinoma of breast	3.55	0.02	17,682	84.5	95.4	0.3	46.91	0.65	233,346
R	2	Metaplastic carcinoma of breast	0.06	0	303	57.2	65.7	3.4	0.56	0.04	2800
R	2	Salivary gland type tumours of breast	0.05	0	262	77.3	85.4	2.7	0.49	0.04	2443
R	2	Epithelial tumour of male breast	0.47	0.02	2338	60.3	77.1	1.3	3.52	0.18	17,536
	1	EPITHELIAL TUMOURS OF CORPUS UTERI	10.4	0.04	51,743	69.5	79.5	0.2	133.11	0.61	662,186
C	2	Adenocarcinoma with variants of corpus uteri	9.53	0.03	47,393	71.7	81.3	0.2	126.65	0.61	630,048
R	2	Squamous cell carcinoma with variants of corpus uteri	0.12	0	581	46.2	53.5	2.3	0.95	0.05	4721
R	2	Adenoid cystic carcinoma of corpus uteri	0	0	7	70	74.5	15.4	0.29	0.05	1445
R	2	Transitional cell carcinoma of corpus uteri	0	0	1	NE	NE	NE	0.01	0	31
	1	EPITHELIAL TUMOURS OF CERVIX UTERI	6.08	0.03	30,227	62	66.7	0.3	106.46	0.66	529,610
R	2	Squamous cell carcinoma with variants of cervix uteri	4.28	0.02	21,295	62.9	67.4	0.3	76.24	0.56	379,273
R	2	Adenocarcinoma with variants of cervix uteri	1.01	0.01	5023	62.3	66.8	0.7	15.59	0.24	77,548
R	2	Undifferentiated carcinoma of cervix uteri	0.03	0	125	30.2	34.4	4.6	0.32	0.03	1589
	1	MIXED EPITHELIAL AND MESENCHYMAL TUMOURS OF UTERUS	0.44	0.01	2213	31.4	37.3	1.2	2.59	0.08	12,888
R	2	Mixed epithelial and mesenchymal tumours of uterus	0.44	0.01	2213	31.4	37.3	1.2	2.59	0.08	0
	1	EPITHELIAL TUMOURS OF OVARY AND FALLOPIAN TUBE	9.39	0.03	46,735	33	37.7	0.3	59.78	0.44	297,397
R	2	Adenocarcinoma with variants of ovary	5.97	0.03	29,692	33	36.9	0.3	39.13	0.37	194,668
R	2	Mucinous adenocarcinoma of ovary	0.85	0.01	4206	52.5	58.1	0.8	9.55	0.18	47,536
R	2	Clear cell adenocarcinoma of ovary	0.32	0.01	1611	50	53.9	1.3	2.55	0.08	12,691
R	2	Adenocarcinoma with variants of fallopian tube	0.26	0.01	1316	42.5	47.8	1.5	1.99	0.07	9866
	1	NON-EPITHELIAL TUMOURS OF OVARY	0.43	0.01	2153	57.9	62.6	1.1	6.69	0.17	33,286
R	2	Mixed epithelial/mesenchymal tumours of ovary	0.16	0	775	15.9	18.2	1.5	0.49	0.03	2461
R	2	Sex cord tumours of ovary	0.13	0	670	76.1	82.7	1.7	1.85	0.08	9224
R	2	Malignant/Immature teratomas of ovary	0.07	0	337	80.5	83.3	2.1	1.5	0.09	7481

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Rare (R) or common (C) (middle tier only)	Tier	Top tier (upper case) and middle tier (lower case) tumour categories	Crude incidence per 100,000 per year	Standard error incidence	Expected new cases per year	Observed 5-year survival (%)	Relative 5-year survival (%)	Standard error relative survival (%)	Complete prevalence per 100,000	Standard error complete prevalence	Prevalent Cases
R	2	Germ cell tumour of ovary	0.07	0	371	83.5	84.3	1.8	2.23	0.16	11,128
	1	EPITHELIAL TUMOURS OF VULVA AND VAGINA	1.91	0.02	9517	47	60.9	0.7	15.34	0.18	76,299
R	2	Squamous cell carcinoma with variants of vulva and vagina	1.5	0.01	7480	46.4	59.6	0.7	12.42	0.17	61,791
R	2	Adenocarcinoma with variants of vulva and vagina	0.08	0	383	35.5	43.2	2.9	0.52	0.03	2610
R	2	Paget's disease of vulva and vagina	0.05	0	249	77.5	97.8	3.2	0.47	0.04	2338
R	2	Undifferentiated carcinoma of vulva and vagina	0.01	0	40	26.3	31.5	8	0.05	0.01	235
	1	TROPHOBLASTIC TUMOUR OF PLACENTA	0.02	0	119	89.6	90	2.7	0.86	0.12	4275
R	2	Choriocarcinoma of placenta	0.02	0	119	89.6	90	2.7	0.86	0.12	3886
	1	EPITHELIAL TUMOURS OF PROSTATE	47.89	0.08	238,222	54.2	74.4	0.1	303.98	1.42	1,512,168
C	2	Adenocarcinoma with variants of prostate	40.51	0.07	201,518	58.8	78.8	0.2	278.96	1.36	1,387,707
R	2	Squamous cell carcinoma with variants of prostate	0.11	0	562	33.4	45.1	2.7	0.75	0.04	3753
R	2	Infiltrating duct carcinoma of prostate	0.47	0.01	2335	59.3	77.3	1.5	4.5	0.09	22,403
R	2	Transitional cell carcinoma of prostate	0.06	0	320	33.2	48.5	3.6	0.29	0.02	1459
R	2	Salivary gland type tumours of prostate	0	0	8	36.4	50	19.9	0.01	0	36
	1	TESTICULAR AND PARATESTICULAR CANCERS	3.15	0.02	15,679	93	94.8	0.2	87.77	0.75	436,638
R	2	Paratesticular adenocarcinoma with variants	0	0	7	66.7	81.4	23.5	0.01	0	60
R	2	Non-seminomatous testicular cancer	1.21	0.01	6031	92.4	93.3	0.3	33.53	0.6	166,788
R	2	Seminomatous testicular cancer	1.71	0.01	8518	95.5	97.4	0.2	46.01	0.58	288,900
R	2	Spermatocytic seminoma	0.03	0	137	90.6	100.5	2.8	0.75	0.05	3731
R	2	Teratoma with malignant transformation	0	0	7	59.2	62.4	19.3	0.04	0.01	199
R	2	Testicular sex cord cancer	0.02	0	109	77.6	83.7	4.8	0.44	0.04	2207
	1	EPITHELIAL TUMOURS OF PENIS	0.62	0.01	3101	56.7	71.7	1.1	5.54	0.11	27,557
R	2	Squamous cell carcinoma with variants of penis	0.57	0.01	2851	58.1	72.8	1.1	5.03	0.1	25,045
R	2	Adenocarcinoma with variants of penis	0	0	25	35.8	51.9	13.7	0.03	0.01	140
	1	EPITHELIAL TUMOURS OF KIDNEY	10.55	0.04	52,472	47.6	56.6	0.3	72.81	0.45	362,188
C	2	Renal cell carcinoma with variants	8.35	0.03	41,521	54.9	63.6	0.3	67.18	0.44	334,179
R	2	Squamous cell carcinoma spindle cell type of kidney	0.01	0	35	6.5	7.9	5.4	0.01	0.01	73

R	2	Squamous cell carcinoma with variants of kidney	0.04	0	175	10.3	12.4	2.7	0.06	0.01	306
	1	EPITHELIAL TUMOURS OF PELVIS, URETER AND URETHRA	1.58	0.01	7870	42.8	53.5	0.7	10.96	0.15	54,515
R	2	Transitional cell carcinoma of pelvis, ureter and urethra	1.37	0.01	6805	45.1	56	0.7	9.85	0.15	49,030
R	2	Squamous cell carcinoma with variants of pelvis, ureter and urethra	0.05	0	254	25.8	32.1	3.3	0.21	0.02	1043
R	2	Adenocarcinoma with variants of pelvis, ureter and urethra	0.04	0	185	40.2	48.2	4.5	0.2	0.02	1025
R	2	Salivary gland-type tumours of pelvis, ureter and urethra	0	0	1	0	0	0	0	0	8
	1	EPITHELIAL TUMOURS OF BLADDER	20.11	0.05	100,031	50	65.6	0.2	148.17	0.58	737,090
C	2	Transitional cell carcinoma of bladder	17.41	0.05	86,610	52.7	68.5	0.2	134.96	0.56	671,365
R	2	Squamous cell carcinoma with variants of bladder	0.43	0.01	2120	25.2	33.6	1.2	1.75	0.06	8711
R	2	Adenocarcinoma with variants of bladder	0.29	0.01	1425	31.9	40.3	1.5	1.38	0.05	6862
R	2	Salivary gland type tumours of bladder	0	0	6	50	66.3	23.4	0	0	20
	1	EPITHELIAL TUMOURS OF EYE AND ADNEXA	0.04	0	177	66.5	85	4.3	0.35	0.04	1741
R	2	Squamous cell carcinoma with variants of eye and adnexa	0.02	0	119	66.9	88.5	5.3	0.18	0.02	895
R	2	Adenocarcinoma with variants of eye and adnexa	0.01	0	32	62.9	74.3	10.1	0.07	0.02	348
	1	EPITHELIAL TUMOURS OF MIDDLE EAR	0.03	0	151	34.5	41.9	4.5	0.23	0.02	1122
R	2	Squamous cell carcinoma with variants of middle ear	0.02	0	111	26.1	32.2	4.8	0.14	0.02	709
R	2	Adenocarcinoma with variants of middle ear	0	0	18	79.1	90.2	10.6	0.04	0.01	213
	1	MALIGNANT MESOTHELIOMA	1.9	0.02	9437	4.5	5.5	0.3	2.38	0.07	11,841
R	2	Mesothelioma of pleura and pericardium	1.6	0.01	7964	4	4.9	0.3	1.97	0.06	9824
R	2	Mesothelioma of peritoneum and tunica vaginalis	0.12	0	617	9.8	11.4	1.4	0.22	0.02	1072
	1	MALIGNANT SKIN MELANOMA	12.41	0.04	61,752	74.5	84.3	0.2	202.32	0.91	1,006,430
C	2	Malignant skin melanoma	12.41	0.04	61,752	74.5	84.3	0.2	202.32	0.91	1,006,430
	1	MALIGNANT MELANOMA OF MUCOSA	0.26	0.01	1293	32.1	40.6	1.8	1.51	0.06	7485
R	2	Malignant melanoma of mucosa	0.26	0.01	1293	32.1	40.6	1.8	1.51	0.06	7485
	1	MALIGNANT MELANOMA OF UVEA	0.51	0.01	2533	59.4	68.9	1.6	5.97	0.13	29,676
R	2	Malignant melanoma of uvea	0.51	0.01	2533	59.4	68.9	1.6	5.97	0.13	29,676
	1	EPITHELIAL TUMOURS OF SKIN	48.58	0.08	241,674	74.1	97.8	0.1	554.33	1.13	2,757,555
C	2	Basal cell carcinoma of skin	32.05	0.06	159,410	79.8	100.8	0.1	389.91	1.05	1,939,620

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Rare (R) or common (C) (middle tier only)	Tier	Top tier (upper case) and middle tier (lower case) tumour categories	Crude incidence per 100,000 per year	Standard error incidence	Expected new cases per year	Observed 5-year survival (%)	Relative 5-year survival (%)	Standard error relative survival (%)	Complete prevalence per 100,000	Standard error complete prevalence	Prevalent Cases
C	2	Squamous cell carcinoma with variants of skin	16.39	0.05	81,554	63.5	91.6	0.3	152.86	0.65	760,420
	1	ADNEXAL CARCINOMA OF SKIN	0.28	0.01	1378	64.3	87.1	1.8	2.67	0.08	13,304
R	2	Adnexal carcinoma of skin	0.28	0.01	1378	64.3	87.1	1.8	2.67	0.08	13,304
	1	EMBRYONAL NEOPLASMS	0.34	0.01	1713	76.4	76.8	1	7.96	0.41	39,580
R	2	Neuroblastoma and ganglioneuroblastoma	0.12	0	603	59.7	59.9	1.9	1.58	0.12	7862
R	2	Nephroblastoma	0.14	0	705	85.6	86	1.3	3.65	0.26	18,145
R	2	Retinoblastoma	0.05	0	268	97.1	97.4	1	1.05	0.06	5200
R	2	Hepatoblastoma	0.02	0	112	61.6	62.4	4.3	0.54	0.15	2692
R	2	Pulmonary blastoma	0	0	21	43.2	44.8	11.6	0.12	0.05	614
R	2	Pancreatoblastoma	0	0	4	100	100.2	0	NE	NE	NE
	1	EXTRAGONADAL GERM CELL TUMOURS	0.13	0	630	68.1	69.5	1.9	3.4	0.15	17,027
R	2	Extragonadal malignant/immature teratomas	0.04	0	207	64	65.5	3.3	0.91	0.09	4549
R	2	Extragonadal germ cell tumours	0.09	0	423	70.1	71.4	2.2	2.51	0.25	12,478
	1	SOFT TISSUE SARCOMA	4.74	0.02	23,574	48.6	55.8	0.4	46.86	0.4	233,097
R	2	Soft tissue sarcoma of head and neck	0.29	0.01	1431	51.5	64.7	1.6	2.94	0.1	14,628
R	2	Soft tissue sarcoma of limbs	1.03	0.01	5124	57.5	67.1	0.8	11.63	0.2	57,837
R	2	Soft tissue sarcoma of superficial trunk	0.46	0.01	2307	40.8	47.5	1.2	4.02	0.12	20,003
R	2	Soft tissue sarcoma of mediastinum	0.03	0	129	19.9	22.2	3.8	0.1	0.02	503
R	2	Soft tissue sarcoma of heart	0.01	0	74	12.6	13.1	3.9	0.05	0.01	248
R	2	Soft tissue sarcoma of breast	0.19	0	927	71.7	78.5	1.6	2.21	0.08	10,994
R	2	Soft tissue sarcoma of uterus	0.5	0.01	2466	46.8	50.6	1.1	4.88	0.13	24,295
R	2	Other soft tissue sarcomas of genitourinary tract	0.24	0.01	1185	41.2	47.6	1.6	2.16	0.09	10,746
R	2	Soft tissue sarcoma of viscera	0.51	0.01	2517	34.2	40.1	1.1	2.64	0.08	13,145
R	2	Soft tissue sarcoma of paratestis	0.03	0	162	71.8	87.1	4.1	0.3	0.03	1511
R	2	Soft tissue sarcoma of retroperitoneum and peritoneum	0.29	0.01	1419	32.2	37.1	1.4	1.24	0.05	6192
R	2	Soft tissue sarcoma of pelvis	0.01	0	71	30.8	35.6	6	0.08	0.02	391

R	2	Soft tissue sarcoma of skin	0.31	0.01	1524	82	92.3	1.1	4.54	0.15	22,582
R	2	Soft tissue sarcoma of paraorbit	0.01	0	33	60.6	65.7	9.2	0.23	0.04	1166
R	2	Soft tissue sarcoma of brain and other parts of nervous system	0.19	0	947	51.2	56	1.8	2.12	0.08	10,527
R	2	Embryonal rhabdomyosarcoma of soft tissue	0.06	0	305	66.6	67.4	2.6	1.67	0.23	8307
R	2	Alveolar rhabdomyosarcoma of soft tissue	0.03	0	161	40.6	41.7	3.9	0.2	0.02	984
R	2	Ewing's family tumours of soft tissue	0.05	0	263	43.6	44.9	3.2	0.55	0.03	2713
	1	BONE SARCOMA	0.8	0.01	4003	56.6	60.6	0.8	9.29	0.18	46,193
R	2	Osteogenic sarcoma	0.23	0.01	1135	52.3	54.6	1.5	3.17	0.12	15,834
R	2	Chondrogenic sarcomas	0.24	0.01	1215	67.1	73.9	1.4	3.55	0.11	17,691
R	2	Notochordal sarcomas, chordoma	0.04	0	218	57.4	64.5	3.8	0.42	0.03	1959
R	2	Vascular sarcomas	0	0	16	25	28	10.8	0.02	0.01	88
R	2	Ewing's family of tumours	0.13	0	647	49.7	50	1.9	2.33	0.19	11,381
R	2	Epithelial tumours, adamantinoma	0.01	0	43	74	83.9	7.4	0.11	0.02	576
R	2	Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	0.02	0	90	46.7	52.5	5.5	0.16	0.02	783
	1	GASTROINTESTINAL STROMAL SARCOMA	0.07	0	331	60.4	70.3	4.3	§	§	§
R	2	Gastrointestinal stromal sarcoma	0.07	0	331	60.4	70.3	4.3	§	§	§
	1	KAPOSI SARCOMA	0.34	0.01	1716	54.6	63.8	1.3	2.11	0.09	10,516
R	2	Kaposi sarcoma	0.34	0.01	1716	54.6	63.8	1.3	2.11	0.09	10,516
	1	NEUROENDOCRINE TUMOURS	2.53	0.02	12,587	43	50.7	0.5	20.1	0.25	100,003
R	2	Well differentiated endocrine tumours, carcinoid	0.37	0.01	1828	27.6	32.2	1.3	1.57	0.06	7791
R	2	Well differentiated endocrine tumours, atypical carcinoid	0	0	4	100	101.8	0	0.01	0	35
R	2	Poorly differentiated endocrine carcinoma (lung small cell carcinoma and skin excluded)	0.52	0.01	2596	10.4	12.8	0.7	1.34	0.06	6679
R	2	Mixed endocrine–exocrine carcinoma	0	0	11	30	34.8	16.8	0.02	0.01	96
R	2	Endocrine carcinoma of thyroid gland	0.22	0.01	1084	74.7	80.5	1.4	3.25	0.11	16,164
R	2	Well differentiated not functioning endocrine carcinoma of pancreas and digestive tract	1.26	0.01	6244	55.6	64.3	0.7	12.8	0.2	63,691
R	2	Well differentiated functioning endocrine carcinoma of pancreas and digestive tract	0.02	0	122	45.5	50.4	4.8	0.21	0.02	1070

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Rare (R) or common (C) (middle tier only)	Tier	Top tier (upper case) and middle tier (lower case) tumour categories	Crude incidence per 100,000 per year	Standard error incidence	Expected new cases per year	Observed 5-year survival (%)	Relative 5-year survival (%)	Standard error relative survival (%)	Complete prevalence per 100,000	Standard error complete prevalence	Prevalent Cases
R	2	Endocrine carcinoma of skin	0.13	0	667	39.1	57.6	3	0.86	0.04	4273
	1	CARCINOMA OF ENDOCRINE ORGANS	4.13	0.02	20,563	77.9	84.4	0.3	65.82	0.5	327,441
R	2	Carcinomas of pituitary gland	0.04	0	206	57.3	67.9	4	0.87	0.06	4334
R	2	Carcinomas of thyroid gland (medullary carcinoma included)	3.65	0.02	18,137	81.7	88.1	0.3	61.68	0.5	306,808
R	2	Carcinomas of parathyroid gland	0.02	0	109	65.2	73.5	5.2	0.28	0.03	1418
R	2	Carcinoma of adrenal gland	0.18	0	902	36	39.3	1.7	1.15	0.06	5698
	1	GLIAL TUMOURS OF CENTRAL NERVOUS SYSTEM (CNS)	5.35	0.03	26,610	18.4	20	0.3	26.29	0.41	130,764
R	2	Astrocytic tumours of CNS	4.8	0.02	23,859	13.7	15.1	0.2	20.42	0.37	101,593
R	2	Oligodendroglial tumours of CNS	0.35	0.01	1759	51.8	54	1.2	2.65	0.09	13,187
R	2	Ependymal tumours of CNS	0.2	0	992	68.8	71.3	1.5	3.85	0.14	19,125
	1	NON-GLIAL TUMOURS OF CNS AND PINEAL GLAND	0.22	0.01	1116	52.5	53	1.5	4.73	0.24	23,569
R	2	Embryonal tumours of CNS	0.22	0.01	1085	52.6	53.1	1.5	4.31	0.23	21,470
R	2	Choroid plexus carcinoma of CNS	0.01	0	31	45.5	46.9	10.5	0.35	0.06	1735
	1	MALIGNANT MENINGIOMAS	0.15	0	756	54.2	61.7	2	1.75	0.07	8699
R	2	Malignant meningiomas	0.15	0	756	54.2	61.7	2	1.75	0.07	8699
	1	GLIAL TUMOURS OF CRANIAL AND PERIPHERAL NERVES, AUTONOMIC NERVOUS SYSTEM	0.01	0	51	83.4	86.5	5.2	0.41	0.06	2030
R	2	Astrocytic tumours of cranial and peripheral nerves, autonomic nervous system	0	0	25	66.7	68.7	9.3	0.16	0.04	820
R	2	Ependymal tumours of cranial and peripheral nerves and autonomic nervous system	0.01	0	26	100	104.4	0	0.1	0.02	473
	1	NON-GLIAL TUMOURS OF CRANIAL ANDPERIPHERAL NERVES, AUTONOMIC NERVOUS SYSTEM AND PARAGANGLIA	0.1	0	488	60.4	63.9	2.3	1.18	0.07	5896
R	2	Embryonal tumours of cranial and peripheral nerves, autonomic nervous system	0.07	0	365	64.3	67.6	2.6	0.87	0.06	4366
R	2	Paraganglioma	0.02	0	124	47	51	5.2	0.27	0.03	1345
	1	LYMPHOID DISEASES	29.09	0.06	144,707	45.9	55.2	0.2	229.39	1.13	1,141,118
R	2	Hodgkin lymphoma	2.44	0.02	12,158	77.9	82.3	0.4	46.89	0.46	233,280

R	2	Precursor B/T lymphoblastic leukaemia/lymphoblastic lymphoma (and Burkitt leukaemia/lymphoma)	1.45	0.01	7216	56.3	58.9	0.6	26.79	0.5	133,279
R	2	T cutaneous lymphoma (Mycosis fungoides, Sezary syndrome)	0.52	0.01	2562	67.9	80.4	1.1	5.18	0.1	25,753
R	2	Other T cell lymphomas and NK cell neoplasms	0.47	0.01	2351	37.6	43.2	1.2	2.83	0.08	14,082
R	2	Diffuse and follicular B lymphoma	4.91	0.02	24,413	48.5	56.7	0.4	31.04	0.5	154,392
R	2	Hairy cell leukaemia	0.29	0.01	1434	78.4	89.7	1.2	3.12	0.09	15,521
R	2	Plasmacytoma/multiple myeloma (and heavy chain diseases)	5.86	0.03	29,139	25.9	32.8	0.3	22.59	0.5	112,380
C	2	Other non-Hodgkin, mature B cell lymphoma	6.22	0.03	30,963	51.1	65.1	0.4	40.96	0.5	203,735
	1	ACUTE MYELOID LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS	3.69	0.02	18,376	16.3	19.8	0.3	10.98	0.17	54,619
R	2	Acute promyelocytic leukaemia (AML with t(15;17) with variants)	0.11	0	547	56.7	61.2	2.2	0.65	0.04	3219
R	2	Acute myeloid leukaemia	3.39	0.02	16,868	15	18.2	0.3	10.75	0.19	53,486
	1	MYELOPROLIFERATIVE NEOPLASMS	3.07	0.02	15,269	48.7	59.8	0.5	20.34	0.43	101,158
R	2	Chronic myeloid leukaemia	1.25	0.01	6212	34.6	41.7	0.7	5.63	0.12	28,002
R	2	Other myeloproliferative neoplasms	1.81	0.01	8980	58.6	73	0.6	17.13	0.22	85,215
R	2	Mast cell tumour	0.02	0	76	66.8	71.7	5.8	0.2	0.03	982
	1	MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/ MYELOPROLIFERATIVE DISEASES	1.79	0.01	8907	23.5	34.7	0.7	5.64	0.12	28,078
R	2	Myelodysplastic syndrome with 5q syndrome	0	0	2	NE	NE	NE	NE	NE	NE
R	2	Other myelodysplastic syndrome	1.5	0.01	7460	25	37.2	0.8	5.02	0.12	24,958
R	2	Chronic myelomonocytic leukaemia	0.29	0.01	1432	15.7	22.6	1.4	0.69	0.04	3442
R	2	Atypical chronic myeloid leukaemia BCR/ABL negative	0	0	4	0	0	0	0	0	19
	1	HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	0.05	0	243	68.7	71.6	3	1.06	0.07	5264
R	2	Histiocytic and dendritic cell neoplasms	0.05	0	243	68.7	71.6	3	1.06	0.07	5264

NE = not estimated.

§ = this entity definition is too recent for prevalence estimation.

Table 2: RARECARE estimates of incidence, survival and prevalence of cancers for EU27, together with expected number of new cases per year and prevalent cases in EU72

epithelial tumours of oesophagus, liver and intra-hepatic bile tract, and ovary: for these top tier categories (Table 2), the incidence was greater than the sum of incidences of the specific rare (middle tier) subcategories and the difference is due to NOS cases.
In addition, the incidence of a few entities, including gastrointestinal stromal tumours and several haematological malignancies, is almost certainly underestimated because they were newly erected during the study period (specific morphological codes introduced for the first time only with ICD-O-3) and would not have been recognised by manypathologists at that time 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 is registration bias and results in incidence and prevalence underestimation. To assess the extent of registration bias, 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). Briefly, the great majority of NOS morphology caseswere 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 the oral cavity epithelial cancers were reclassified from NOS to more specific diagnoses: 8% were reclassified as squamous cell carcinoma (commoner) 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.

How representative are our EU27 estimates?

In providing rare cancer burden estimates, we assumed that the population covered by our CRs was representative of the population of the EU27 as a whole. It is important to assess to what extent this assumption may be true. For rare cancers, this is not possible because morphology information (essential for identifying a rare cancer) is not available in published incidence estimates. For common cancers the assumption of representativity can be tested by comparison of our incidence estimates with those of GLOBOCAN, considered the best available.[13] We found that RARECARE incidence rates for major cancers (lung 56.2, colorectal 61, breast 64, all sites 454) were closely similar to those of GLOBOCAN for EU27 (lung 56.5, colorectal 61.2, breast 59.8, all sites 450.6), suggesting that the RARECARE population is as representative of the EU27 population as the population covered by GLOBOCAN.

RARECARE definition of rare cancers

We used a new incidence-based criterion for defining rare cancers. In Europe[1] rare cancers are often defined according to the prevalence criterion of <50/100,000, in the same way as rare diseases in general. However, prevalence has shortcomings as a measure of cancer rarity since some cancers with low incidence but good survival will fall into the common category as good survival pushes up prevalence; examples are squamous cell carcinoma of the uterine cervix and thyroid carcinoma. Similarly, some commonly-occurring diseases for which survival is poor are considered rare because poor survival pushes prevalence down. Examples are

Country	Registry	Number of malignant cancers	Data quality indicators					
			Death Certificate only (%)	Autopsy (%)	Microscopic Verification (%)	Cases 1995-1998 censored before 5 years (%)	Morphology (b) code NOS (%)	Topography code NOS (%)
Austria	Austria	304,493	8.9	0	85.2	5.9	10.1	0.6
Belgium	Flanders	144,715	0	0.2	89.8	0	7.3	0.5
France	Bas Rhin	13,113	0	0	95.8	3.3	3.9	0.2
	Calvados	5695	0	0	98.1	6.1	2.5	0.3
	Calvados digestive	2801	0	0	87	4.4	10.5	0.3
	Côte d'Or digestive	4376	0	0	82.8	0.5	17.5	0.2
	Côte d'Or haematol.	1884	0	0	100	7.2	0	0.5
	Doubs	5742	0	0	95.8	2.1	3.2	0.3
	Haut Rhin	9073	0	0	96.4	5.8	2.9	0.1
	Hérault	10,505	0	0	0	6.4	1.5	0.1
	Isère	12,526	0	0	94.1	4.6	4.1	0.1
	Loire Atlantique	3746	0	0	100	6.8	0	0
	Manche	6267	0	0	96.5	2.7	3.4	0.3
	Marne and Ardennes	168	0	0	100	3.6	0	0
	Somme	6481	0	0	94.2	6.6	5.5	0.8
	Tarn	4935	0	0	93.8	2	5.9	1.3
Germany	Saarland	54,132	3.9	0	91.8	5.8	8	0.5
Iceland	Iceland	8854	0.1	1.4	96.6	0	3.5	0
Ireland	Ireland	156,529	2	0.3	86.7	0	11	0.7
Italy	Alto Adige	18,676	0.7	0	89.5	0	9.2	0.5
	Biella	11,770	1.3	0.4	87	0	12.5	0.3
	Ferrara	23,740	1.1	0	88.1	0.4	9.7	0.6
	Firenze	66,097	0.9	0.1	80.4	0.4	17.7	0.8
	Friuli V.G.	78,882	0.6	1.9	91	0.3	9.8	2.1
	Genova	44,207	1.8	0	81.4	0	16.6	0.9
	Macerata	10,396	1.3	0	87.4	0.2	13.1	0.6
	Modena	34,947	0.5	0	88.6	0.4	11.8	0.5
	Napoli	8145	3.9	0	73	1.9	17.6	1.4
	Palermo	581	2.2	0	92.6	0	7.2	0
	Parma	23,836	1	0	86	0.3	13.1	0.7
	Ragusa	10,687	1.9	0.8	80.9	0.1	24.6	0.6
	Reggio Emilia	22,152	0.2	0	88.1	0	13.8	0.5
	Romagna	60,667	2.4	0	87.9	0.1	12.3	0.5
	Salerno	26,917	2.5	0	77.5	4	23.7	1.1
	Sassari	18,084	2.9	0.2	84.4	0	16.4	0.7

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	Trento	17,788	2	0	85	0.3	27.8	3.8
	Umbria	45,221	0.7	0	84	0.1	12.6	0.6
	Varese	24,728	1.1	0	89	11.5	10.8	0.4
	Veneto	84,528	1.5	0.2	87.5	0.8	13.7	1.7
Malta	Malta	9848	1.9	0.1	87.6	0	12.9	0.7
Norway	Norway	197,240	1	0.4	93.1	0.1	6.7	0.6
Poland	Cracow	24,545	1.1	0.1	75.2	2.9	27.2	1.2
	Kielce	34,123	0	0	80.2	0	21.7	1
	Warsaw	50,238	3.4	0	80.2	0.2	19.1	0.8
Portugal	South Portugal	32,917	0	0	93.9	0	7.2	0.4
Slovakia	Slovakia	128,686	12.8	1.5	81.8	0.5	17.9	1.6
Slovenia	Slovenia	56,632	1.6	1.1	90.8	0.1	9.6	0.7
Spain	Albacete	1941	4.7	0	89.3	0.3	11.9	0
	Basque Country	44,809	4.2	0	86.3	0.1	11.4	0.7
	Castillon	1608	4.7	0	95	0	5.4	0
	Girona	19,936	3.8	0.1	87.7	0.1	12.8	0.6
	Granada	7298	2.1	0.1	89.3	0	10.8	0
	Murcia	14,068	3.5	0.1	88	2.5	11.1	1
	Navarra	15,381	2.2	0.6	90.9	0.6	7.6	0.4
	Tarragona	12,412	4.8	0	86.4	0.1	13.3	0.7
Sweden	Sweden	347,616	0	2.2	98.2	0.1	2.6	1.3
Switzerland	Basel	13,654	0	4.3	99	3.8	0.2	0
	Geneva	16,775	0.5	1.1	92.6	1.7	6.2	0.7
	Grisons	2788	0.7	0.5	91.9	2.4	6.3	0
	St. Gallen	16,588	0.7	1.2	92.8	0.5	4.4	0.4
	Ticino	10,784	3	0.3	91.4	0.6	6.8	1.4
	Valais	4533	1.5	0.4	91.2	2.4	8.2	0.9
	Zurich	777	0.3	3.9	97.3	2.7	2.2	0
Netherlands	Amsterdam	95,439	0	0.5	95.7	0.6	4.2	0.1
	Eindhoven	27,985	0	0	95.7	0.1	4.1	0.2
	North Netherlands	58,508	0	1	94.7	0	5.3	0.2
	Twente	41,217	0	0.7	95.1	0.1	5.1	0.3
UK England	East Anglia	131,829	0.5	0.9	86.4	10.1	0.6	0.3
	Northern and Yorkshire	265,499	1.1	0.4	86.8	0	3.9	0.3
	Oxford	85,848	0.8	0.4	88.8	0	0.4	0.5
	South Western	168,672	7.8	0.1	70.2	0	10.6	1.3
	Trent	109,768	7.3	0	74	0	2.4	0.8
	West Midlands	190,726	5.1	1.1	81.9	0	4.2	0.4
UK North Ireland	Northern Ireland	69,558	1.2	0.4	83.4	0	16.7	0.6

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UK Scotland	Scotland	263,710	0.9	0.1	86.4	0	5.8	0.5
UK Wales (a)	Wales	120,606	12.7	0	51	0	6.3	0.8
RARECARE		4,082,646	3	0.5	85.9	1.2	8.2	0.7

a MV status not ascertainable for all cases from Wales CR.

b Morphology codes NOS (Not otherwise specified) are M8000–8001; topography codes NOS are C260, C268, C269, C390, C398, C399, C559, C579, C639, C689, C729, C759-C765 and C767–C768.

Table 3 – Data quality indicators and other characteristics of malignant cancers diagnosed in European cancer registries 1995–2002 and included in the analyses.

adenocarcinoma of stomach and lung and squamous cell carcinoma of lung (Table 2). These considerations suggest that incidence is better for defining rare cancers, and is also in harmony with the sub-acute clinical course of most rare cancers; whereas most rare non-neoplastic diseases have a chronic course so prevalence is a better measure.

The RARECARE rarity threshold at <6/100,000/year might be considered too high. However, if the lower threshold of <3/100,000/year were adopted, glial tumours, epithelial cancers of the oral cavity and lip, epithelial cancers of gallbladder and extrahepatic biliary tract, soft tissue sarcomas, tumours of testis and paratestis, carcinomas endocrine organs, myeloproliferative neoplasms and acute myeloid leukaemia, would all be excluded. Yet these forms are often inadequately diagnosed and treated in relation both to 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.[14] Thus the <6/100,000 /year threshold includes several forms with the problems typically present in rare cancers.

		Crude incidence per 100,000 per year	Standard error	Estimated incident cases in EU27 per year	Incidence distribution (%)	Prevalence per 100,000	Standard error	Estimated prevalent cases in EU27 per year	Prevalence distribution (%)
Rare	Digestive tract	17.5	0.1	87,280	15	50.9	0.4	254,473	11
Common	Digestive tract	75.7	0.1	378,507	67	399.3	1.2	1,996,625	84
All	Digestive tract	113.7	0.1	568,548	100	476	1.4	2,380,246	100
Rare	Respiratory tract	13.6	0	68,147	21	60	0.4	300,193	46
Common	Respiratory tract	31.5	0.1	157,445	49	56	0.3	279,942	43
All	Respiratory tract	63.9	0.1	319,349	100	129.7	0.6	648,321	100
Rare	Skin	1.5	0	7649	2	14.8	0.3	73,849	2
Common	Skin	60.8	0.1	304,186	96	744.9	1.5	3,724,477	96
All	Skin	63.2	0.1	316,171	100	779.9	1.5	3,899,301	100
Rare	Breast	4.4	0	22,041	7	60.2	0.7	300,759	9
Common	Breast	47.5	0.1	237,529	74	519.9	4.1	2,599,432	74
All	Breast	64.1	0.1	320,548	100	700.2	6.3	3,500,906	100
Rare	Female genital tract	16.1	0	80,699	55	176.2	0.8	880,922	53

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Common	Female genital tract	9.5	0	47,639	32	126.7	0.6	633,280	38
All	Female genital tract	29.5	0.1	147,433	100	331.8	1.1	1,658,891	100
Rare	Male genital tract	4.4	0	21,872	8	93.1	0.8	465,363	23
Common	Male genital tract	40.6	0.1	202,766	78	279.4	1.4	1,396,883	70
All	Male genital tract	51.9	0.1	259,642	100	399.5	1.6	1,997,563	100
Rare	Urinary system	2.6	0	12,740	8	18.3	0.4	91,683	8
Common	Urinary system	25.8	0.1	128,798	78	202.1	0.7	1,010,735	85
All	Urinary system	33	0.1	164,983	100	237.7	0.8	1,188,660	100
Rare	Haematopoietic system	15.9	0	79,409	72	90.1	0.7	450,444	70
Common	Haematopoietic system	4.8	0	24,091	22	32.3	0.3	161,618	25
All	Haematopoietic system	22	0.1	109,738	100	129.5	0.7	647,596	100
Rare	All sites	108.3	0.1	541,296	22	859.5	2.2	4,297,365	24
Common	All sites	297.4	0.2	1,486,956	59	2368.3	4.8	11,841,483	66
All	All sites	502.1	0.3	2,510,662	100	3566.4	7.2	17,831,883	100

Table 4: RARECARE estimates of incidence and prevalence for rare and common cancers by site in EU27.

Survival

Overall, rare cancer survival was worse than common cancer survival. Relative survival was lower at 1 year and continued to diverge up to 3 years, while the gap remained constant from 3 to 5 years after diagnosis. However in children and adolescents) among whom rare cancers are more common than common cancers) survival was similar to that of the common cancers. Advances in treatment as a result of clinical trials have markedly improved prognoses for many childhood cancers over the last 30–40 years.[15] Perhaps this lesson can be applied to rare cancers in adults; however it is unclear why survival for rare cancers is low 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.

Prevalence

Since the definition of rare diseases is based on prevalence and the EU directive on orphan drugs[16] provides incentives to foster research and development of orphan drugs for rare diseases, the availability of prevalence data for rare cancers should facilitate application of the EU orphan drug directive. If the existing European definition of rare diseases were used (prevalence <50/100,000), rare cancers would be 24% of total cancer prevalence as estimated by RARECARE.

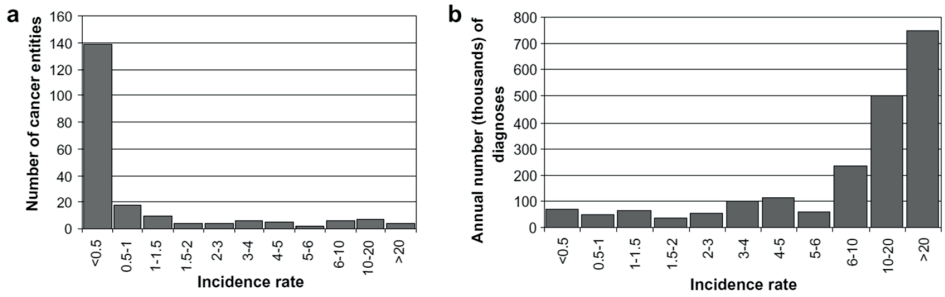

Fig. 1: Distribution of number of cancer types (1a) and annual number of diagnoses (1b) in EU27 according to categories of incidence rate

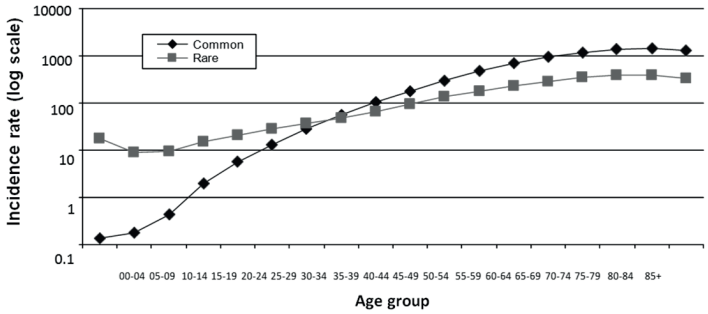

Fig. 2: RARECARE estimates of age-specific incidence rates for rare and common cancers in EU 27.

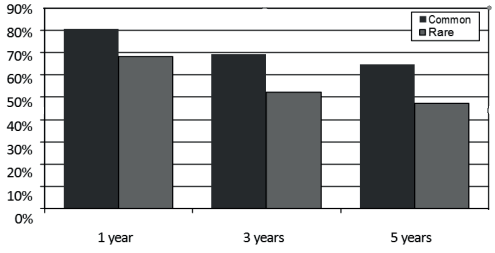

Fig. 3: RARECARE estimates of relative survival for rare and common cancers in EU27 by year since diagnosis

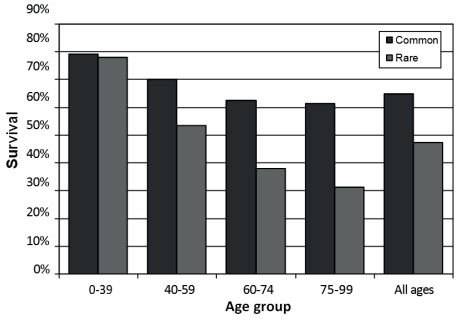

Fig. 4: RARECARE estimates of relative survival for rare and common cancers in EU27 by age group

Concluding remarks

We have at last put numbers to a problem long known to exist. Our estimates indicate that 22% of all cancers diagnosed in the EU27 each year are rare. In absolute terms, this is slightly more than half a million new rare cancer cases each year, while 4,300,000 rare cancers are prevalent in the population.

It is noteworthy that 30% of Europeans with a rare cancer have one of the particularly rare forms that affect <1/100,000/year (Fig. 1) and this is important, because low incidence is a major obstacle to conducting clinical trails to develop effective treatments.[6] One way to overcome this obstacle would be to establish centres of excellence for rare cancers and international collaborative groups to network centres across the EU to thereby achieve necessary organisational structure, critical mass and patients for carrying out clinical trials, developing alternative study designs and methodological approaches to clinical experimentation and improving accuracy and standardisation of staging procedures for rare cancers. RARECARE (http://www.rarecare.eu) will continue to encourage initiatives to put these cancers on the map.

The RARECARE working group consists of:

Austria: M. Hackl (Austrian National Cancer Registry); Belgium: E. Van Eycken; D. Schrijvers (Ziekenhuisnetwerk Antwerpen, ZNA – Hospital Network), H. Sundseth, Jan Geissler (European Cancer Patient Coalition), S. Marreaud (European Organisation for Research and Treatment of Cancer), R. Audisio (European Society of Surgical Oncology); Estonia: M. Mägi(Estonian Cancer Registry); France: G. Hedelin, M. Velten (Bas-Rhin Cancer Registry); G. Launoy (Calvados Digestive Cancer Registry); A.V. Guizard (Calvados General Cancer Registry); A.M. Bouvier (Cô te d'Or Digestive Cancer Registry); M. Maynadié , (Côte d'Or Haematological Malignancies Registry); M. Mercier (Doubs Cancer Registry); A. Buemi (Haut-Rhin Cancer Registry); B. Tretarre (Hérault Cancer Registry); M. Colonna (Isère Cancer Registry); F. Molinié (Loire Atlantique Breast and Colon Cancer Registry); B. Lacour, (Manche Cancer Registry); C. Schvartz (Marne and Ardennes Thyroid Cancer Registry); O. Ganry (Somme Cancer Registry); P. Grosclaude (Tarn Cancer Registry); E. Benhamou, M. Grossgoupil (Institute Gustave Roussy), I.R. Coquard, J.P. Droz (Centre Le´on Bérard), S. Baconnier (Connective tissue cancer network – CONTICANET); Germany: B. Holleczek (Saarland Cancer Registry); M.Wartenberg (Global GIST Network), R. Hehlmann (European Leukemia-Net); 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); C. Cirilli (Modena Cancer Registry); M. Fusco (Napoli Cancer Registry); A. Traina (Palermo Breast Cancer Registry); M. Michiara (Parma Cancer Registry); A. Giacomin (Piedmont Cancer Registry, Province of Biella); G. Pastore (Childhood Cancer Registry of Piedmont-CPO); R. Tumino (Cancer Registry and Histopathology Unit, 'M.P. Arezzo' Civic Hospital, Ragusa); L. Mangone (Reggio Emilia Cancer Registry); F. Falcini (Romagna Cancer Registry); G. Senatore (Salerno Cancer Registry), M. Budroni (Sassari Cancer Registry); S. Piffer (Trento Cancer Registry); E. Crocetti (Tuscan Cancer Registry); F. La Rosa, (Umbria Cancer Registry); P. Contiero (Varese Cancer Registry); P. Zambon (Veneto Cancer Registry); F. Berrino, P.G. Casali, G. Gatta,

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Conflict of interest statement

The authors declare no conflicts of interest.

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Chapter 3

Rare cancers in the Netherlands:

A population based study

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Abstract

The conventional definition for rare disease is based on prevalence. Because of differences in prognosis, a definition on the basis of incidence was deemed to be more appropriate for rare cancers. Within the European RARECARE project, a definition was introduced that defines cancers as rare when the crude incidence rate is less than six per 100,000 per year. In this study, we applied the RARECARE definition for rare cancer to the Netherlands; this to identify the usefulness of the definition in a single country and to provide more insight into the burden of rare cancers in the Netherlands. Data for 2004 through 2008 were extracted from the Netherlands Cancer Registry and classified according to the RARECARE entities (tumour groupings). Crude and European standardized incidence rates were calculated. Out of the 260 entities, 223 (86%) were rare according to the definition, accounting for 14,000 cancers (17% of all). Considerable fluctuations in crude rates over years were observed for the major group of cancers. Rare tumours in the Netherlands constituted 17% of all newly diagnosed tumours, but were divided over 223 different entities indicating the challenge that faces clinicians. To make the definition of rare cancers better applicable, it should be refined by taking into consideration the sex-specific incidence for sex-specific cancer sites. Moreover, a mean incidence over 5 years will provide more solid insight into the burden, eliminating large fluctuations in time of most of the cancers.

Introduction

Clinicians consider patients with rare cancers in most cases as a challenge because they do not encounter a patient with this specific type of cancer regularly and are therefore less experienced with diagnostics, staging and treatment.
Until recently, only a definition for rare diseases on the basis of the prevalence rate existed. Diseases are defined as rare when the prevalence is less than 50 per 100,000 in the community.[1] Moreover, the American Orphan Drug Act defines rare diseases as those affecting fewer than 200 000 individuals in the USA.[2] For cancer, however, using prevalence as a measure of rarity may not be the most suitable. Some cancers with a low incidence but a good survival will have a high prevalence and would therefore not be considered rare. Still, the low incidence means limited opportunities to become acquainted with the specifics of diagnosis and treatment. Therefore, in the RARECARE project, a new definition was developed defining rare cancers, which was based on a wide consensus among organizations representing medical professionals (surgeons, pathologists and medical oncologists). Cancer should be considered rare when the crude incidence rate is less than six per 100,000 per year.[3,4]
The RARECARE project provided a list of rare cancers for Europe and not for the separate European countries.[3] Applying the definition to a single country will provide information on the usefulness of the definition on a national level. Furthermore, knowledge of
the burden of rare cancers for a specific country could give an impulse in awareness and might lead to the development of (inter)national guidelines supporting the clinicians in diagnoses and treatment decision making. Moreover, the discussion on (virtual) centralizing the care for these patients within a country or even between countries could be supported; concentration of knowledge by increasing volume will identify caveats and tackle gaps of knowledge related to the management of patients with rare forms of cancer. It can also give an impulse to research focusing on diagnosis and treatment for this diverse group of patients in relation to outcome.

In this paper, we applied the RARECARE definition for rare cancer to the Netherlands for 2004 to 2008 to identify the usefulness of and to quantify rare cancers on a national level to provide more insight into the burden of rare cancers in the Netherlands.

	2004			2005			2006			2007			2008			2004–2008		
Rare first-layer entities	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	Annual *N*	Annual CR	Annual ESR
Epithelial tumour of the nasal cavity and sinuses	99	0.6	0.5	107	0.7	0.6	112	0.7	0.6	117	0.7	0.6	123	0.7	0.6	112	0.7	0.6
Epithelial tumour of the nasopharynx	70	0.4	0.4	40	0.2	0.2	58	0.4	0.3	55	0.3	0.3	62	0.4	0.3	57	0.3	0.3
Epithelial tumour of major salivary glands and salivary gland type tumour	198	1.2	1.1	202	1.2	1.1	175	1.1	0.9	211	1.3	1.1	240	1.5	1.3	205	1.3	1.1
Epithelial tumour of the hypopharynx and larynx	868	5.4	4.9	945	5.8	5.3	898	5.5	4.9	821	5	4.4	897	5.5	4.7	886	5.4	4.8
Epithelial tumour of the oropharynx	477	2.9	2.7	438	2.7	2.5	449	2.8	2.5	471	2.9	2.5	545	3.3	2.9	476	2.9	2.6
Epithelial tumour of the oral cavity and lip	781	4.8	4.2	844	5.2	4.5	857	5.3	4.5	874	5.3	4.4	875	5.3	4.3	846	5.2	4.4
Epithelial tumour of the small intestine	89	0.5	0.5	118	0.7	0.6	126	0.8	0.6	130	0.8	0.6	135	0.8	0.6	120	0.7	0.6
Epithelial tumour of the anal canal	105	0.6	0.5	126	0.8	0.7	148	0.9	0.8	135	0.8	0.7	157	1	0.8	134	0.8	0.7
Epithelial tumour of liver and intrahepatic bile tract	318	2	1.7	327	2	1.8	333	2	1.7	390	2.4	2	421	2.6	2.1	358	2.2	1.9
Epithelial tumour of gallbladder and extrahepatic biliary duct	534	3.3	2.7	553	3.4	2.6	565	3.5	2.7	652	4	3	577	3.5	2.7	576	3.5	2.7
Epithelial tumour of the trachea	10	0.1	0.1	9	0.1	0.1	15	0.1	0.1	8	0	0	11	0.1	0.1	11	0.1	0.1
Epithelial tumour of the thymus	38	0.2	0.2	40	0.2	0.2	30	0.2	0.2	41	0.3	0.2	47	0.3	0.2	39	0.2	0.2
Mixed epithelial and mesenchymal tumour of the uterus	38	0.5	0.4	32	0.4	0.3	29	0.4	0.3	47	0.6	0.4	48	0.6	0.4	39	0.5	0.4
Nonepithelial tumour of the ovary	65	0.8	0.7	62	0.8	0.7	58	0.7	0.6	44	0.5	0.5	67	0.8	0.7	59	0.7	0.6
Epithelial tumour of the vulva and vagina	285	3.5	2.5	304	3.7	2.6	309	3.7	2.6	349	4.2	3.1	332	4	2.8	316	3.8	2.7
Trophoblastic tumour of the placenta	4	0	0	4	0	0	8	0.1	0.1	10	0.1	0.1	12	0.1	0.2	8	0.1	0.1
Epithelial tumour of the penis	113	1.4	1.3	106	1.3	1.2	117	1.4	1.3	108	1.3	1.2	123	1.5	1.3	113	1.4	1.3
Epithelial tumour of the pelvic ureter and urethra	311	1.9	1.7	351	2.2	1.8	354	2.2	1.8	389	2.4	1.9	417	2.5	2	364	2.2	1.8
Epithelial tumour of the eye and adnexa	12	0.1	0.1	13	0.1	0.1	8	0	0	9	0.1	0	13	0.1	0.1	11	0.1	0.1
Epithelial tumour of the middle ear	4	0	0	4	0	0	5	0	0	6	0	0	9	0.1	0	6	0	0
Malignant mesothelioma	447	2.8	2.5	501	3.1	2.8	491	3	2.6	460	2.8	2.4	497	3	2.5	479	2.9	2.6
Malignant melanoma of the mucosa	152	0.9	0.8	167	1	0.9	174	1.1	0.9	187	1.1	1	194	1.2	1	175	1.1	0.9
Malignant melanoma of the uvea	183	1.1	1	160	1	0.9	179	1.1	1	170	1	0.9	184	1.1	1	175	1.1	1
Adnexal carcinoma of the skin	92	0.6	0.5	88	0.5	0.4	96	0.6	0.5	115	0.7	0.6	95	0.6	0.4	97	0.6	0.5

Embryonal neoplasms	53	0.3	0.4	69	0.4	0.5	69	0.4	0.5	56	0.3	0.5	61	0.4	0.5	62	0.4	0.5
Extragonadic germ cell tumour	37	0.2	0.2	31	0.2	0.2	31	0.2	0.2	27	0.2	0.2	23	0.1	0.2	30	0.2	0.2
Soft tissue sarcoma	824	5.1	4.6	825	5.1	4.5	831	5.1	4.6	848	5.2	4.6	797	4.8	4.2	825	5.1	4.5
Bone sarcoma	172	1.1	1	167	1	1	208	1.3	1.2	222	1.4	1.3	210	1.3	1.3	196	1.2	1.2
Gastrointestinal stromal sarcoma	142	0.9	0.7	150	0.9	0.8	152	0.9	0.8	146	0.9	0.7	161	1	0.8	150	0.9	0.8
Kaposi sarcoma	49	0.3	0.3	53	0.3	0.3	52	0.3	0.3	39	0.2	0.2	57	0.3	0.3	50	0.3	0.3
Neuroendocrine tumours	659	4	3.5	733	4.5	3.8	777	4.8	4	805	4.9	4.1	803	4.9	4	755	4.6	3.9
Carcinoma of endocrine organs	436	2.7	2.4	474	2.9	2.6	443	2.7	2.4	457	2.8	2.5	494	3	2.7	461	2.8	2.5
Glial tumour of the CNS and pineal gland	856	5.3	4.9	897	5.5	5	886	5.4	5	903	5.5	5	930	5.7	5.1	894	5.5	5
Nonglial tumour of the CNS and pineal gland	38	0.2	0.3	44	0.3	0.3	33	0.2	0.2	51	0.3	0.4	48	0.3	0.3	43	0.3	0.3
Malignant meningiomas	14	0.1	0.1	8	0	0	8	0	0	9	0.1	0.1	6	0	0	9	0	0
Glial tumour of the autonomic nervous system and paraganglioma	3	0	0	1	0	0	–	–	–	2	0	0	–	–	–	1	0	0
Nonglial tumour of the autonomic nervous system and paraganglioma	18	0.1	0.1	16	0.1	0.1	17	0.1	0.1	16	0.1	0.1	13	0.1	0.1	16	0.1	0.1
Acute myeloyd leukaemia and related precursor neoplasms	646	4	3.5	595	3.7	3.2	617	3.8	3.3	576	3.5	3	635	3.9	3.2	614	3.8	3.2
Myeloproliferative neoplasms	429	2.6	2.3	558	3.4	2.9	565	3.5	2.9	578	3.5	2.9	553	3.4	2.8	537	3.3	2.8
Myelodysplastic syndrome	409	2.5	2.1	452	2.8	2.2	457	2.8	2.2	538	3.3	2.6	510	3.1	2.4	473	2.9	2.3
Myelodysplastic myeloproliferative	89	0.5	0.5	79	0.5	0.4	86	0.5	0.4	82	0.5	0.4	97	0.6	0.5	87	0.5	0.4
Histiocytic and dendritic cell neoplasms	8	0	0.1	12	0.1	0.1	2	0	0	7	0	0	8	0	0.1	7	0	0.1

CNS, central nervous system; CR, Cancer Registry; ESR, European standardized rate.

Table 1 Incidence of rare first-layer entities in the Netherlands, 2004-2008

	2004			2005			2006			2007			2008			2004–2008		
Rare second layer entities included in nonrare first layer entities	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	Annual *N*	Annual CR	Annual ESR
Epithelial tumour of the oesophagus																		
Squamous cell carcinoma and variants of the oesophagus	543	3.3	2.9	499	3.1	2.6	534	3.3	2.7	527	3.2	2.7	604	3.7	3	541	3.3	2.8
Salivary gland type tumour of the oesophagus	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Undifferentiated carcinoma of the oesophagus	5	0	0	3	0	0	2	0	0	3	0	0	3	0	0	3	0	0
Epithelial tumour of the stomach																		
Squamous cell carcinoma and variants of the stomach	5	0	0	5	0	0	9	0.1	0	5	0	0	3	0	0	5	0	0
Undifferentiated carcinoma of the stomach	4	0	0	4	0	0	1	0	0	3	0	0	0	0	0	2	0	0
Epithelial tumour of the colon																		
Squamous cell carcinoma and variants of the colon	0	0	0	2	0	0	3	0	0	1	0	0	1	0	0	1	0	0
Epithelial tumour of the rectum																		
Squamous cell carcinoma and variants of the rectum	3	0	0	2	0	0	4	0	0	7	0	0	1	0	0	3	0	0
Epithelial tumour of the pancreas																		
Squamous cell carcinoma and variants of the pancreas	3	0	0	3	0	0	2	0	0	0	0	0	1	0	0	2	0	0
Acinar cell carcinoma of the pancreas	2	0	0	5	0	0	3	0	0	6	0	0	6	0	0	4	0	0
Mucinous cyst adenocarcinoma of the pancreas	2	0	0	3	0	0	4	0	0	1	0	0	4	0	0	3	0	0
Intraductal papillary mucinous carcinoma invasion of the pancreas	4	0	0	2	0	0	1	0	0	7	0	0	7	0	0	4	0	0
Solid pseudopapillary carcinoma of the pancreas	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
Carcinoma with osteoclast-like giant cells of the pancreas	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0
Epithelial tumour of the lung																		
Well differentiated endocrine carcinoma of the lung	112	0.7	0.6	112	0.7	0.6	107	0.7	0.6	109	0.7	0.6	134	0.8	0.7	115	1.2	0.6
Bronchioloalveolar carcinoma of the lung	159	1	0.9	172	1.1	0.9	171	1	0.9	207	1.3	1.1	214	1.3	1.1	185	1.1	1
Salivary gland type tumour of the lung	5	0	0	3	0	0	8	0	0	8	0	0	10	0.1	0.1	7	0	0
Sarcomatoid carcinoma of the lung	38	0.2	0.2	31	0.2	0.2	40	0.2	0.2	42	0.3	0.2	38	0.2	0.2	38	0.2	0.2
Undifferentiated carcinoma of the lung	29	0.2	0.1	30	0.2	0.2	35	0.2	0.2	18	0.1	0.1	4	0	0	23	0.1	0.1
Epithelial tumour of the breast																		
Mammary Paget's disease of the breast	41	0.2	0.2	36	0.2	0.2	45	0.3	0.2	56	0.3	0.3	46	0.3	0.2	45	0.3	0.2
Special types of adenocarcinoma of the breast	337	2	1.7	317	1.9	1.5	342	2.1	1.6	372	2.2	1.7	386	2.3	1.8	351	2.1	1.7

Metaplastic carcinoma of the breast	38	0.2	0.2	44	0.3	0.2	39	0.2	0.2	51	0.3	0.3	31	0.2	0.2	41	0.2	0.2
Salivary gland type tumour of the breast	11	0.1	0.1	19	0.1	0.1	8	0	0	14	0.1	0.1	16	0.1	0.1	14	0.1	0.1
Epithelial tumour of the male breast	88	0.5	1	93	0.6	1.1	70	0.4	0.8	88	0.5	0.9	92	0.6	1	86	0.5	1
Epithelial tumour of the corpus uteri																		
Squamous cell carcinoma and variants of the corpus uteri	3	0	0	5	0.1	0.1	4	0	0	4	0	0	1	0	0	3	0	0
Transitional cell carcinoma of the corpus uteri	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Epithelial tumour of the cervix uteri																		
Adenocarcinoma and variants of the cervix uteri	129	1.6	1.4	138	1.7	1.5	126	1.5	1.4	144	1.7	1.6	126	1.5	1.4	133	1.6	1.5
Undifferentiated carcinoma of the cervix uteri	0	0	0	2	0	0	2	0	0	3	0	0	2	0	0	2	0	0
Epithelial tumour of the ovary and fallopian tube																		
Mucinous adenocarcinoma of the ovary	106	1.3	1.1	103	1.2	1.1	91	1.1	1	87	1.1	0.9	91	1.1	1	96	1.2	1
Clear cell adenocarcinoma of the ovary	50	0.6	0.6	55	0.7	0.6	62	0.8	0.7	58	0.7	0.6	58	0.7	0.6	57	0.7	0.6
Adenocarcinoma and variants of the fallopian tube	47	0.6	0.5	37	0.4	0.4	32	0.4	0.3	29	0.4	0.3	23	0.3	0.2	34	0.4	0.3
Epithelial tumour of the prostate																		
Squamous cell carcinoma and variants of the prostate	2	0	0	1	0	0	2	0	0	0	0	0	3	0	0	2	0	0
Infiltrating duct carcinoma of the prostate	17	0.2	0.2	13	0.2	0.1	69	0.9	0.8	75	0.9	0.8	44	0.5	0.4	44	0.5	0.5
Transitional cell carcinoma of the prostate	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Salivary gland type tumour of the prostate	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Tumour of the testis and paratestis																		
Adenocarcinoma and variants of the paratestis	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Malignant immature teratomas of the testis	167	2.1	2.2	179	2.2	2.3	173	2.1	2.2	172	2.1	2.3	187	2.3	2.4	176	2.2	2.3
Germ cell tumour seminomatous of the testis	304	3.8	3.5	270	3.3	3.2	328	4.1	3.9	334	4.1	4	364	4.5	4.4	320	4	3.8
Germ cell tumour nonseminomatous of the testis	95	1.2	1.2	126	1.6	1.6	103	1.3	1.3	89	1.1	1.2	119	1.5	1.6	106	1.3	1.4
Trophoblastic tumour of the testis	1	0	0	0	0	0	4	0	0	0	0	0	2	0	0	1	0	0
Sex cord tumour of the testis	1	0	0	1	0	0	2	0	0	3	0	0	4	0	0	2	0	0
Epithelial tumour of the kidney																		
Squamous cell carcinoma spindle cell type of the kidney	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
Squamous cell carcinoma and variants of the kidney	2	0	0	1	0	0	1	0	0	0	0	0	3	0	0	1	0	0

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Rare second layer entities included in nonrare first layer entities	2004			2005			2006			2007			2008			2004–2008		
	N	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	*N*	CR	ESR	Annual *N*	Annual CR	Annual ESR
Epithelial tumour of the bladder																		
Squamous cell carcinoma and variants of the bladder	48	0.3	0.3	67	0.4	0.3	73	0.4	0.4	60	0.4	0.3	58	0.4	0.3	61	0.4	0.3
Adenocarcinoma and variants of the bladder	31	0.2	0.2	20	0.1	0.1	26	0.2	0.1	34	0.2	0.2	29	0.2	0.1	28	0.2	0.1
Salivary gland type tumour of the bladder	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lymphoid diseases																		
Classical Hodgkin lymphoma	362	2.2	2.2	363	2.2	2.2	374	2.3	2.3	383	2.3	2.3	406	2.5	2.4	378	2.3	2.3
Hodgkin lymphoma nodular lymphocyte predominant	29	0.2	0.2	26	0.1	0.2	20	0.2	0.1	28	0.2	0.2	37	0.2	0.2	28	0.2	0.2
Composite Hodgkin NHL	1	0	0	0	0	0	0	0	0	1	0	0	4	0	0	1	0	0
Precursor BT lymphoblastic leukemia lymphoblastic lymphoma	184	1.1	1.2	220	1.3	1.5	230	1.4	1.5	228	1.4	1.5	224	1.4	1.5	217	1.3	1.4
Non-Hodgkin mature T-cell and NK-cell neoplasms	233	1.4	1.3	261	1.6	1.4	238	1.5	1.3	246	1.5	1.3	231	1.4	1.2	242	1.5	1.3

BT, B cell and T cell; CR, Cancer Registry; ESR, European standardized rate; NHL, non-Hodgkin's lymphoma; NK, natural killer.

Table 2 Incidence of rare second-layer entities that are included in nonrare first-layer entities, the Netherlands 2004–2008

Methods

Study population

In this study, data from the population-based Netherlands Cancer Registry (NCR) were included. The NCR covers the complete Dutch population and receives lists of newly diagnosed cancer cases from the nationwide Automated Pathology System (PALGA) on a weekly basis.[5] In addition, lists of discharged cancer patients from the national regstry of hospital discharge diagnosis are obtained to capture cancer cases with only a clinical diagnosis.[6] Completeness checks showed a national coverage of about 95% of incident cancers.[7]

A high level of data quality is secured by the specially trained registry clerks who abstract patient, tumour and treatment characteristics directly from the patient files. International standards set by the International Association for Cancer Registries and the European Network of Cancer Registries are used.[8] The International Classification of Disease for Oncology, 3rd ed. (ICD-O-3) developed by the WHO is used.[9] To study fluctuations in incidence over several years, we selected data over the period 2004–2008, covering a 5-year period.

The period 2004–2008 was selected as this period had the most complete data at the time of data inclusion.

Tumour grouping

The RARECARE project performed a data selection using the EUROCARE 4 database. The RARECARE data collection was carried out following the EUROCARE protocol and using the RARECARE inclusion criteria; this enables the working group to standardize and obtain data checks for analyses.[4,10] The RARECARE project linked their newly developed definition to a predefined list of cancers that follows a three-layer structure of cancer type groupings (entities), including all existing ICD-O-3 topography and malignant morphology codes.[9] Layer one entities are considered family of cancers relevant for healthcare organizations, created by grouping layer two entities. Layer two entities are defined in a clinically sound manner (perceived by clinicians as single diseases and relevant for clinical decision making and research) and are based on the third layer that corresponds to the WHO names of individual cancer entities and their corresponding ICD-O-3 codes. The definition for rare and common cancer entities only applies to the first two levels, with a total of 260 cancer types in Europe (59 first layers/201 second layers). For this study, we classified all cancers according to the RARECARE list (http://www.rarecare.eu).[3]

Methods of analysis

The number of newly diagnosed cancers was counted per year per entity for the selected period. Annual incidence rates were calculated per 100,000 person-years using the annual mid-year population size obtained from Statistics Netherlands (CBS).

Furthermore, the European standardized rate (ESR) was computed by correcting the crude incidence rate for sex and age using the European standardized population. For the sex-specific cancer entities, we calculated the crude incidence and ESR using the sex-specific population at

risk. For all rates, the mean for the 5-year period was determined. All outcomes were compared with the RARECARE results as presented on their website (http:// www.rarecare.eu).

Results

In the Netherlands, 86% of the RARECARE-defined entities and 17% (N≈ 14,000) of all newly diagnosed cancers should be considered rare according to the RARECARE definition.
Out of the total 260 entities defined by RARECARE, we identified 223 entities (86%) with a crude incidence rate of less than 6.0 per 100,000 per year in the Netherlands over 5 years. 'Squamous cell of the cervix uteri' and the 'tumours of the testis and paratestis' were considered rare in Europe, but common in the Netherlands, whereas 'Tumours of the liver and intrahepatic bile tract' and the 'epithelial tumours of the hypopharynx and larynx' were rare cancers in the Netherlands, but common in Europe. The 223 rare entities included 42 rare first-layer cancer entities (Table 1) and 181 second layer entities. Of these second layer entities, 54 (incidence rate <6.0 per 100,000 person-years) were included in 15 nonrare first-layer entities (incidence rate ≥6.0 per 100,000 person-years) (Table 2). An example is the rare second-layer entity 'epithelial tumour of the male breast', which is included in the not rare first-layer entity 'epithelial tumour of the breast'.

						2004–2008	
	2004	2005	2006	2007	2008	Total	Average per year
N of rare tumours	13,421	13,980	14,218	14,668	15,108	71,395	14,279
N of all tumours[a]	80,616	81,632	84,119	86,800	89,228	422,395	84,479
Rare tumours (%)	16.6	17.1	16.9	16.9	16.9	16.9	16.9

[a] Source Netherlands Cancer Registry, available at: *http://www.cijfersoverkanker.nl*

Table 3 Number of rare and all tumours for the years 2004–2008

In the years 2004–2008 combined, more than 71,000 patients were newly diagnosed with a rare cancer type. On an average, the crude number resulted in 14,279 rare cancers (range 13,421–15,108) per year out of a total of 84,479 cancers (range 80,616–89,228) per year in the Netherlands (Table 3).
Table 4 shows that for the period 2004–2008, the group with an annual incidence rate of up to 0.5 per 100,000 comprised an estimated number of 881 cases per year, representing 6.2% of all rare cancers. This group of very rare cancers consists of a relatively large number of entities (N= 85). Of these, 54 entities were rare secondlayer entities within nonrare first-layer entities, representing 23.9% of all rare tumours and 4.0% of all cancers. The annual crude incidence rate was generally very low for these entities, with the exception of squamous cell carcinoma and variants of the 'Oesophagus' and 'Germ cell seminomatous tumours of the testis' (crude incidence rate > 3 per 100,000 person-years) (Table 2).

	N per year	Percentage of all rare	Percentage of all tumours	N of entities	Percentage of N entities
≤ 0.5	881	6.2	1	85	33
> 0.5 < 1.0	816	5.7	1	25	9.6
≥ 1.0 < 2.0	1607	11	1.9	21	8.1
≥ 2.0 < 3.0	3865	27	4.6	28	11
≥ 3.0 < 4.0	2904	20	3.4	26	10
≥ 4.0 < 5.0	755	5.3	0.9	9	3.5
≥ 5.0 < 6.0	3451	24	4.1	29	11
Total	14,279	100	16.9	223	85.8

Table 4 Incidence per year on actual number of tumours for 2004–2008 and number of entities included

We observed fluctuations in incidence rates for many cancer types through the years 2004–2008 for some firstlayer entities. The difference in crude rate was 0.9 per 100,000 person-years (149 cases) for 'Myeloproliferative neoplasms' between 2004 and 2007 (Table 1). However, the largest difference in ESR between the highest and the lowest count was 0.9 per 100,000 person-years for the 'Epithelial tumour of the hypopharynx and larynx', accounting for an absolute difference of 124 cancer cases between 2005 and 2007 (Table 1). Fluctuations in incidence over the years also showed that the cut-off of less than six per 100 000 person-years could be crossed during the time period. An example is the entity 'Adenocarcinoma and variants of the oesophagus', for which a crude incidence rate of 5.4 per 100,000 person-years was calculated in 2004, which increased steadily to 7.2 per 100,000 per year in 2008, crossing the limit of 6.0 per 100,000 per year in 2006.

Discussion

In this study, the recently developed European definition for rare cancers was applied to the Netherlands. In the Netherlands, 86% of the RARECARE-defined entities and 17% (N≈14,000) of all newly diagnosed cancers should be considered rare according to this definition of a crude incidence rate of less than six cases per 10,000 per year. For the 5-year period 2004–2008, over 71,000 newly diagnosed rare cancers were observed. Under the assumption that there would be an even distribution over all hospitals, a crude incidence of six per 100,000 person-years would account for a maximum of 11 newly diagnosed patients with a specific type of rare cancer per hospital per year or 1,000 incident cases person-years in the Netherlands on the basis of 16.7 million inhabitants and over 90 hospitals. Furthermore, these patients would probably be diagnosed and treated by different clinicians in each hospital. Of course, this assumption does not reflect daily practice. Some patients will be referred to, for instance, university hospitals, resulting in even fewer or no patients per year in a general hospital.
The percentage of rare cancer types among all cancer diagnoses was similar to the RARECARE findings (about 17%) and was divided over a similar number of entities.
We observed fluctuations of almost one per 100,000 person-years in crude rates over the years. This may have consequences for the entities with a crude rate around six per 100,000

person-years. These entities could be classified as rare one year and as nonrare the next year. We suggest using the average incidence rate over 5 years to limit random fluctuations affecting the classification as rare cancer or not. An example in our results is oesophageal adenocarcinoma, which would be classified as rare in 2004 (not shown), but would be considered not rare in the following years because of increasing incidence. A European study also observed increasing incidence rates for oesophageal adenocarcinoma.[11]

Some sex-related cancers, such as 'Tumours of the testis and paratestis' and 'Squamous cell of the cervix uteri', were classified as non rare in the Netherlands, but as rare in the RARECARE data set. This difference is the result of different methods used to calculate the crude incidence rate. In the RARECARE project, the total population without differentiating for sex was used, whereas in our study, we only used the population at risk for the sex-related tumours, which results in higher incidence rates. This same effect is detectable in all sex-related tumours, but does not result in differences in classification. Owing to the definition of the incidence rate, we suggest use of the sex-specific population at risk. However, we do agree that the limit should then also be changed to 12 per 100,000 for sex-specific cancers and that this limits the applicability of the new definition.

Four entities were not rare in Europe but rare in the Netherlands or vice versa. One of those entities concerns 'Epithelial tumours of the hypopharynx and larynx'. This difference was mainly because of the second-layer group 'Squamous cell carcinoma and variants of the larynx', and not 'Squamous cell carcinoma of the hypopharynx'. The remaining difference was found at the first-layer level, which includes unspecified and not otherwise specified codes. Because some cancers are classified as not otherwise specified, we expect an underestimation for the incidence rates in the second-layer entities. We observed this clearly in the data for 'Epithelial tumours of the pancreas', where a nonrare first layer crude incidence of 10.4 per 100,000 per year was observed, whereas the sum of all rare second-layer crude incidences equalled only 6.4 per 100 000 per year. This phenomenon was also observed within European RARECARE data, and will affect cancers that are mainly diagnosed clinically (without pathological confirmation) more strongly. The RARECARE project also reports this effect for the epithelial tumours of the oesophagus. Our findings suggest a better classification in the NCR because the sum of the incidence rates of all second-layer entities comes close to the incidence rate for the first nonrare layer entity. This indicates a more detailed pathologic diagnostic workup and coding in the Netherlands compared with overall RARECARE data. Differences in outcome between RARECARE and NCR data may partly be explained by the inclusion of different incidence years (1995–2002 for RARECARE and 2004–2008 for the Netherlands). Because tumour classification evolves continuously because of improved knowledge and better techniques, a yearly update of the analyses carried out by the RARECARE project, on the basis of the average for the most recent five incidence years for which data are available, should be carried out to provide an overview and monitor the current situation of rare cancers in Europe. To determine the differences in rare cancer between countries, we propose that each country develop a national list of rare cancers. Country-specific incidence rates would

also provide insight into the experience level of countries with specific cancer entities. This knowledge may subsequently lead to further clinical and/or scientific collaboration.

Diagnosing and registering rare cancers, however, will always be more difficult than diagnosing and registering non rare cancers because rare cancers (by definition) are encountered less regularly. Therefore, misclassifications may have occurred. Within the RARECARE project, a data quality check was carried out, which covered the years 1995–2002 and included three Dutch Cancer Registries, covering 44.5% of the total population of the Netherlands. These results were published on the RARECARE website; http://www.rarecare.eu. In summary, the quality check for the Netherlands included a review of 1018 cancers using the original patient files. Overall, for all cases reviewed, the majority was found to be registered correctly. For the selection of Dutch Cancer Registries, a percentage ranging from 4.1 to 5.3 unspecified morphology cases was found, which was one of the lowest percentages for the participating Cancer Registries.

In conclusion, some improvements to the definition of rare cancers could be made. First, by determining the cut-off on the basis of an average annual rate of less than six per 100,000 over 5 years instead of 1 year, the influence of fluctuations on the classification can be obviated. Second, a sex-specific incidence limit should be introduced.

In the Netherlands, almost one in six cancer patients is affected by a cancer that is considered to be rare. Many of these rare tumour entities were very rare, with an incidence rate below 0.5, equalling ~100 cases per year, in the Netherlands, indicating the challenge that faces clinicians confronted with a patient with such a rare cancer. This also shows the need for (inter) national collaboration in caring for these patients. Furthermore, exploration of diagnostic, treatment and outcome, and referral patterns is needed and may help to identify caveats to research, which can help to enhance the care for patients with rare cancers.

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Conflicts of interest

There are no conflicts of interest.

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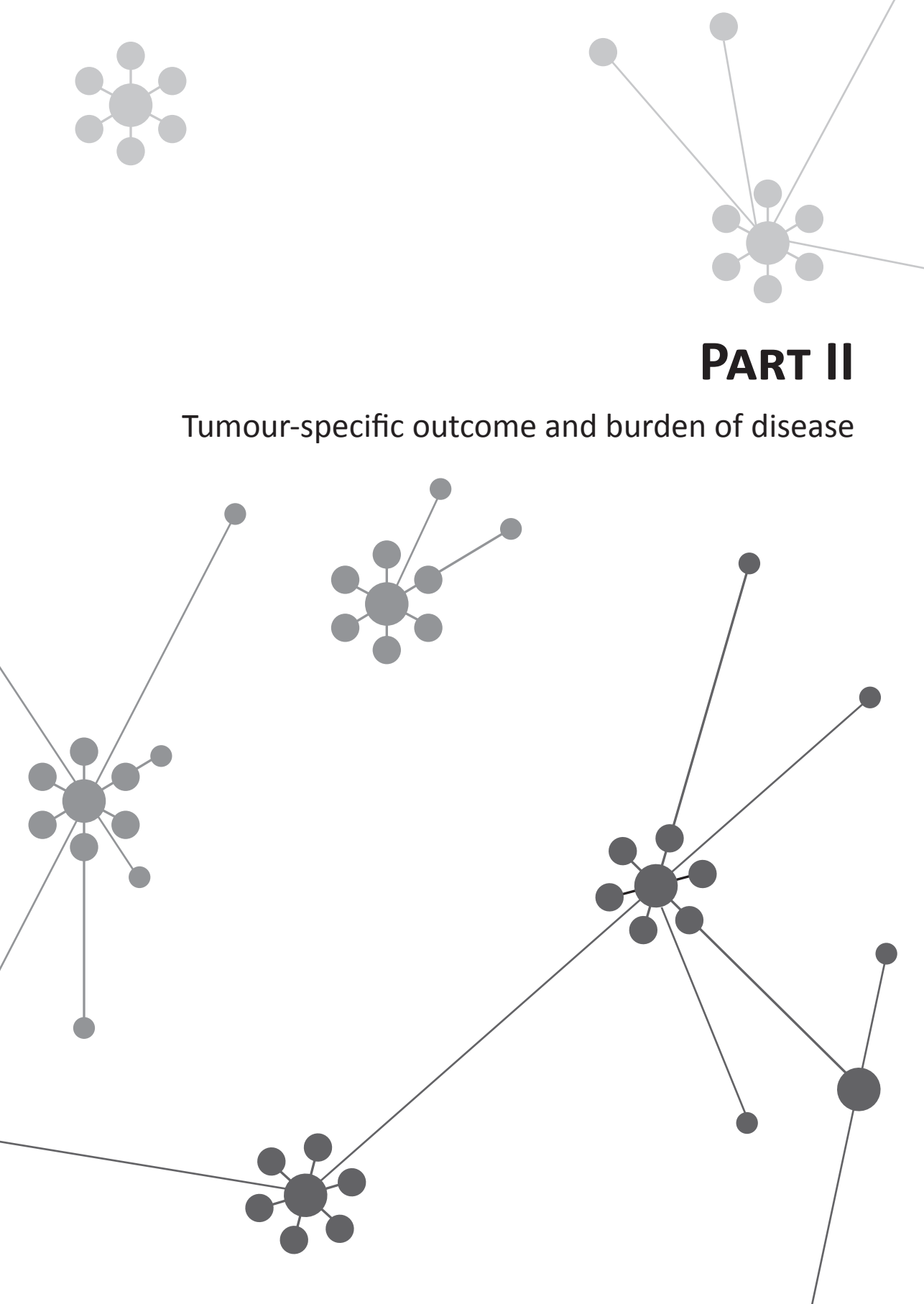

Part II

Tumour-specific outcome and burden of disease

Chapter 4

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 incidence in Central and Southern Europe.[2] Highest incidence in mesothelioma was seen in UK and Ireland[23] and lowest in Eastern Europe.[4]

Patients with tumours of the thymus had the best prognosis (1-year survival 85%, 66% at 5 years). Five year survival was lowest for the mesothelioma 5% compared to 14% of patients with tumours of the trachea. Mesothelioma was the most prevalent rare cancer (12,000 cases), followed by thymus (7000) and trachea (1400).

Cancer Registry (CR) data play an important role in revealing the burden of rare thoracic cancers and monitoring the effect of regulations on asbestos use and smoking related policies.

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/year 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.

Patients and methods

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-3[5] 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). and mesothelioma of peritoneum and tunica vaginalis (C48 and C63.7).

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, covering variable proportions of their respective national populations. Countries were divided into five regions: Northern Europe (Iceland, Sweden and Norway), Central Europe (Austria, Belgium, France, Germany, Switzerland and The Netherlands), Eastern Europe (Poland and Slovakia), Southern Europe (Malta, Italy, Portugal, Slovenia and Spain) and UK and Ireland (England, Ireland, Northern Ireland, Scotland and Wales).

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.[1]

Tier	Cancer entity (ICD-O-3 topography code)	Number of malignant cancers 1995–2002	Death certificate only	Autopsy	Microscopic verification	Cases 1995–1998 censored before 5 years	Morphology code NOS[a]
		N	(%)	(%)	(%)	(%)	(%)
1	**Epithelial tumour of trachea (C33)**	**1104**	**3.6**	**0.8**	**86**	**0.5**	**12**
2	Squamous cell carcinoma and variants of trachea	672	1.2	0.7	98	0.6	–
2	Adenocarcinoma and variants of trachea	108	0.9	0.0	98	0.0	–
2	Salivary gland type tumours of trachea	80	0.0	1.3	100	0.0	–
1	**Epithelial tumour of thymus (C37)**	**1346**	**1.6**	**0.7**	**92**	**1.4**	**5.4**
2	Malignant thymoma	1104	0.5	0.6	97	1.4	–
2	Squamous cell carcinoma of thymus	38	0.0	0.0	97	0.0	–
2	Undifferentiated carcinoma of thymus	20	0.0	5.0	100	0.0	–
2	Lymphoepithelial carcinoma of thymus	6	0.0	0.0	100	0.0	–
2	Adenocarcinoma and variants of thymus	16	0.0	0.0	94	6.3	–
1	**Malignant mesothelioma**	**15,322**	**2.1**	**1.5**	**89**	**0.2**	**–**
2	Mesothelioma of pleura and pericardium (C38)	12,914	1.4	1.5	91	0.2	–
2	Mesothelioma of peritoneum and tunica vaginalis (C48, C63.7)	1010	0.9	1.8	94	0.4	–

a NOS, not otherwise specified; morphology codes NOS are M8000–8001. They were included in the tier 1 only; except in 'MALIGNANT MESOTHELIOMA'.

Table 1 Data quality indicators of rare thoracic cancers diagnosed in all RARECARE cancer registries, cases diagnosed 1995–2002.

Data selection for relative survival analysis

Relative survival was estimated according to the Hakulinen method.[7] Period survival indicators for the years 2000–2002 were also estimated using the Brenner algorithm.[8] Forty six CRs out of the 76 European CRs had data available for this period and could be included for analyses. Period analysis provides more up-to-date survival experience by exclusively considering survival experience in 2000–2002.

Data selection for prevalence analysis

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[9] based on 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]

Data quality analysis

The main data quality indicators for the cases included were defined in the EUROCARE study[13] 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%).

Results

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 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.

Entity	EU overall			Sex				Age						Estimated number of cases arising in EU per year
				Male		female		0-24 years		25-64 years		65+ years		
	Observed cases 1995–2002	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	
Rare thoracic cancers	*17,688*													*10,937*
Epithelial tumour of trachea	**1084**	**1.4**	**0.04**	**1.9**	**0.07**	**0.84**	**0.05**	**0.01**	**0.01**	**1.1**	**0.05**	**4.8**	**0.19**	**670**
Squamous cell carcinoma and variants of trachea	660	0.82	0.03	1.2	0.06	0.45	0.03	<0.01	<0.01	0.69	0.04	2.9	0.15	408
Adenocarcinoma and variants of trachea	108	0.13	0.01	0.2	0.02	0.11	0.02	<0.01	~	0.13	0.02	0.40	0.06	67
Salivary gland type tumours of trachea	78	0.10	0.01	0.1	0.02	0.09	0.01	0.01	0.01	0.13	0.02	0.17	0.04	48
Epithelial tumour of thymus	**1341**	**1.7**	**0.05**	**1.8**	**0.07**	**1.6**	**0.06**	**0.13**	**0.02**	**1.8**	**0.06**	**4.2**	**0.18**	**829**
Malignant tymoma	1100	1.4	0.04	1.4	0.06	1.4	0.06	0.10	0.02	1.5	0.06	3.4	0.16	680
Squamous cell carcinoma of thymus	38	0.05	0.01	0.06	0.01	0.03	0.01	0.01	0.01	0.05	0.01	0.11	0.03	23
Undifferentiated carcinoma of thymus	20	0.02	0.01	0.03	0.01	0.02	0.01	<0.01	<0.01	0.03	0.01	0.06	0.02	12
Lymphoepithelial carcinoma of thymus	6	0.01	0.00	0.01	0.01	<0.01	0.00	<0.01	~	0.01	0.01	0.01	0.01	4
Adenocarcinoma and variants of thymus	16	0.02	0.00	0.02	0.01	0.02	0.01	<0.01	~	0.03	0.01	0.04	0.02	10
Malignant mesothelioma	**15,263**	**19.0**	**0.15**	**31.8**	**0.28**	**6.8**	**0.13**	**0.09**	**0.02**	**12.8**	**0.17**	**77.1**	**0.78**	**9437**
Mesothelioma of pleura and pericardium	12,881	16.0	0.14	27.2	0.26	5.4	0.11	0.04	<0.01	10.8	0.16	65.1	0.72	7964
Mesothelioma of peritoneum and tunica vaginalis	998	1.2	0.04	1.6	0.06	0.9	0.05	0.04	<0.01	1.0	0.05	4.4	0.19	617

~ Statistic could not be calculated

Table 2: Incidence cases, annual rates x 1,000,000 and standard errors (SE) in Europe, rates and SE by sex and age, and estimated incident cases of rare thoracic cancers arising in Europe per year

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).

Entity	European region											
	Northern Europe		Central Europe		Eastern Europe		Southern Europe		UK and Ireland		EU Overal	
	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE
Epithelial tumour of trachea	**0.68**	**0.08**	**0.96**	**0.07**	**2.0**	**0.17**	**1.8**	**0.10**	**0.91**	**0.05**	**1.2**	**0.04**
Squamous cell carcinoma and variants of trachea	0.43	0.06	0.64	0.06	1.3	0.14	0.99	0.07	0.55	0.04	0.71	0.03
Adenocarcinoma and variants of trachea	0.08	0.03	0.12	0.02	0.11	0.04	0.25	0.04	0.06	0.01	0.12	0.01
Salivary gland type tumours of trachea	0.12	0.03	0.08	0.02	0.10	0.04	0.12	0.03	0.08	0.02	0.09	0.01
Epithelial tumour of thymus	**0.92**	**0.09**	**1.9**	**0.10**	**1.2**	**0.13**	**2.3**	**0.12**	**1.1**	**0.06**	**1.5**	**0.04**
Malignant thymoma	0.80	0.08	1.6	0.09	0.96	0.12	1.8	0.11	0.93	0.06	1.3	0.04
Squamous cell carcinoma of thymus	0.02	0.01	0.08	0.02	0.04	0.02	0.04	0.02	0.03	0.01	0.04	0.01
Undifferentiated carcinoma of thymus	0.02	0.01	0.03	0.01	0.04	0.03	0.03	0.01	0.01	0.01	0.02	0.01
Lymphoepithelial carcinoma of thymus	0.00	~	0.01	0.01	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.00
Adenocarcinoma and variants of thymus	0.00	~	0.02	0.01	0.01	0.01	0.02	0.01	0.02	0.01	0.02	0.00
Malignant mesothelioma	**11.3**	**0.30**	**13.4**	**0.25**	**4.2**	**0.24**	**12.8**	**0.26**	**22.6**	**0.26**	**15.6**	**0.13**
Mesothelioma of pleura and pericardium	10.0	0.28	12.1	0.24	3.3	0.21	11.4	0.25	18.2	0.23	13.2	0.12
Mesothelioma of peritoneum and tunica vaginalis	1.04	0.10	0.99	0.07	0.66	0.10	1.3	0.08	1.1	0.06	1.06	0.03

~Statistic could not be calculated

Table 3: Age standardised annual incidence rates (x1,000,000) and standard errors (SE) of rare thoracic cancers by European region for the period 1995–2002.

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).

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.

Entity	Variable	Survival							
		1 year				5 years			
		Cases analysed	Observed	Relative		Cases analysed	Observed	Relative	
		N	%	%	SE	N	%	%	SE
Epithelial tumour of trachea		288	37	38	3.0	338	12	14	2.3
	Male	198	36	37	3.6	240	12	14	2.8
	Female	92	39	40	5.2	106	12	15	4.2
	Age 0–24	2	100	100	0	2	100	100	0.0
	Age 25–64	131	48	49	4.5	150	16	17	3.5
	Age 65+	157	27	28	3.7	190	8.2	11	2.9
	Northern Europe	40	53	54	8.1	40	26	29	14
	Central Europe	51	63	64	7.1	66	29	33	8.2
	Eastern Europe	43	28	29	7.0	51	1.5	1.7	1.8
	Southern Europe	85	24	24	4.7	121	6.3	7.5	2.5
	UK and Northern Ireland	69	32	33	5.8	93	12	14	5.2
Epithelial tumour of thymus		403	83	85	1.9	460	60	65.6	2.7
	Male	210	84	86	<0.1	233	58	65	3.9
	Female	193	83	84	<0.1	227	62	66	3.7
	Age 0–24	9	89	89	11	9	78	78	14
	Age 25–64	244	89	89	2.1	267	66	68	3.2
	Age 65+	150	75	77	3.8	186	50	60	4.9
	Northern Europe	42	86	87	5.5	48	64	70	8
	Central Europe	131	81	82	3.7	150	64	70	4.9
	Eastern Europe	25	88	89	6.6	35	71	75	9.7
	Southern Europe	111	86	87	3.4	132	62	67	4.8
	UK and Northern Ireland	94	82	83	4.1	104	47	53	5.8
Malignant mesothelioma		4893	35	37	0.7	5185	4.4	5.4	0.4
	Male	3967	35	36	<0.1	4209	3.6	4.5	0.4
	Female	929	38	39	0.2	976	7.9	9.3	1,1
	Age 0–24	6	83	83	15.7	7	31	31	25
	Age 25–64	1705	47	48	0.1	1846	7.7	8.1	0.7
	Age 65+	3185	29	31	<0.1	3353	2.5	3.4	0.4
	Northern Europe	555	38	39	0.2	564	4.3	5.3	1,1
	Central Europe	994	37	39	0.2	1219	5.3	6.3	0.8
	Eastern Europe	107	34	35	0.5	107	10	12	3.5
	Southern Europe	749	47	49	0.2	944	7	8.4	1.1
	UK and Northern Ireland	2488	31	32	<0.1	2488	2.7	3.4	0.5

Table 4: Observed survival rates, estimated relative survival rates and standard errors (SE) by 1 and 5 years, and number of cases analysed of rare thoracic cancers. Period survival analysis 2000–2002.

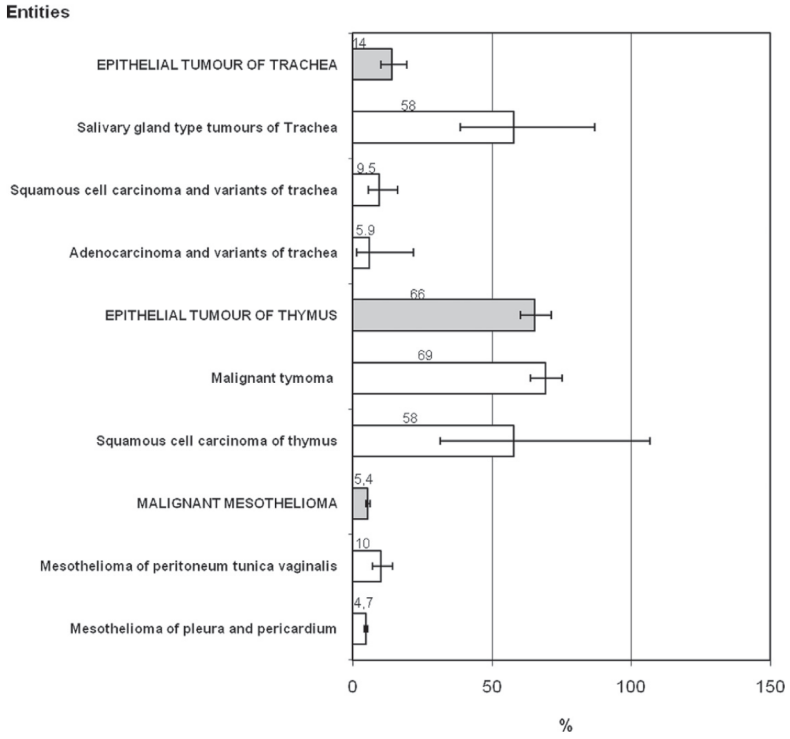

Fig. 1: Period analysis – estimated cumulative 5 year relative survival rates by entity.

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.

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.

Entity	Duration						EU complete prevalence 1st January 2003		
	2 years		5 years		15 years				
	Prop.	SE	Prop.	SE	Prop.	SE	Prop.	SE	No. of cases
Rare thoracic cancers									
Epithelial tumour of trachea	0.84	0.11	1.40	0.15	2.40	0.19	2.80	0.24	1396
Squamous cell carcinoma and variants of trachea	0.51	0.09	0.76	0.11	1.10	0.13	1.20	0.14	602
Adenocarcinoma and variants of trachea	0.05	0.03	0.06	0.03	0.16	0.05	0.24	0.08	119
Salivary gland type tumours of trachea	0.23	0.06	0.40	0.08	0.76	0.11	1.10	0.16	523
Epithelial tumour of thymus	2.8	0.2	5.5	0.3	9.7	0.4	14.0	0.6	6962
Malignant thymoma	2.4	0.2	4.9	0.3	8.5	0.4	12.2	0.6	6055
Squamous cell carcinoma of thymus	0.06	0.03	0.09	0.04	0.14	0.05	0.24	0.08	119
Undifferentiated carcinoma of thymus	0.00	0.00	0.03	0.02	0.03	0.02	0.03	0.02	16
Lymphoepithelial carcinoma of thymus	0.03	0.02	0.03	0.02	0.08	0.03	0.12	0.06	60
Adenocarcinoma and variants of thymus	0.03	0.02	0.04	0.03	0.04	0.03	0.08	398.00	40
Malignant mesothelioma	16.2	0.50	19.80	0.56	22.30	0.59	23.80	0.65	11,841
Mesothelioma of pleura and pericardium	14.3	0.47	17.10	0.52	18.90	0.54	19.80	0.58	9824
Mesothelioma of peritoneum and tunica vaginalis	0.64	0.10	1.20	0.14	1.70	0.17	2.20	0.21	1072

Table 5: Observed prevalence proportion x1000,000 and standard errors (SE) by duration (2, 5, 15 years) and estimated complete prevalence with SE and number of prevalent cases in Europe.

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.[14] 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 probably 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 autoptic mesothelioma cases was 14% versus <5% in the other regions.[15]

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 reviewed the pathology reports of a sample of 678 long survivors (alive 2 or more years after the diagnosis of mesothelioma). The majority of them were confirmed as long survivors, only 3% of them were erroneously diagnosed as mesothelioma, while 10% died within 2 years after diagnosis. We also revised 846 cases of pleural cancers. We found that 68 of them were mesothelioma and 43 should have been classified as pleural sarcoma. For the Eastern registries the proportion of mesothelioma from the revision of pleural cancers was 11%, while it was 8% for the others registries. Again the majority of cases were confirmed as non-specific pleural cancer (62%). The impact of data revision on incidence and survival rates was trivial, also because the proportions of long survivors and pleural cancers, in the analysed data, were low (no more than 13%).[6]

Due to the very long latency time of the epithelial cancers and mesothelioma between the exposure to several risk factors and the diagnoses of the tumour we determined the highest incidence in the oldest age group (64% of all cases was older than 65 years).

A study using the EUROCIM dataset (Cancer incidence and mortality in Europe) described a great deal of geographical variation in the risk of mesothelioma.[16] Geographical differences in (most pleural) mesothelioma incidence could be related to the exposure to asbestos in shipyards and factories. 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,[23] single institution experiences[24] 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,[26] particularly those with squamous cell carcinoma (93%)[24] 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 trachea can be 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.[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.[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.[36] Inter-relation between the different prognostic factors (Masaoka staging, myasthenia gravis, WHO histology) are of great importance.[37] Surgical resection is the recommended treatment for early stage thymic epithelial malignancies, where complete resection increases survival.[38] A 20% recurrence rate has been described for stage I patients with peritumoural adherences found at surgery (Masaoka stage II),[39] whereas patients who received radiotherapy in this situation had not recurrences.[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 the 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.[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).

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Conflict of interest statement

None declared.

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Chapter 5

Carcinoma of endocrine organs:

Results of the RARECARE project

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Abstract

The rarity or the asymptomatic character of endocrine tumours results in a lack of epidemiological studies on their incidence and survival patterns. The aim of this study was to describe the incidence, prevalence and survival of endocrine tumours using a large database, which includes cancer patients diagnosed from 1978 to 2002, registered in 89 population-based cancer registries (CRs) with follow-up until 31st December 2003. These data give an unique overview of the burden of endocrine carcinomas in Europe. A list of tumour entities based on the third International Classification of Diseases for Oncology was provided by the project Surveillance of rare cancer in Europe (RARECARE) project. Over 33,594 cases of endocrine carcinomas were analysed in this study. Incidence rates increased with age and were highest in patients 65 years of age or older. In 2003, more than 315,000 persons in the EU (27 countries) were alive with a past diagnosis of a carcinoma of endocrine organs. The incidence of pituitary carcinoma equalled four per 1,000,000 person-years and showed the strongest decline in survival with increasing age. Thyroid cancer showed the highest crude incidence rates (four per 100,000 person-years) and was the only entity with a gender difference: (female-to-male ratio: 2:9). Parathyroid carcinoma was the rarest endocrine entity with two new cases per 10,000,000 person-years. For adrenal carcinoma, the most remarkable observations were a higher survival for women compared to men (40% compared to 32%, respectively) and a particularly low relative survival of 24% in patients 65 years of age or older.

Introduction

Endocrine tumours arise from hormone secreting endocrine glands such as pituitary, thyroid, parathyroid and adrenal glands and can be separated from the neuroendocrine tumours based on histology. Endocrine tumours have in common that all are negative for granules like Chromogranine A. Either the rarity or the asymptomatic character of endocrine tumours results in a lack of epidemiological studies on their incidence and survival patterns.[1] The available studies for endocrine tumours, with the exception of thyroid cancer, are generally based on case reports or clinical series and cannot be used as a reference because of unavoidable selection bias. 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 endocrine tumours. The RARECARE project produced a list of tumours based on both cancer topographies and morphologies according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3),[2] which is probably more useful for the health care organisation than the one usually adopted which is based on the anatomic site only. An incidence rate less than 6/100,000/year was used as a threshold for rarity. The aim of this work was to provide the clinicians information currently available on basic indicators like incidence, prevalence and survival on rare endocrine tumours. For the first time ever complete prevalence estimates will be reported for this specific group of rare tumours.

Material and methods

Tumour grouping

In the present work, we describe the burden of carcinomas of the pituitary, thyroid, parathyroid and adrenal glands. A new operational definition and order of all rare tumour entities was established by the 'Surveillance of rare cancer in Europe project' (RARECARE) working group in consensus with delegates of organizations representing the majority of the European clinicians and pathologists. This resulted in a rationale for and grouping of tumour entities in two different tiers; the tier 1 tumour entities require the same clinical expertise and patient referral pattern structure and is created by grouping tier 2 entities. The tier 2 tumour entities require specific clinical management and research. Tumour entities were considered rare and therefore included if the incidence rate was less than six per 100,000 person-years. The selection and definition of rare endocrine carcinomas according to the ICD-O-3 is shown in Table 1. For this study the tier 1 included is the carcinoma of endocrine organs, including the tier 2 entities carcinoma of the pituitary-, thyroid-, parathyroid- and adrenal gland. Neuroendocrine thyroid cancers (ICD-O-3 morphology codes: 8041, 8510, 8345-8347) are excluded and will be described in an article on neuroendocrine tumours (chapter 6). Therefore the medullary carcinoma NOS, medullary carcinoma with amyloid stroma, mixed medullary-follicular carcinoma and the mixed medullary- papillary thyroid

cancers are excluded from analyses (1764 cases).[3]

Cancer entity	Tier	Number malignant cancers 1995–2002 (76 CRs)[b]	Data quality indicators				ICD-O-3 codes	
			DCO[a]	Autopsy	Microscopic verification	Cases 1995-1998 censored before five years	Topography	Morphology
		N	%	%	%	%		
Carcinoma of endocrine organs	1	33,594	1.5	1.1	92	2.4	C73.9–C75.1	8000-8001
Pituitary carcinoma	2	333	9.3	1.2	30	1.2	C75.1	8010-8011,
Thyroid cancer	2	29,657	0.27	1.0	98	2.6	C73.9	8014-8035,
Parathyroid carcinoma	2	176	1.1	1.1	94	1.1	C75.0	8046-8149,
Adrenal carcinoma[b]	2	1,464	1.8	2.4	88	1.2	C74.0–C74.9	8158-8239,8250-8344, 8350-8509,8511-8576, 8588-8591,8700

a DCO = Death Certificate Only, ICD-O = International Classification of Diseases for Oncology.

b Phaeochromocytomas included.

Table 1: Quality indicators of carcinoma of endocrine organs diagnosed in 76 RARECARE cancer registries. Cases diagnosed 1995–2002.

Cancer registry (CR) selection and population coverage

RARECARE gathered data from the EUROCARE-4 study which was 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 EUROCARE-4 study does not provide information on stage because this information is not standardised among registries. The mean population covered was about 162,000,000 corresponding to 39% of the population of the 21 countries participating in RARECARE. The European member states were covered for 32% of the total population by the RARECARE project.[3] 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 (Belgium, England, France, Germany, Italy, Poland, Portugal, Spain, Switzerland and The Netherlands) were represented by regional CRs, covering variable proportions of their respective national populations.[3]

Data selection for incidence analysis

Incidence rates were estimated after the exclusion of CRs which did not classify cancers according to the ICD-O-3 and specialised registries. Rates were calculated as the number of new primary malignant cases occurring from 1995 to 2002 divided by the total persons- years in the general population (male and female). The standard European population was used to calculate age-standardised rates. The age-adjusted incidence rates were also calculated and stratified by European region (Northern Europe, Central Europe, Eastern Europe, Great Britain and Ireland and Southern Europe). This classification was based on the grouping previously used in the EUROCARE-4 study and has been described extensively in the final

Technical Report,[3] as well as some basic indicators for rare cancers and health care related macro indicators (Gross National Product and Total National Expenditure on Health).[3]

Data selection for prevalence analysis

The observed prevalence of cases within 2, 5 and 15 years of the index date was estimated by applying the counting method[4] to incidence and follow-up data from 22 CRs from 1988 to 2002, choosing 1st January 2003 as the index date. The completeness index method[5] was used to estimate the complete prevalence: briefly, the observed 15-year prevalence was corrected by adding the estimated number of surviving cases diagnosed prior to 1988 to those counted in 1988–2002. The unobserved prevalence fraction for a given tumour entity and registration time length was estimated using a parametric approach modelling incidence data from 1985 to 1999 with a logistic exponential or polynomial function on age and 1988–1999 survival with mixture cure models.[6] The expected number of new cases per year and of prevalent cases in Europe (EU27) was estimated multiplying the 2003 crude incidence and complete prevalence rates to the 2008 European population (497,455,033 on 2nd April 2008, provided by EUROSTAT).

Data selection for relative survival analysis

Relative survival rates for the years 2000–2002 by sex, age and European regions were estimated using the period approach by Brenner.[7] Forty six out of the 76 CRs had data available for this period and could be included in the survival analyses.

Overall data quality analysis

In total we were able to identify 41,919 cases of benign and malignant endocrine cases between 1995 and 2002 in 76 CRs. As our study concerns the carcinomas only and not all CRs do register benign cases as well, we excluded all benign endocrine cases. For the pituitary and the parathyroid gland this resulted in an expected major reduction in cases (3523 and 8325 benign cases, respectively). International standards for CRs set by the International Association for Cancer Registries (IACR) and the European Network of Cancer Registries (ENCR) secures the quality of the CRs.[8] In summary, during the registration process there was access to comprehensive sources like the pathologic reports, examinations, symptoms, signs and the different clinical reports. Therefore malignant cases are only defined malignant, if this can be concluded out of a combination of all sources. Especially for endocrine cases it is of major importance to have access to, and use all these sources to come to a correct definition of the endocrine case. However registry clerks record the final diagnosis of the clinicians.

The main quality indicators for 33,594 malignant cancer cases diagnosed between 1995 and 2002 and registered by 76 CRs are presented in Table 1. Overall, 1.5% of the cases were Death Certificate Only (DCO) ranging from 0.3% for thyroid cancer to 6.3% for pituitary carcinomas. About 90% of the registered tumours were microscopically verified, with the exception of pituitary gland carcinomas, of which only 30% were microscopically verified. A

small proportion of cases (2.4%) diagnosed between 1995 and 1998 were censored before 5 years of follow up (lost to follow up), ranging from 1.1% for parathyroid carcinomas to 2.6% for the thyroid cancer. The proportion of cases diagnosed with morphology not otherwise specified (NOS) code was 6.5%.

Results

Incidence

Table 2 shows the incidence of the included entities in Europe, as well the sex and age specific incidence rates and the estimated number of new cases diagnosed per year in the EU27. Thyroid cancer showed the highest crude incidence rate of 3.7 per 100,000 (N = 29,333), followed by adrenal carcinoma (N = 1459) with a rate of 0.2 per 100,000 and pituitary carcinoma (N = 333) and parathyroid gland (N = 176) with a rate below 0.1 per 100,000. The incidence of thyroid cancer was higher in females than males, with a female-to-male ratio of 2:9. There was a minimal gender difference in incidence rates for the pituitary carcinomas and no gender difference in parathyroid and adrenal carcinomas. The incidence rate increased with age and was the highest in patients 65 years of age or older for all endocrine cancers considered. However, thyroid cancer and adrenal carcinoma are also diagnosed in children, adolescents and young adults. The number of new cases per year in the EU (EU27) was estimated at 20,563. The majority would be thyroid cancer with an estimated 18,137 new cases per year, followed by adrenal carcinoma with 902 new cases, pituitary carcinoma with 206 and parathyroid carcinoma with 109 new cases (Table 2).

Cancer entity	EU overall (64 cancer registries (CRs))			Sex[b]				Age (years)[a]								Estimated number of cases arising in EU27[c] per year
				Male		Female		0–14		15–24		25–64		65+		
	Observed cases 1995-2002	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	
Carcinoma of endocrine organs	**33,257**	**4.1**	**0.02**	**2.1**	**0.02**	**5.4**	**<0.04**	**0.2**	**0.01**	**1.4**	**<0.04**	**5.1**	**<0.03**	**7.8**	**0.08**	**20,563**
Pituitary carcinoma	333	0.04	<0.01	0.04	<0.01	0.03	<0.01	<0.01	<0.01	<0.02	<0.01	0.03	<0.01	0.13	0.01	206
Thyroid cancer	29,333	3.7	0.02	1.8	0.02	5.0	<0.03	0.09	0.01	1.3	<0.04	4.6	<0.03	6.3	0.07	18,137
Parathyroid carcinoma	176	0.02	<0.01	0.02	<0.01	<0.02	<0.01	0	~	<0.01	<0.01	0.02	<0.01	0.07	0.01	109
Adrenal carcinoma[d]	1459	0.2	<0.01	0.2	0.17	0.17	0.01	0.03	<0.01	0.04	0.01	0.21	0.01	0.4	<0.02	902

~ Statistic could not be calculated.

a Crude rate.

b Age standardised rate.

c European 27 member states population (497,455,033).

d Phaeochromocytomas included.

Table 2: Incident cases and rates (x100,000) in Europe, incidence rates (x100,000) by sex and age, estimated number of cases arising in Europe (27 countries)

Table 3 shows age-adjusted incidence rates by European region for 1995–2002. Endocrine carcinomas showed a remarkable geographical variation, due to the variation in incidence rates for thyroid cancer, which ranged from 6.0 per 100,000 (Standard Error 0.06) per year in Southern Europe to 1.9 per 100,000 (Standard Error 0.03) per year in the United Kingdom (UK) and Ireland.

Cancer entity	European region											
	Northern Europe		Central Europe		Eastern Europe		Southern Europe		UK and Ireland		EU overall (64 CRs)	
	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE
Carcinoma of endocrine organs	**3.3**	**0.05**	**3.9**	**0.04**	**4.2**	**0.08**	**6.8**	**0.07**	**2.2**	**0.03**	**3.8**	**0.02**
Pituitary carcinoma	<0.01	<0.01	0.03	<0.01	0.06	0.01	0.04	<0.01	0.04	<0.01	0.04	<0.01
Thyroid cancer	3.1	0.05	3.5	0.04	3.6	0.07	6.03	0.06	1.9	0.03	3.4	0.02
Parathyroid carcinoma	<0.02	<0.01	0.01	<0.01	<0.01	<0.01	0.02	<0.01	0.02	<0.01	0.02	<0.01
Adrenal carcinoma[a]	0.17	0.01	0.17	0.01	0.15	0.01	0.17	0.01	0.17	0.01	0.17	<0.01

SE = Standard Error, CRs = cancer registries

a Phaeochromocytomas included

Table 3: Age-adjusted incidence rates (x100.000)overall and by European region for the period 1995–2002.

Prevalence

Table 4 shows the estimated complete prevalence in Europe and the observed prevalence proportion of those diagnosed 2, 5 and 15-years before the index date (1st January 2003). More than 315,000 persons in the EU were alive on 1st January 2008 with a past diagnosis of a carcinoma of endocrine organs. Of these, 12.2% (38,760 over 317,681) and 26.3% (83,397 over 317,681) were diagnosed within 2 and 5 years before the index date, respectively. The difference (14.1%) between these two proportions represents the proportion of cases still alive, diagnosed more than 2 years but less than 5 years before the index date. The remaining fraction of 73.8% represents long-term survivors (alive for more than 5 years after diagnoses), and 136,458 (43.0% of the total) even survived longer than 15 years after diagnosis.

Cancer entity	EU27[a] prevalence at 1st January 2008			Number of years of diagnosis before 1st January 2003								
				Diagnosed within 2 years before 1st January 2003			Diagnosed within 5 years before 1st January 2003			Diagnosed within 15 years before 1st January 2003		
	N. of cases	Prop.	SE	N. of cases	Prop.	SE	N. of cases	Prop.	SE	N. of cases	Prop.	SE
Carcinoma of endocrine organs	**317,681**	**64**	**0.50**	**38,760**	**7.8**	**0.11**	**83,397**	**17**	**0.16**	**181,223**	**37**	**0.24**
Pituitary carcinoma	4334	0.87	0.06	186	0.04	0.01	407	0.08	0.01	2332	0.47	0.03
Thyroid cancer	306,808	62	0.50	36,216	7.3	0.11	78,404	16	0.16	168,191	34	0.23
Parathyroid carcinoma	1418	0.28	0.03	247	0.05	0.01	473	0.10	0.01	880	0.18	0.02
Adrenal carcinoma[b]	5698	1.15	0.06	1024	0.21	0.02	2001	0.40	0.03	3867	0.78	0.03

N. of cases: number of cases

Prop.: Proportion. SE = Standard Error

a European 27 member states population (497,455,033)

b Phaeochromocytomas included

Table 4: Two, 5, 15-year prevalence proportions (per 100,000)and estimated complete prevalence in Europe.

The distribution of the observed prevalence by time since diagnosis varied widely among cancer sites (Table 4). Adrenal carcinomas showed the highest proportion of cases being diagnosed within the first 2 years before the prevalence date (18.0%) (1024 over 5698) and the lowest proportion of those being diagnosed more than 15 years before the index date, with 67.9% (3867 over 5698) of cases diagnosed within 15 years before 1st January 2003. Pituitary carcinoma and thyroid cancer showed a relatively high proportion of people surviving more than 15 years (46.2%and 45.2%, respectively). The largest variation in prevalence by time was observed for pituitary carcinoma. For this group of tumours, the proportion of those diagnosed 5 and 15 years before the index date equalled 9.4% and 53.8%, respectively.

Survival

Fig. 1 shows the 5-year relative survival of first and second tier cancer entities of the endocrine carcinomas. Thyroid cancer showed the highest 5-year relative survival rate (90.5%; 95% confidence interval (CI): 89.7–91.3), while adrenal carcinoma showed the worst prognosis with a rate of 36.3% (95% CI: 31.7.5–41.5). Parathyroid carcinoma and pituitary carcinoma showed a good to intermediate prognosis, with 5-year relative survival rates of 80.5% (95% CI: 67.9–95.5) and 65.6% (95% CI: 54.0–79.8), respectively. Five-year survival rates for all endocrine cancer entities were higher for females than for males (Table 5). The largest difference was observed for pituitary carcinoma (70.2%; 95% CI: 54.3–90.8% compared to 62.6%; 95% CI: 45.5–86.2, respectively) and adrenal carcinoma (39.9%; 95% CI: 33.2–46.3 compared to 32.3%; 95% CI: 25.4–39.1, respectively) (Table 5). The relative survival in all second tier entities, with the exception of carcinoma of the parathyroid gland, was lower for persons 65 years of age or older (Table 5).

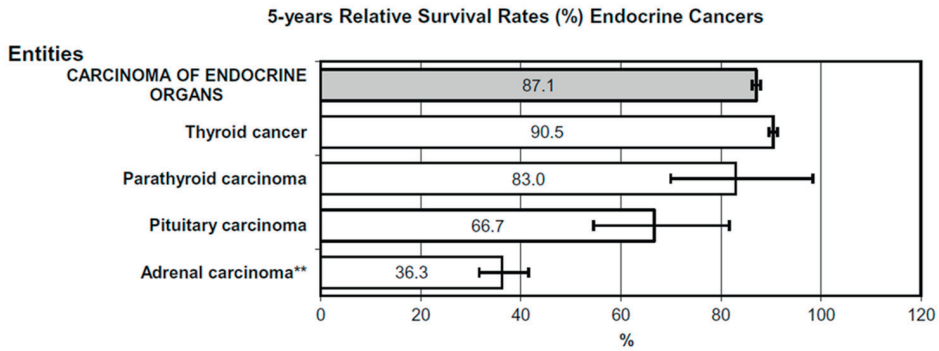

Fig. 1: Five-year relative survival (%)* by cancer entity for endocrine cancers. Period survival analysis 2000–2002 46 cancer registries included.
*Due to incomplete case ascertainment survival rates might have been under or overestimated. ** Phaeochromocytomas included

Cancer entity	Sex				Age (yrs)						Overall (46 CRs)	
	Male		Female		0–24		25–64		65+			
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Carcinoma of endocrine organs	**80**	**0.97**	**90**	**0.45**	**95**	**0.97**	**94**	**0.33**	**64**	**1.2**	**87**	**0.42**
Pituitary carcinoma	63	10	70	9.0	100	0.00	76	8.2	48	10	66	6.4
Thyroid cancer	85	0.98	92	0.43	99	0.58	96	0.30	69	1.3	90	0.41
Parathyroid carcinoma	80	12	84	9.1	NE	NE	73	10.5	89	11.2	81	6.9
Adrenal carcinoma[b]	32	3.6	40	3.4	39	8.8	42	3.1	24	4.2	36	2.5

NE = Not enough data to calculate.

SE = Standard Error.

a Due to incomplete case ascertainment survival rates might have been under or overestimated.

b Phaeochromocytomas included.

Table 5: Five year relative survival (%)[a] of Endocrine carcinomas by gender and age category. Period survival analysis 2000–2002.

Discussion

This is the first large scale European study on carcinomas of the endocrine organs using a high quality population based database. In this study, we aim to provide the clinician with accurate information on the burden of rare tumour entities of the endocrine organs. This gives us the opportunity to compare our large scale EU data on endocrine carcinomas with previous small cohort studies, reviews, case reports and large cohort studies from other continents. Unfortunately, for most carcinomas of the endocrine organs discussed here, there are only a few studies available to compare our data with (Correa et al.[9]; Lee et al.[10]).
Pituitary carcinoma accounts for about four new cases per 10,000,000 person-years in the RARECARE dataset. In the whole of the EU27 we estimated to find 206 cases annually. Of these carcinomas only 30.3% has been microscopically verified, due to the specificity of the pituitary gland it is known that pathology reports are lacking for a proper diagnoses. Even microscopically verified cases could still include adenomas and metastases since it is difficult to differentiate these from carcinomas,[11,12] only the presence of distance metastases can confirm a malignancy. This shows the importance that endocrine cases, included in this study were based on comprehensive sources like pathological reports, examination results, symptoms, signs and the different clinical reports. We observed the highest incidence rates in those 65 years of age or older. A literature review identified a study done by Pernicone et al., describing gender differences in patients diagnosed with pituitary gland carcinoma.[13] This study described 15 cases showing no differences in gender and age for pituitary cancer.[14] Never-the-less those 15 cases used for analysing the female male ratio are in strong contrast to the 333 cases used for our analyses. So finding a small predominance in males is expected to be more representative for the European population. Our findings towards the fact that pituitary carcinoma is affecting all age classes is confirming the results found in a

clinicopathological review that pituitary carcinoma affects adults of all ages.[12] Besides these findings we were able to show that incidence per 100,000 person-years of pituitary carcinoma increased with age.

Thyroid cancer contributed over 29,500 cases for the analyses of the endocrine carcinomas, which accounts for 88% of the total burden of the carcinomas of the endocrine organs. We excluded medullar, mixed medullary- follicular and mixed medullary-papillary thyroid cancer, since we classified these tumours as rare neuroendocrine tumours. Excluding these specific morphologies (1764 cases) made it not easy to compare our data with previously published studies as they often categorise these morphologies as carcinomas of the thyroid gland.[15–17] Of all cases analysed 97.6% were microscopically verified, which indicates the high quality of the data analysed. Risk factors for cancer of the thyroid gland have been studied extensively.[1,8,16] The most important risk factors are iodine deficiency[1,8,18] and exposure to nuclear radiation, e.g. as a result of the Chernobyl disaster.[15,19] We did not find higher incidence rates in the region 'Eastern Europe'. This is probably due to the way the EU regions are grouped and which CRs participated in RARECARE. Only Polish and Slovakian registries were included in the Eastern EU region. Within the Southern EU region, radiation contaminated countries[20] like Slovenia and Italy are included.[21] The incidence of thyroid cancer was higher for women (2.8:1 ratio), which is in agreement with the findings in other studies,[16,22] and could be related to hormonal differences between age categories and male to female ratios.[23] The 5-year relative survival rate of 90.5% found in our study is low compared to the 95% reported in literature using the SEER population.[24] A study population based study of 15,698 cases presented the survival per histological subtype, showing particularly low survival rates for the anaplastic subtype.[25] Therefore the distribution of the different histology types within our data analysed might have caused the difference in relative survival compared to this SEER study. The high number of long term survivors shows the need to monitor follow up for possible late therapy effects, especially for those diagnosed at a younger age. Research needs to be developed in this field and health care planners have to make an appropriate long term plan.

Parathyroid carcinoma was the rarest carcinoma of the endocrine organs with about two new cases per 10,000,000 person-years, which leads to an estimated 109 new cases annually in the EU27. The largest studies to date are studies with data from the National Cancer Data Base of the United States[26] and a review about 271 cases of parathyroid carcinoma diagnosed in England in the period 1933–1989,[27] both studies confirm the rarity of the parathyroid carcinoma.

In our study, 94% of the carcinomas were microscopically verified. It has been reported that differentiating parathyroid carcinomas and adenomas is problematic as there are no specific differentiating characteristics,[28] again only distant metastases confirms a malignancy. A population based in depth study on parathyroid carcinomas covering the Dutch population for the period 1989–2003 showed a revision of 43 malignant cases of parathyroid tumours. As a result only two patients had to be excluded for further analyses due to misclassification.[29]

A female predominance of 3–4 times the number of cases in men has been described for adenomas of the parathyroid gland, while no gender predominance was reported for carcinomas.[28] Our results show no gender predominance, supporting that only carcinomas were included.

An increase in age adjusted incidence was found with increasing age; the highest age adjusted incidence was found in patients 65 years of age or older. A retrospective cohort study including 286 cases[26] found a peak incidence in the age category 45–59. In this study, no correction for the age distribution in the population analysed was made, which makes it difficult to compare results with other studies that used other populations.[26] The relative survival rate for patients with parathyroid carcinoma was relatively good with an overall 5 year survival rate of 80.5%. This same study reported a higher 5 year relative survival rate of 85.5%,[26] this might be due to the difference in stage at the time of diagnoses. As parathyroid carcinoma usually grows slowly but progressively, a longer follow up period would have been preferable to compare our results on the longer term. This slow growing process was confirmed by the strong decrease in survival reported in literature between 5 and 10 year relative survival, having strong increase starting after 8 years of relative survival resulting in a 10 year relative survival of 49.1%.[26]

For adrenal carcinoma we identified 1464 carcinomas resulting in respectively two new cases each year in 1,000,000 person-years. About 88% of those carcinomas were microscopically verified. We included both the cortex and the medulla of the adrenal gland for analyses and included adrenocortical carcinomas as well as malignant phaeochromocytoma. Since malignant phaeochromocytoma can only be diagnosed in the case of distant metastases, having comprehensive access to different medical reports are necessary to come to the correct diagnoses of phaeochromocytoma.

We didn't find a gender difference, while the literature reports a predominance in male patients,[30] but also a predominance in female patients (7:3 ratio) for functional tumours and a male predominance in non functional tumours (3:2 ratio).[31] Unfortunately, we did not have information on the hormonal status and therefore we were not able to distinguish functional and non-functional endocrine tumours. Adrenal carcinoma affected all age categories, with the highest age-adjusted incidence rates in those 65 years of age or older. We cannot confirm the reported peak incidence around the 5th decade of life.[31] The prognosis of adrenal carcinoma is bad, with a 5-year relative survival rate of 36.3%, which was in agreement with the findings by Kopf et al.[32] Noteworthy is the difference in survival between males (32%) and females (40%). Also, the variation in 5 year relative survival is relatively large for the different age groups, with the lowest survival (23.7%) in people 65 years or older and a 5-year relative survival of 42.0% in people 25 to 64 years of age. A study on adrenal cortical carcinomas in the United States reported a major difference in survival by stage at diagnoses.[16] Unfortunately, we did not have information on the stage in this study. Based on the observed low survival rates, adrenal carcinoma could be identified as carcinomas in need of more diligent research efforts, which should ultimately contribute towards improving survival.

Overall, our study has limitations, like incomplete case ascertainment due to asymptomatic disease, the lack of information on stage and hormonal data. These limitations should create awareness and start the discussion on the investment in more high quality studies on rare cancers, collecting additional information, e.g. on the stage and therapeutic approach. In future this might be of help in partly explaining the observed variations. Nevertheless this is the first time ever we were able to give the clinician and other related professionals an European overview on the burden of the carcinomas of the endocrine organs.

The RARECARE working group consists of:

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Conflict of interest statement

None declared.

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Chapter 6

Rare neuroendocrine tumours:

Results of the surveillance of rare cancers in Europe project

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Abstract

Because of the low incidence, and limited opportunities for large patient volume experiences, there are very few relevant studies of neuroendocrine tumours (NETs). A large population-based database (including cancer patients diagnosed from 1978 to 2002 and registered in 76 population-based cancer registries [CRs]), provided by the project 'surveillance of rare cancers in Europe' (RARECARE) is used to describe the basic indicators of incidence, prevalence and survival of NETs, giving a unique overview on the burden of NETs in Europe. NETs at all cancer sites, excluding lung, were analysed in this study. In total over 20,000 incident cases of NETs were analysed and a data quality check upon specific NETs was performed. The overall incidence rate for NETs was 25/1,000,000 and was highest in patients aged 65 years and older with well differentiated endocrine carcinomas (non-functioning pancreatic and gastrointestinal) (40 per 1,000,000). We estimated that slightly more than 100,000 people were diagnosed with NETs and still alive in EU27 at the beginning of 2008. Overall, NETs had a 5 year relative survival of 50%; survival was low (12%) for poorly differentiated endocrine carcinoma, and relatively high (64%) for well differentiated carcinoma (not functioning of the pancreas and digestive organs). Within NETs, endocrine carcinoma of thyroid gland had the best 5-year relative survival (82%). Because of the complexity and number of the different disciplines involved with NETs (as they arise in many organs), a multidisciplinary approach delivered in highly qualified reference centres and an international network between those centres is recommended.

Introduction

Neuroendocrine tumours (NETs) can develop in most organs.[1] NETs are usually slow growing tumours with behaviour ranging from relatively benign to highly malignant.[2–4] Due to their heterogeneous embryological origin, NETs are ubiquitous and because of their rarity can be difficult to distinguish by biologic and histopathologic features.[5–7]

NETs are widely regarded as a rare tumour, with an incidence of 1–5 cases per 100,000 person-years.[3,8,9] The low incidence rate has resulted in only a few relevant studies, and makes a large experience for any single healthcare professional unlikely.[10–12] A high quality database with reliable diagnoses, which needs large clinical experience, is a condition sine qua non for epidemiological research on any rare disease.[13]

A major step forward in predicting the biological behaviour of NETs was made in 2000 by the development of a new World Health Organization (WHO) morphological classification, including NETs, based on histopathological and biological characteristics.[6,10,14] Later, a Tumour-Node and Metastases (TNM) classification and the European Neuroendocrine Tumour Society (ENETS) grading system for NETs became available.[10,15]

Multiple systems of nomenclature, grading and staging have been proposed, however, none has achieved universal acceptance. In general, the current WHO guidelines divide neuroendocrine neoplasms into two clinically distinct pathologic classes: well- and poorly differentiated. The well-differentiated NETs can be classified as either grade 1 or grade 2 depending on proliferation and histology. Well-differentiated grade 1 and grade 2 NETs have traditionally been referred to as carcinoids, regardless of grade or site of origin. The WHO 2010 guidelines apply the term 'carcinoid' to grade 1 NETs only.

The poorly differentiated grade 3 neuroendocrine carcinomas are characterised by rapid dissemination, resistance to therapeutic interventions and a highly aggressive course.

A comprehensive analysis of NETs in Europe is lacking within the available literature. This paper delineates the burden of NETs in Europe, providing estimates of the incidence, prevalence and survival of these tumours diagnosed from 1988 to 2002, based on the definition and list provided by the project surveillance of rare cancers in Europe (RARECARE). Although the recent improvements regarding pathologic diagnosis and grading of NET are a major step forward, the RARECARE list, and therefore our analysis, are based on the nomenclature during the time of our study period 1995–2002.

Materials and methods

Tumour grouping

The present analyses are based on the list of cancers provided by the RARECARE project. RARECARE included data between 1978 and 2002 and followed the 2000 WHO guidelines that distinguished NETs in four main groups: well differentiated endocrine tumours; well differentiated endocrine carcinoma; poorly differentiated endocrine carcinoma and mixed endocrine–exocrine carcinoma.

The RARECARE list of NETs is organised in two hierarchical tiers and based on the International Classification of Diseases for Oncology third edition (ICD-O-3).[16] Tier 1 consists of cancers that require the same clinical expertise and patient referral structure, created by grouping tier 2 entities. Tier 2 includes cancers that are similar from the point of view of clinical management and research, and is based on the combination of topographical and morphological ICD-O-3 codes.

For NETs described in this paper (Table 1), there is one tier 1: 'neuroendocrine tumours' and eight tiers 2 (including: well differentiated endocrine tumours [identified in the ICD-O-3 as carcinoids]; well differentiated endocrine carcinoma [identified in the ICD-O-3 as atypical carcinoids]; well differentiated endocrine carcinomas of the pancreas and digestive organs [non-functioning]; well differentiated endocrine carcinomas of the pancreas and digestive tract [functioning]; poorly differentiated endocrine carcinomas [skin and thyroid excluded]; mixed endocrine–exocrine carcinomas; endocrine carcinomas of thyroid gland and endocrine carcinomas of the skin). Table 1 presents the ICD-O-3 morphology and topography codes of NETs considered in the present study.

The RARECARE list grouped NETs from all anatomic sites. In this study well differentiated endocrine carcinomas of the pancreas and digestive organs are divided according to WHO grouping into functioning and non-functioning endocrine carcinomas. Well differentiated endocrine carcinomas (functioning) produce hormones and other local mediators and are associated with syndromes related to this hormone over secretion. Well differentiated endocrine carcinomas (non-functioning) exhibit immuno-positivity for endocrine markers but are not related to any hyperfunctional clinical syndrome.[17] This differentiation results in grouping them separately from well differentiated endocrine tumours and well differentiated endocrine carcinomas of other sites.

We included two separate tiers for thyroid and skin NETs: endocrine carcinoma of the thyroid gland and endocrine carcinoma of the skin. Including these two specific tiers results in the exclusion of skin and thyroid from poorly differentiated endocrine carcinomas, and from the well differentiated endocrine tumours and well differentiated endocrine carcinomas. The morphology codes for thyroid endocrine carcinomas include medullary carcinomas, poorly differentiated thyroid endocrine tumours and mixed medullary-follicular carcinoma. Endocrine carcinomas of the skin include Merkel cell carcinoma. Finally, poorly differentiated endocrine carcinomas include small cell endocrine carcinoma and large cell endocrine carcinoma of all

sites except skin and thyroid. NETs of the lung will not be described in this article as their European incidence rate was 7.3 per 100.000 person-years, and therefore not considered to be rare.[18]

Entity	Tier	Number malignant cancers 1995–2002 (76 CRs)	Data quality indicators				International Classification of Diseases for Oncology third edition (ICD-O-3) codes	
			DCO* only	Autopsy	Microscopic verification	Cases 1995–1998 censored before 5 years	Topography	Morphology
		N	(%)	(%)	(%)	(%)		
Neuroendocrine tumours	**1**	**20,994**	**0.34**	**1.7**	**97**	**1.2**		
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	2	3202	0.81	0.84	96	0.69	All cancer sites except C15-C26, C34, C44	8240–8246
Well diff endocrine atypical carcinoid tumours (skin and GI tract excluded)	2	6	0.00	0.00	100	0.00	All cancer sites except C15-C26, C34, C44	8249
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning)	2	10,276	0.17	2.5	98	1.5	C15–26	8240–8246, 8249, 8150
Well diff endocrine carcinoma of pancreas and ofdigest tract (functioning)	2	200	1.0	1.5	85	2.5	C15–26	8151–8153, 8155–8157
Poorly diff endocrine carcinoma (skin and thyroid excluded)	2	4429	0.56	1.3	97	0.40	All cancer sites except C34, C44, C73	8013, 8041–8045
Mixed endocrine–exocrine carcinoma	2	18	5.6	0.00	89	0.00	All cancer sites except C34, C44	8154
Endocrine carcinoma of thyroid gland	2	1784	0.00	1.3	98	2.4	C73	8013, 8041–8045,8510, 8345–8347
Endocrine carcinoma of skin Merkel cell carcinoma	2	1018	0.09	0.00	100	1.1	C44	8041–8044, 8240–8247

* DCO: death certificate only; NOS: not otherwise specified.

Table 1: Data quality indicators for neuroendocrine cancers diagnosed 1995–2002 and archived in 76 surveillance of rare cancers in Europe (RARECARE) cancer registries.

CRs selection and population coverage

RARECARE gathered data on cancer patients diagnosed from 1978 to 2002, registered in 89 populationbased CRs, all of which had information on follow-up available up to at least 31st December 2003. However this paper considered data from 76 CRs, excluding CRs which did not classify cancers according to the ICD-O-3, and also those which collected data on childhood cancers only.

Data selection for incidence analysis

The incidence analysis considered incident cases between 1995 and 2002. We excluded twelve specialised CRs, as those registered data on specific cancer sites only. As a result, the incidence analyses were restricted to 64 CRs. Incidence rates were estimated as the number of new cases occurring between 1995 and 2002 divided by the total person-years in the general population (male and female) in the CR areas considered, over the same period. For age-standardised rates, the European standard population was used.[19] For estimating the number of cases that arises per year in all 27 European member states (EU27), the observed RARECARE incidence rates 1995–2002 were multiplied to the total 2008 EU27 population (497,455,033 at 2nd April 2008) provided by EUROSTAT. In providing NET burden estimates, we assumed that the population covered by the CRs included was representative of the population of the EU27 as a whole.

Data selection for prevalence analyses

The observed prevalence of cases within 2, 5 and 15 years before the index date of 1st January 2003 was estimated by applying the counting method.[20] Only 22 CRs had incidence and follow-up data available for the 15 year period 1988–2002, choosing January 2003 as index date. The completeness index method[21] was used to estimate the EU complete prevalence, which involved adding the estimated surviving cases diagnosed prior to 1988 to those observed in 1988–2002. The completeness index was obtained on the basis of a parametric approach, by modelling 1985–1999 incidence data with a logistic exponential or polynomial function on age, and 1988–1999 survival with mixture cure models.[22] The expected number of prevalent cases in EU27 was estimated by multiplying the prevalence estimates to the 2008 European population (497,455,033 at 2nd April 2008 provided by EUROSTAT).

Data selection for survival analyses

Period survival indicators for the years 2000–2002 were estimated using the Brenner algorithm.[23] Period analysis provides more up-to-date survival experience by considering survival experience in 2000–2002. Forty-six CRs out of the 76 European CRs had data available for this period, and could be included for survival analyses.

Data quality analysis

International standards for CRs set by the International Association for Cancer Registries (IACR) and the European Network of Cancer Registries (ENCR) attempt to secure the quality of the CRs, but consideration must be given to constraints on their activity placed by local health care systems.[24] In summary, during the registration process there was access to comprehensive sources including pathologic reports, diagnostic examinations and clinical dossiers. Especially for NETs, it is important to have access to, and use of all sources provided by multidisciplinary teams (including experienced pathologists) to come to a correct definition of NETs.

The main data quality indicators for the 21,066 NETs are shown in Table 1. These cases were diagnosed between 1995 and 2002 and archived by the 76 CRs considered in the study. Overall, 0.34% of the cases were Death Certificate Only (DCO), ranging from 0.00% for well differentiated endocrine tumours (atypical carcinoid) (N=6 in four CRs) and endocrine carcinomas of thyroid gland (N=1784 in 64 CRs) to 5.6% for the mixed endocrine–exocrine carcinomas of the pancreas (N=18 in 16 CRs).

Nearly 97% of all NETs included in the RARECARE database were histologically verified (MV), however the proportion of MV cases ranged from 100% for the six cases of well differentiated endocrine tumours (atypical carcinoid) to 85% for the well differentiated endocrine carcinoma (functioning of pancreas and of digestive tract).

The proportion of cases diagnosed between 1995–1998 and censored before 5 years of follow-up (lost to follow-up) was 1.2%, ranging from 0.00% for the well differentiated endocrine tumours to 2.5% for the well differentiated endocrine carcinomas (functioning pancreas and digestive tract).

EU regions

Differences among European regions have been established by grouping the RARECARE participating cancer registries by country and grouping the countries into 5 main European regions following the European cancer registry-based study on survival and care of cancer patients (EUROCARE) study:[25] Northern Europe (Iceland, Norway, Sweden), United Kingdom and Ireland (England, Scotland, Wales, Northern Ireland, Republic of Ireland), Central Europe (Belgium, Austria, France, Germany, the Netherlands, Switzerland), Eastern Europe (Poland, Slovakia), and Southern Europe (Italy, Malta, Portugal, Slovenia, Spain). For 11 countries, CRs covered the entire national population (Austria, Iceland, Ireland, Malta, Norway, Slovakia, Slovenia, Sweden, Northern Ireland, Scotland, Wales and England). The other 10 countries were represented by regional CRs, covering variable proportions of their respective national populations.

Results

Incidence

The incidence rate is presented per 1,000,000 person-years in Europe (crude rate) in Table 2. Table 2 shows also rates by sex (age adjusted rate), age group and the estimated number of new cases expected in EU27 every year. Well differentiated endocrine carcinomas of the pancreas and digestive organs (non-functioning) were the most common tumours among NETs, with a crude incidence rate of 13 per 1,000,000 person-years, followed by poorly differentiated endocrine carcinomas (skin and thyroid excluded), with a crude rate of 5.2 per 1,000,000 person-years. For all other entities the crude incidence rate was below 4.0 per 1,000,000 person-years (Table 2).

Entity	EU overall			Sex[b]				Age[a]						Estimated number of cases arising in EU per year
				Male		female		0-24 years		25-64 years		65+ years		
	Observed cases 1995–2002	Rate	SE	Adj Rate	SE	Adj Rate	SE	Rate	SE	Rate	SE	Rate	SE	
Neuroendocrine tumours	**20,357**	**25**	**0.18**	24	0.24	19	0.20	2.0	<0.10	20	0.22	88	0.83	12,586
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	2956	3.7	<0.10	3.4	0.09	2.8	<0.10	0.10	<0.10	3.0	<0.10	13	0.32	1826
Well diff endocrine atypical carcinoid tumours(skin and GI tract excluded)	6	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	0.00	~	<0.10	<0.10	<0.10	<0.10	5
Well diff endocrine carcinoma of the pancreas and digest organs (non- functioning) -Carcinoid tumours, NOS/islet cell carcinoma	10,099	13	0.13	12	0.17	9.7	0.15	1.14	<0.10	11	0.16	40	0.57	6243
Well diff endocrine carcinoma of pancreas and of digest tract (functioning) -Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours	197	0.25	<0.10	0.25	<0.10	0.21	<0.10	0.08	<0.10	0.29	<0.10	0.6	<0.10	119
Poorly diff endocrine carcinoma (skin and thyroid excluded) -Small cell endocrine carcinoma/Large cell endocrine carcinoma	4181	5.2	<0.10	5.4	0.10	3.3	<0.10	0.13	<0.10	3.30	<0.10	22	0.41	2587
Mixed endocrine–exocrine carcinoma	17	<0.10	<0.10	<0.10	0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	10
Endocrine carcinoma of thyroid gland - Medullary carcinoma - Mixed medullary-follicular carcinoma	1771	2.2	<0.10	1.8	<0.10	2.3	<0.10	0.55	<0.10	2.6	<0.10	4.2	0.18	1094
Endoccine carcinoma of skin / Merkel cell carcinoma	1079	1.3	<0.10	0.99	<0.10	0.87	<0.10	<0.10	<0.10	0.35	0.10	7.3	0.24	667

Statistic could not be calculated. NOS: not otherwise specified.

a Crude rate. b Age standardised rate.

Table 2: Observed cases with crude incidence (rate per million/year) and standard errors (SE) for neuroendocrine tumours in Europe. Rates and SE by sex and age, with estimated incident cases in Europe (EU27). Cases diagnosed 1995–2002 in 64 European CRs.

The localisation of NETs was 65% at 8 different sites: small intestine (18%), thyroid gland (8.6%), pancreas (8.0%), colon (7.0%), stomach (6.9%), appendix (5.5%), rectum (5.3%) skin (5.0%). The other 35% were located at sites such as female and male genital organs, head and neck and other sites. Within these 35% we found that there was no specific site registered for 19% of all NETs, which accounted for 60% of the column included 'others' (Table 3).

NETs were more common in men, except for endocrine carcinoma of the thyroid gland. The incidence rate was highest in patients aged 65 years and older, ranging from <0.10 up to 40 per 1,000,000 person-years. We estimated 12,600 new cases per year for EU27, of which 6250 (50%) were well differentiated endocrine carcinomas of the pancreas and digestive organs (non-functioning) (Table 2).

Table 4 shows the age standardised incidence rate by European region between 1995 and 2002. There was a geographical variation in age standardised incidence, with the highest rates in Northern Europe (32 per 1,000,000 person-years) and the lowest in Eastern Europe (7.5 per 1,000,000) (Table 4).

Entity	All tumours	Head and neck	Thyroid	Stomach	Small Intestine	Appendix	Colon	Rectum	Pancreas	Skin	Male genital	Female genital	Others
	N	N	N	N	N	N	N	N	N	N	N	N	N
Neuroendocrine tumours	20,357	136	1753	1400	3669	1126	1425	1072	1635	1028	282	524	6307
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	2956	41	9	0	0	0	0	0	0	0	67	227	2612
Well diff endocrine atypical carcinoid tumours(skin and GI tract excluded)	6	0	0	0	0	0	0	0	0	0	0	0	6
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning) -Carcinoid tumours, NOS/islet cell carcinoma	10,099	0	0	1245	3636	1124	1337	986	1313	0	0	0	458
Well diff endocrine carcinoma of pancreas and of digest tract (functioning) -Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours	197	0	0	9	9	0	1	0	177	0	0	0	1
Poorly diff endocrine carcinoma (skin and thyroid excluded) -Small cell endocrine carcinoma/Large cell endocrine carcinoma	4184	91	0	143	24	2	86	86	128	0	211	289	3121
Mixed endocrine–exocrine carcinoma	17	0	0	1	0	0	0	0	15	0	0	0	1
Endocrine carcinoma of thyroid gland - Medullary carcinoma - Mixed medullary-follicular carcinoma	1771	0	1771	0	0	0	0	0	0	0	0	0	0
Endoccine carcinoma of skin / Merkel cell carcinoma	1097	0	0	0	0	0	0	0	0	1018	0	0	63
Percentage of the total		**0.67**	**8.6**	**6.9**	**18**	**5.5**	**7.0**	**5.3**	**0.8**	**5.0**	**1.4**	**2.6**	**31**

Table 3: Observed cases for neuroendocrine tumours per localisation in 1995–2002 in 64 European CRs.

Prevalence

Table 5 shows the estimated complete prevalence in Europe and the observed prevalence proportion of those diagnosed 2, 5 and 15-years before the index date (1st January 2003). Over 100,000 people (last column of Table 5) were estimated to be alive in EU at the beginning of 2008 with a diagnosis of NET. Of these, 20% (20,262 over 100,003) and 40% (39,717 over 100,003) were diagnosed within 2 and 5 years before the index date, respectively. The difference (20%) between these two proportions represents the proportion of cases diagnosed 3–4 years before the index date, and therefore presumably still undergoing clinical follow-up. The remaining 60% represents those surviving over 5 years after diagnosis, 34,200 of those (34% of the total) surviving more than 15 years after their initial diagnosis.

Well differentiated endocrine carcinomas of the pancreas and digestive organs (non-functioning) were estimated for the year 2008 to be the most prevalent endocrine tumours (63,700 cases), followed by endocrine carcinomas of thyroid gland (16,200 cases), well differentiated endocrine carcinoid tumours (7800 cases), and poorly differentiated endocrine carcinomas (skin and thyroid excluded) (6700 cases). The remaining second tier entities of NETs accounted for less than 6000 prevalent cases.

The distribution of prevalent cases by time since diagnosis varied between the different tumour entities depending on the prognosis of the specific tumour type and the mean age of incidence (Table 5). Endocrine carcinomas of the thyroid gland had the highest proportions of very long term survivors who survived over 15 years following diagnosis (44%). Around 70% of endocrine carcinoma of the thyroid gland occurred in the age groups under 65 years of age.

Entity	European region										EU Overall	
	Northern Europe		Central Europe		Eastern Europe		Southern Europe		UK and Ireland			
	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE
Neuroendocrine tumours	32	0.51	27	0.36	7.5	0.33	18	0.32	19	0.24	21	0.15
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	4.7	0.19	4.1	0.14	0.42	<0.10	2.1	0.11	3.0	0.10	3.1	<0.10
Well diff endocrine atypical carcinoid tumours(skin and GI tract excluded)	0.00	~	<0.10	<0.10	<0.10	<0.10	0.00	~	0.00	~	<0.10	<0.10
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning) -Carcinoid tumours, NOS/islet cell carcinoma	18	0.39	13	0.26	3.5	0.22	8.3	0.22	9.2	0.17	11	0.10
Well diff endocrine carcinoma of pancreas and of digest tract (functioning) -Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours	0.33	<0.10	0.21	<0.10	0.22	<0.10	0.20	<0.10	0.21	<0.10	0.23	<0.10
Poorly diff endocrine carcinoma (skin and thyroid excluded) -Small cell endocrine carcinoma/Large cell endocrine carcinoma	4.7	0.19	5.7	0.16	1.2	0.13	2.9	0.12	4.4	0.11	4.2	<0.10
Mixed endocrine–exocrine carcinoma	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
Endocrine carcinoma of thyroid gland - Medullary carcinoma -Mixed medullary-follicular carcinoma	1.9	0.13	2.7	0.12	2.0	0.2	3.1	0.1	1.2	<0.10	2.1	<0.10
Endoccine carcinoma of skin / Merkel cell carcinoma	1.6	0.10	0.86	<0.10	0.13	<0.10	1.0	<0.10	0.77	<0.10	0.91	<0.10

Table 4: Age-standardised (Adj) incidence rates (per 1,000,000 person-years) for neuroendocrine cancers in 1995–2002, with standard errors (SE) by European Region.

Entity	Observed prevalence									Estimated prevalence		
	Two years after diagnose			Five years after diagnose			Fifteen years after diagnose			Complete		EU27 2008
	Prev	SE	N of cases	Prev	SE	N of cases	Prev	SE	N of cases	Prev	SE	N of cases
Neuroendocrine tumours	4.1	<0.10	20,262	7.9	0.11	39,717	13	0.14	66,133	20	0.25	100,003
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	0.56	<0.10	2786	0.95	<0.10	4734	1.2	<0.10	6239	1.6	<0.10	7791
Well diff endocrine atypical carcinoid tumours(skin and GI tract excluded)	<0.10	<0.10	15	<0.10	<0.10	23	<0.10	<0.10	23	<0.10	<0.10	35
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning) -Carcinoid tumours, NOS/islet cell carcinoma	2.3	<0.10	11,693	4.9	<0.10	24,294	8.4	0.11	41,801	13	0.2	63,691
Well diff endocrine carcinoma of pancreas and of digest tract (functioning) -Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours	<0.10	<0.10	210	<0.10	<0.10	413	0.15	<0.10	747	0.22	<0.10	1070
Poorly diff endocrine carcinoma (skin and thyroid excluded) -Small cell endocrine carcinoma/Large cell endocrine carcinoma	0.34	<0.10	1681	0.54	<0.10	2695	0.9	<0.10	4495	1.3	<0.10	6679
Mixed endocrine–exocrine carcinoma	<0.10	<0.10	23	<0.10	<0.10	31	<0.10	<0.10	55		<0.10	96
Endocrine carcinoma of thyroid gland - Medullary carcinoma -Mixed medullary-follicular carcinoma	0.47	<0.10	2370	<0.10	<0.10	4866	1.8	<0.10	9028	3.2	0.11	16,164
Endoccine carcinoma of skin / Merkel cell carcinoma	0.28	<0.10	1414	0.51	<0.10	2528	0.7	<0.10	3506	0.86	<0.10	4273

N of cases: number of cases; SE: standard error; Prop.: proportion; NOS: not otherwise specified.

Table 5: Two, 5, 15-year prevalence proportions (per 100.000 person-years) and estimated complete prevalence in Europe.

Survival

Fig. 1 shows 5-year relative survival for the different NET entities. Within NETs, endocrine carcinoma of thyroid gland had the best 5-year relative survival, with a rate of 82% (N=599). The most frequent NETs, well differentiated endocrine carcinomas of the pancreas and digestive organs (non-functioning) had the second best 5-year relative survival with a rate of 64% (N=3540). Well differentiated endocrine tumours, and poorly differentiated endocrine carcinomas (skin and thyroid excluded) had the poorest 5-year relative survival: 30% (N=1144) and 12% (N=1543) respectively (N not in tables). The 5 year relative survival for mixed endocrine–exocrine carcinomas was 62% but based on only seven cases. The number of cases (N=6) was too little to calculate the 5-year relative survival with the period survival method[23] for well differentiated endocrine tumours atypical carcinoid.

Fig. 2 shows that NETs of appendix and thyroid gland had the highest survival, followed by NETs diagnosed in the rectum and the small intestine. NETs of the pancreas and the Head and Neck had the poorest survival with a 5-year relative survival rate of 41% (N=564) and 31% (N=54).

Survival was consistently lower for patients of 65 years or over than for younger patients (data not shown).

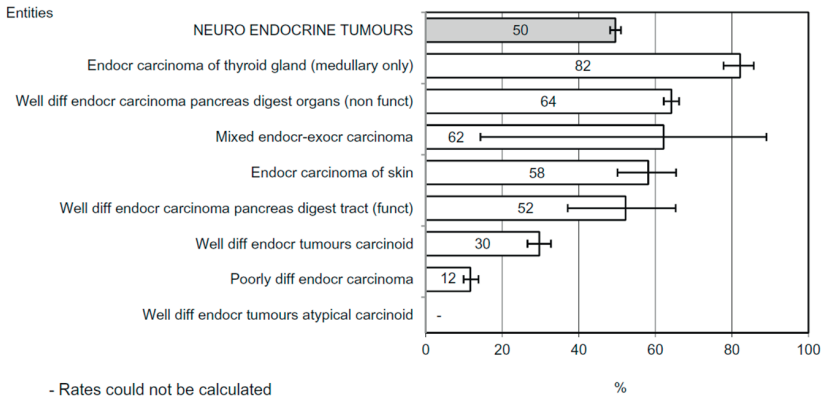

Fig. 1: Five year relative survival (%) for neuroendocrine tumours in Europe 2000–2002. Error bars are 95% confidence interval.

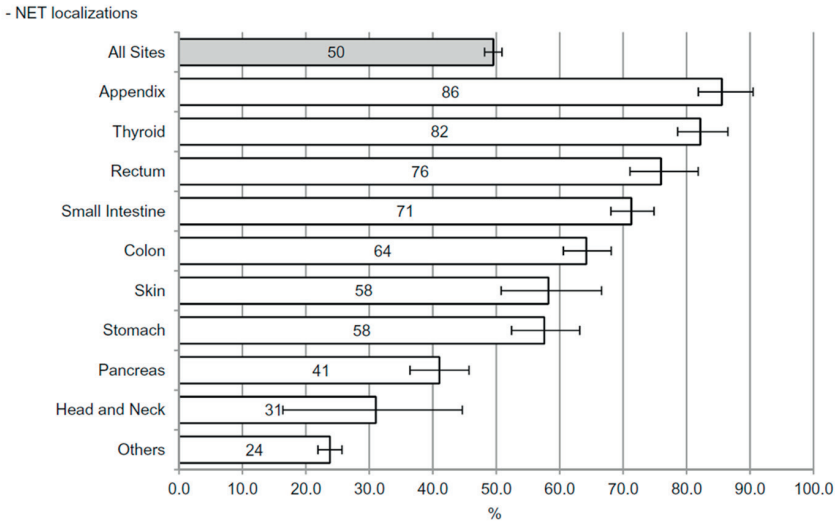

Fig 2. Five year relative survival (%) for the main localisations of neuroendocrine tumours in Europe 2000–2002. Error bars are 95% confidence interval.

Discussion

The availability of a high quality European database has given us the opportunity to obtain a large scale European study on NETs. This study gives a unique possibility to compare our large scale EU data on NETs with already existing small cohort studies, reviews, case reports and

large cohort studies from other countries and continents.[8,26,27]

The major indicators of data quality (Table 1) indicate a high quality dataset with 97% of cases histologically confirmed. However, the main concern when studying such rare tumours, relates to the accuracy of diagnosis and the completeness of registration. The recent improvements regarding pathologic diagnosis and grading of NETs are a major step forward, however we had to use the nomenclature at the time of our study period 1995–2002, and we had to rely on the diagnosis reported in the clinical records.

The RARECARE group assessed the quality of data and the extent of registration bias undertaking a dedicated study in collaboration with CRs providing the data. RARECARE reviewed the original data of a selected sample (N=3000) focusing on undifferentiated (ICD-O-3 code 8020/3) and anaplastic (ICD-O-3 code 8021/3) carcinomas of the digestive tract (ICD-O-3 code C15 to C25).[28] The objective of this review was to identify additional cases, if any. This check led to only 10 additional cases out of 929 cases of undifferentiated and anaplastic carcinomas identified. Also, all carcinoids (ICD-O-3 codes 8240–8244) of the digestive tract were reviewed to assess their behaviour. Pathological reports were reviewed looking for information on depth of invasion, tumour size and Ki67 labelling index. Unfortunately, most prognostic information regarding so called carcinoids of the digestive tract were missing in the majority of pathological reports. This finding suggests that the quality of diagnosis was high, although major concerns can be raised regarding the completeness of prognostic parameter evaluation. Our data clearly indicate that the referral of NETs to an expert pathologist would greatly impact on diagnostic accuracy, as well as on evaluation of prognosis across the EU. Where ENETS is giving practical guidelines for diagnosis and treatment of NETs, no information is available on the criteria for expert pathologists.

Our data confirm results presented by other small sets of population based studies that report an incidence rate for NETs (NETs of the lung excluded) of around 2 per 100,000 person-years.[3,8,9] The overall survival rate shown is broadly in line with the literature[27], which seems to relate to anatomic sites, i.e. 86% in the appendix, 71% in the small intestine, and 41% in the pancreas (Fig. 2). A population based study included potential prognostic parameters in their study model including disease stage, primary tumour site, histology, age, sex, race and period of diagnosis, and found all parameters to be significant.[27]

Regarding well differentiated endocrine tumours, our analysis describes four different subgroups of neuroendocrine tumours:

1. well differentiated endocrine tumours
2. well differentiated endocrine carcinoma
3. endocrine carcinoma of the pancreas and digestive organs (non-functioning)
4. the endocrine carcinoma of the pancreas and digestive tract (functioning) (Table 1).

Well differentiated endocrine tumours are less aggressive than poorly differentiated endocrine tumours, indicated by their lower Ki67 index.[29]

The age standardised incidence rates within the well differentiated endocrine tumours

showed a difference between the different EU regions (Table 5). The difference for the well differentiated endocrine carcinoma of the pancreas and digestive tract (non-functioning) was most marked. The highest age adjusted rate was found in the Northern Europe and the lowest rate was found for the Eastern Europe region. Unfortunately, we could not find studies confirming this result. For both regions the percentage of histologically verified cases was similar. The difficulties in reaching a diagnosis (by non-expert pathologists or limited diagnostic mean available), the availability of organised NET centres, the use of endoscopic surveillance or the existence of national hereditary screening programs could all contribute to explain the observed difference in incidence. Differences in incidence could also be due to different distribution of risk factors in the population, however, limited information is available on NET risk factors. An important limitation of this study is that the Eastern region is represented by only four CRs, in contrast to the Northern EU region, represented by National CRs including the whole population of those countries.

Our data are consistent with the literature for the majority of well differentiated endocrine tumours.[30] The literature for carcinoids shows a wide variation in survival rates, related to the different sites in which carcinoids have been found.[31] In our study, the survival for well differentiated endocrine tumours of the digestive tract was 52% for the functioning tumours and 64% for non-functioning, respectively. For the other sites, 5 year relative survival was of 30% (Fig. 1). This low survival can be explained by two facts. Most carcinoids are diagnosed having already metastasised,[30] resulting in limited possibilities for potentially curative treatment.[31] For example, surgery is considered an effective treatment in early stage NETs, but once metastasised there are limited options for potentially curative treatment. Single agent chemotherapy, results in very low response rates of about 10%.[31]

Secondly, the majority of the carcinoids with poor prognosis are those of unknown primary site (ICD-O-3 code C80.9).

Results on incidence, prevalence and survival for the endocrine atypical carcinoid tumours should be interpreted with caution as they were based on a very limited number of cases (N = 6 in three differentiated sites). However, this is the first time these outcomes are reported.

The poorly differentiated endocrine carcinomas are characterised by a high grade of malignancy and poor prognosis.[32] Our study reported a 5-year relative survival of 12%. As the expected number of incident cases covers over 20% of all expected cases of NETs in EU27 this observation seriously affects the overall 5 year relative survival of NETs. We found a predominance in men (1:0.6) and a peak incidence in people older than 65 years. This male predominance was also found by other studies.[33,34]

Endocrine carcinoma of the thyroid, mainly including medullary carcinomas with amyloid stroma, represented just over 8.5% of the total number of NETs. A female predominance and an increase in age standardised incidence rate through age was found, confirming results seen elsewhere in the literature.[35,36] A pooled analysis of 14 different case control studies in different continents found a relationship between having a first child after the age of 25 years and a significantly increased risk for developing medullary thyroid cancer.[36] This could partly

explain the rise in incidence for the female gender through age.

The survival analyses showed better survival following diagnosis at a younger age (ranging from 100% for the age group 0–14 to 70% for the age group >65). This higher survival in age 0–14 might be affected by standardised surveillance programmes, which allows the early detection of micro carcinomas and the possibilities for a complete cure.[37] These cases of early detection are included in our analyses. The literature reports 25% of all medullary thyroid carcinomas being familial.[38,39] These results found are in line with a population based study which included the SEER population for the period 1973–1991.[35]

The 5 year relative survival of the endocrine carcinoma of the thyroid gland (82%) was by far the best seen within NETs (Fig. 1). It is well known that surgery after early detection of thyroid medullary carcinomas offers a near 100% cure rate.[40]

Mixed endocrine–exocrine carcinomas are rare pancreatic neoplasms and most arise as a single type cell, either from the endocrine or exocrine pancreas. To make an accurate diagnosis of these tumours is difficult, because a lesion is only categorised to be a mixed endocrine– exocrine carcinoma when the endocrine cells exceed 25–30% of the tumour[41] and complete resection of the tumour is needed for the final diagnosis. We only identified 18 cases of mixed endocrine–exocrine carcinoma, so no conclusions can be drawn. However, for the mixed endocrine–exocrine carcinomas 89% of the cases included were microscopically verified. We found similar results on survival compared to the study done by Yao et al.,[27] who report a median survival of 135 months. Both, Yao et al. and our study found that mixed forms have a survival similar to well differentiated carcinoid tumours.[27]

Endocrine carcinoma of the skin mainly includes the Merkel cell carcinoma which has an aggressive behaviour.[42] We found an annual incidence rate of 1.3/ 1,000,000, resulting in an estimated number of 600 Merkel cell carcinomas each year in the EU27, with a highest incidence in the age category 65+. The 5 year relative survival of 58% was consistent with the 59% reported in previous studies.[43–46] The Finnish cancer registry found a small predominance in female and a mean age of 76 years at time of diagnosis.[45] This small discrepancy in relation to our study might be caused by the fact that the Finnish cancer registry only included 181 cases of Merkel cell carcinomas, while we observed 1079 Merkel cell carcinomas within our study.

Classifying NETs is an on-going debate.[47] In 2010 the WHO has presented a new classification of NETs in the digestive tract[48], while the classification for NETs of the lung has already existed since 1994.[49] The evolution of the classification of NETs is still incomplete, for example different anatomic site (such as lung) still use different terminologies. This paper, far from trying to resolve such issues, may contribute to improve data quality on this important subset of cancers. We would encourage this debate by publishing population based data collected by CRs all over Europe, showing results based on a relatively large number of cases for a relatively rare tumour.

From the quality check conducted by the RARECARE study we can conclude that despite 97% of the cases being histologically confirmed, the completeness of case ascertainment of NETs is still not always being achieved.[50] It is extremely important that in future

classification nomenclatures become homogenous for all anatomic sites. In addition strong educational efforts should be made in order to familiarise with punctual registration of key prognostic factors such as mitotic count as well as Ki67 labelling index.
In contrast to previous studies, usually based on small numbers of cases, our study is based on a large series of patients. Because of the complexity and lack of knowledge of the different disciplines involved in the management of NETs, a multidisciplinary approach on NETs is desirable.[51] To support this multidisciplinary approach, highly qualified reference centres, guidelines and an international network between those centres is recommended.[18]

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Conflict of interest statement

The authors declare no conflicts of interest. The founding sources had no role in study design, data collection, data analysis, data interpretation, in writing this report, or in the decision to submit for publication.

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Chapter 7

Invasive extra-mammary Paget's disease and the risk for secondary tumours in Europe

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Abstract

The aim of this study was to determine the incidence and survival of Extra-mammary Paget's disease (EMPD) and to describe the possible increased risk of tumours after EMPD.

All invasive cases diagnosed between 1990 and 2002 were selected from the RARECARE database. Incidence was expressed in European standardized rates. Relative survival was calculated for the period 1995-1999, with a follow-up until 31st December 2003. Standardized incidence ratios of second primary tumours were calculated to reveal possible increased risk after EMPD.

European age standardized Incidence of EMPD within Europe is 0.6 per 1000,000 person-years. Five-year relative survival for invasive EMPD was 91.2% (95%CI; 83.5-95.4), 8.6 percent of the EMPD patients developed other malignancies. The highest increased risk of developing a second primary tumour was found in the first year of follow-up (SIR:2.0 95%CI; 1.3-2.9), living in the South European region (SIR:2.3 95%CI; 1.5-3.5) or being female (SIR:1.5 95%CI; 1.1-1.9). Female genital organs displayed greatest increased risk of developing a second primary tumour after EMPD (SIR:15,1 95%CI; 0.38-84.2).

Due to the increased risk of a second primary tumour after EMPD a thorough search for other tumours during their follow-up is recommended.

Introduction

Extra-mammary Paget's Disease (EMPD) is a rare tumour whose precise incidence is not clear[1] because of the non specific clinical findings of EMPD, which easily lead to wrong diagnoses.[2] EMPD mostly affects individuals between the ages 50 and 80 years and is more frequently diagnosed in women than men.[2]

In 1874, James Paget described Mammary Paget's Disease (MPD) as a chronic disease of the skin of the nipple and areola only.[3] In 1888, during a meeting of the Pathological Society of London, Crocker presented a special case of MPD, which was located on the scrotum and penis in a goldsmith, aged sixty years old.[4] In 1889, Crocker officially described EMPD as a special form of ductal carcinoma involving other parts of the body than the breast, as first described by James Paget.[3] The clinical symptoms, eczema-like lesions, had clinical and histological features similar to those of MPD.[4] Histological EMPD is described as a cutaneous adenocarcinoma with typical Paget cells,[5-7] i.e. large cells with large nuclei and abundant cytoplasm which usually stain pale. It occurs with preference in skin zones rich of apocrine glands, but can occur anywhere on the skin or mucosa. Its most common visible symptom of EMPD is signs of pruritus,[6] and it occurs mainly among the elderly, with a higher risk seen in Caucasian women in their 60s and 70s.[8]

Since a possible association with other malignancies, before or after diagnosis of EMPD, has been described,[7,9] a thorough physical examination with a 5-year follow-up after diagnosis has been recommended for patients being diagnosed with EMPD, to discover other regional rectal, urothelial or vulvar malignancies at time of diagnoses or during follow-up.[7,10] The location of the underlying internal malignancy is often linked to the location of the EMPD: a perianal location may signify a malignancy of the gastrointestinal tract and a penile, scrotal or groin location may be associated with an adenocarcinoma of the genitourinary tract.[5]

As it is a rare cancer, no clear guidelines have been established for diagnosis, treatment and follow-up of patients, presenting a challenge for clinical practice, and research is often confined to case reports or small retrospective studies.

The RARECARE database, a European database that contains data from a large group of European cancer registries (CRs), has been developed to describe the burden of rare cancers and allows comparison of different European regions. Furthermore, it allows comparison between countries with different Gross Domestic Products (GDP) and Total National Expenditure on Health (TNEH), which could influence the survival.

The aim of this population-based study was to describe the incidence, survival and risk of developing other malignancies in patients with EMPD within Europe based on the RARECARE database.

Patients and methods

Patients

Data on patients diagnosed with invasive EMPD were provided by European population-based CRs which participated in the RARECARE project. Only registries with detailed data on morphology available were included, resulting in 63 population-based CRs from 16 different European countries. Period coverage of the different registries participating in the RARECARE project is described in Table 1. These were divided into four regions following the EUROCARE project;[11] Northern Europe (Sweden, Norway and Iceland), UK and Ireland (United Kingdom, Ireland), Central Europe (Austria, Belgium, France, Germany, the Netherlands, Switzerland) and Southern Europe (Italy, Malta, Portugal, Slovenia, Spain). For this study, Eastern Europe was not considered as a separate region because only three registries with a few cases could be included, even though these registries are included in the EU overall region.

Data on the macro indicators Gross Domestic Product (GDP) and Total National Expenditure on Health (TNEH) per country was provided by the Organisation for Economic Co-operation and Development (OECD).[12] The GDP and TNEH were categorised in three different levels following the RARECARE project.[13]

Between the 1st of January 1990 and the 31st of December 2002 all participating registries had good equal coverage of data for all participating registries and all cases of invasive EMPD diagnosed in this period were included.

EMPD cases were defined by morphological code 8542 in the third edition of the International Classification of Diseases for Oncology (ICD-O-3),[14] consistent in all the 3 revisions. All cases were histologically confirmed, and excluded if registered based on death certificate only. In total 871 patients with invasive EMPD were diagnosed and included in the period 1990-2002 as a primary malignancy.

For the 5-year cohort survival analyses we used the coverage period 1995-1999, in accordance with the RARECARE project, representing the latest data available included in the RARECARE database. Follow-up was complete until 31 December 2003, resulting in a minimum follow-up time of 4 years.

For the patients included in this study we also analysed all subsequent cancers. Malignant tumours simultaneously diagnosed with the EMPD were counted as a second primary tumour with a follow-up time of zero.

Statistical analyses

Crude incidence rates, age standardized incidence rates and relative survival analyses were calculated by using SEER*stat.[15] The European standardized incidence rate was calculated by age standardisation according to the European Standard Population, STATA version 9.[16]

Relative survival for EMPD was estimated according to the Hakulinen method.[17] The effects of age and gender were determined.

The standardized incidence ratio (SIR) was used to assess the possible increased occurrence

Country	Registry	Part period	N
Northern EU N = 174572328			
Iceland	Iceland	1990-2002	3,504,591
Norway	Norway	1990-2002	56,906,123
Sweden	Sweden	1990-2002	114,161,614
UK and Ireland N = 467814624			
Ireland	Ireland	1994-2002	33,392,186
UK England	UK_East Anglia	1990-2002	31,447,351
	Yorkshire	1990-2002	62,128,982
	UK_Oxford	1990-2002	34,418,304
	UK_South Western	1990-1999	64,946,933
	UK_Trent	1990-2000	52,449,975
	UK_West Midlands	1990-2002	68,557,863
UK N-Ireland	UK_Northern Ireland	1993-2002	16,687,081
UK Scotland	UK_Scotland	1990-2002	66,055,070
UK Wales	UK_Wales	1990-2002	37,730,879
Central EU N = 268438850			
Austria	Austria	1990-2002	103,279,823
Belgium	Flanders	1997-2001	29,667,826
France	Bas Rhin	1990-1997	7,854,673
	Doubs	1990-1997	3,933,278
	Haut Rhin	1990-1997	5,487,824
	Herault	1995-1997	2,583,988
	Isere	1990-1997	8,375,975
	Manche	1994-1997	1,921,214
	Somme	1990-1997	4,404,764
	Tarn	1990-1997	2,738,395
Germany	Saarland	1990-2002	13,994,615
Netherlands	Amsterdam	1990-2002	35,773,250
	Eindhoven	1990-2001	11,425,011
	North Netherlands	1995-2001	11,501,474
Switzerland	Basel	1990-2001	5,209,369
	Geneva	1990-2002	5,189,759
	St. Gallen	1990-2002	6,602,319
	Ticino	1996-2002	2,159,114
	Valais	1990-1999	2,657,940

Country	Registry	Part period	N
Southern EU N = 220209762			
Italy	Alto Adige	1995-2002	3,678,239
	Biella	1995-2002	1,514,102
	Ferrara	1991-2002	4,240,039
	Firenze	1990-2002	15,070,157
	Friuli V.G.	1995-2002	9,507,797
	Genova	1990-2000	9,416,933
	Macerata	1991-1999	2,632,596
	Modena	1990-2002	8,031,077
	Napoli	1996-2000	2,700,828
	Parma	1990-2002	5,137,440
	Ragusa	1990-2002	3,807,761
	Reggio Emilia	1996-2002	3,153,367
	Romagna	1990-2002	11,762,482
	Salerno	1996-2001	6,525,709
	Sassari	1992-2002	5,160,911
	Torino	1990-2001	11,179,984
	Trento	1995-2000	2,761,003
	Umbria	1994-2002	7,478,732
	Varese	1990-2002	8,850,925
	Veneto	1990-2002	23,867,456
Malta	Malta	1993-2002	3,768,270
Portugal	South Portugal	1998-1999	8,803,804
Slovenia	Slovenia	1990-2002	25,877,585
Spain	Basque Country	1991-1999	18,864,835
	Girona	1994-2002	4,804,389
	Murcia	1995-1998	4,374,754
	Navarra	1990-1999	5,255,593
	Tarragona	1990-1999	5,661,233
Other registries			
Poland	Cracow	1990-2002	9,624,286
	Kielce	1995-2002	9,890,783
	Warsaw	1990-2002	21,221,388

Table 1: Included participating registries per region, years of data coverage and N per region and registry during the period 1990-2002.

of cancer in patients with EMPD. This expresses the occurrence of cancer in this patient group relative to what would have been expected in the general population, based on the EU regions according to the participating registries (Table 1), matched by age class and sex. The SIR was calculated for specific cancer sites according to the ICD-O-3[14] to evaluate possible tumour site-specific elevated risks, we did not differentiate for histology. All SIR analyses were conducted using STATA version 9.[16]

Results

Incidence

In the 13-year period, 871 cases of EMPD were registered as primary malignancy (male to female ratio 1:2.8; Table 2). The median age at diagnosis for EMPD for females (n=640) was 74 years (range 36-96 years), similar to the median age for males (n=231) (range 16-95 years).

All Tumours		**Male**	**Female**
Age (yrs)	Range	16-95	36-96
	Median	74	74
Age group	0-64	43	166
	65+	188	474
Localisation	Rectum	0	1
	Anus and Anal Canal	19	21
	Extragenital skin	108	70
	Eyelid	0	1
	Other unspec part of face	0	4
	Skin of trunk	84	55
	Skin of upper limp and shoulder	3	2
	Skin of lower limp and hip	8	3
	Overlapping lesion of skin	3	1
	Skin not otherwise specified	10	4
	Breast	0	8
	Penis	27	0
	Vulva	0	533
	Vagina	0	0
	Female gen tracta	0	3
	Other ill defined sitesb	0	3
	Male genitals (no penis)c	72	0
	Pelvis	3	0
	Unknown	2	1

a Cases counted in: Female genital tract NOS {857}. b Cases counted in: Thorax, Pelvis (857)

c Cases counted in: Scrotum, Other specified parts of male genital organs, Male genital organs NOS {857}.

Table 2: Invasive EMPD overall primary tumours

The most frequent parts of the body in which EMPD occurred were the anus and anal canal (n=40), extragenital skin (n=178), vulva(n=533) and other and unspecified male genital organs (n=72) (Table 2). For females, invasive EMPD 15% of the primary tumours is not located on a gender related site while this is 55% in males.

The mean RARECARE population consisted of 90,163,609 people over the 13 years selected (male to female ratio 1:1).[13] This yields, for the overall EU region, a crude incidence rate of 0.7 per 1,000,000 person-years and a ESR of 0.6 per 1,000,000 person-years (Table 3). In females, the EMPD in the Overall EU region have a crude incidence rate of 0.7 per 1,000,000 person-years. For males there is a large difference in European Standardized Rate (ESR) between Northern EU (0.7 per 1,000,000 person-years) and other regions. A less obvious but somewhat higher ESR was seen in the UK and Ireland region (0.9 per 1,000,000 person-years) in females. For the female ESR in EMPD as well in both sexes combined, the relatively low rate in the Central EU is worthy of note.

Region 1990-2002	Male	Female	Male and female
	(n/ESR)	(n/ESR)	Crude/ESR
Northern EU	79/0.73	103/0.68	1.04/0.70
UK and Ireland	77/0.30	293/0.86	0.79/0.60
Central EU	35/0.26	109/0.57	0.54/0.43
Southern EU	38/0.28	130/0.78	0.76/0.55
Overall EU	231/0.35	640/0.73	0.74/0.56

Northern EU: Sweden, Norway and Iceland (N = 174,572,328*).

UK and Ireland: United Kingdom, Ireland (N = 467,814,624*).

Central EU: Austria, Belgium, France, Germany, Netherlands, Switzerland (N = 268,438,850*).

Southern EU: Italy, Malta, Portugal, Slovenia, Spain (N = 220,209,762*).

Overall EU: Northern EU, UK and Ireland, Central EU, Southern EU, Poland (N =1,171,772,021*).

*The sum of the populations for all years included in the calculation of the associated rate.

Table 3: Count and rate per 1,000,000 person-years for EMPD per EU region for the period 1990-2002

Survival

Five-year relative survival for patients with EMPD diagnosed in 1995-1999 was higher in females than males (Table 4), and was almost similar for patients aged older than 65 years (91.9%; 95%CI: 80.5-96.8) and for those between 25 and 64 years of age (89.5%; 95%CI: 80.1-94.6).

There is a slight difference between the different EU regions, with the UK and Northern Ireland having the highest 5-year survival for EMPD.

Although patients included in the high GDP and high TNEH both have a markedly lower 5-year relative survival rate than the patients included in the middle and low groups of GDP and TNEH, none of these differences were statistically significant.

All tumours		N	Relative
Overall		439	91.2%
Sex	Male	115	85.6%
	Female	324	92.9%
Age cat	Agecat 25e64	105	89.5%
	Agecat 65+	334	91.9%
Eu region	Northern Europe	102	84.0%
	Central Europe	70	93.1%
	Southern Europe	94	91.1%
	UK and Northern Ireland	170	95.0%
	EU Overall	439	91.2%
Gross domestic product	Low GDP 0-20,000	32	95.5%
	Middle GDP 20,000-25,000	321	92.4%
	High GDP > 25,000	85	83.6%
Total National Expenditure on Health	TNEH low 0-1500	32	95.5%
	TNEH middle > 1501-2250	330	91.2%
	TNEH high > 2250	76	88.4%

Table 4: 5 yr relative cohort survival for invasive EMPD (1995-1999) with different indicators calculated using Hakulinen method.[17]

Risk for a second primary tumour

Table 5 shows that, after EMPD, 75 cases of new primary tumours were observed (male to female ratio 1:2.3). For females who had a second primary tumour after being diagnosed with EMPD (n=52), it took an average of 37 months (range 0-129 months) before a second primary tumour was diagnosed. For males who had a second primary tumour after being diagnosed with EMPD (n=23), this took an average of 26 months (range 0-64 months). Four women and two men were diagnosed with EMPD at same time as for the second primary tumour and therefore counted as 0 months between EMPD and their second primary tumour. The most frequent topographies, following the ICD-O-3, in which the second primary tumours occurred after being diagnosed with EMPD were the extragenital skin (n = 21), the breast (n=13) and bladder (n=6). The 21 cases of extragenital skin can be divided into several topographies; 6 cases on the skin of trunk, 4 cases on the skin of other and unspecified parts of the face, 3 cases on the skin of the lower limb and hip, 2 cases the eyelid and on the skin of scalp and the upper limb and shoulder. The other single cases represented a case on the external ear and on the overlapping lesion of skin.

Compared to the standard population all EMPD patients had an increased risk of developing a second primary tumour (SIR 1.4; 95%CI: 1.1-1.7; Table 5). This risk was particularly high in the South European countries (SIR: 2.3; 95%CI: 1.5-3.5). In other areas, the SIR was also greater than 1, but not significant. Women had a significantly increased risk of developing a second primary cancer (SIR: 1.5; 95%CI: 1.1-1.9), for male patients there were no significant risks. In

EMPD patients aged 61 to 79 the risk of developing a second primary tumour after an EMPD was significantly higher (age cat 61-79 SIR 1.5; 95%CI: 1.1-2.0). People diagnosed with EMPD appear to have a lower risk of developing a new primary tumour in the connective tissue (SIR: 0.13; 95%CI: 0.0-0.7). The risk is significant and strongly increased for women developing a second primary tumour on the female genitals (SIR: 15.1; 95%CI: 0.38-84.2), unfortunately only the results on the Connective tissue were significant.

All tumours		Cases observed	Cases expected	SIR	95%CI
Overall		75	53	1.39[a]	1.11-1.73
Age cat	0-60	9	5	1.82	0.83-3.45
	61-79	51	34	1.54[a]	1.14-2.02
	80-84	12	8	1.42	0.73-2.48
	85+	3	7	0.41	0.09-1.21
Sex	Male	23	18	1.24	0.79-1.87
	Female	52	35	1.47[a]	1.10-1.93
Years of	0-1 yr	25	13	1.99[a]	1.29-2.94
follow up	1-5 yr	37	31	1.17	0.93-1.63
	5-10 yr	12	9	1.33	0.66-2.23
	10-15 yr	1	1	1.81	0.05-10.11
EU region	Northern EU	13	12	1.11	0.66-1.77
	UK and Ireland	29	24	1.21	0.81-1.74
	Central EU	10	9	1.1	0.60-2.16
	Southern EU	23	10	2.31[a]	1.46-3.46
Topography	Colon	4	5	0.82	0.82-2.10
	Rectum	3	2	1.69	0.46-4.32
	Lung	3	5	0.61	0.13-1.77
	Connective tissue	1	8	0.13[a]	0.00-0.73
	Breast	13	7	1.87	0.99-3.20
	Female genital/other [b]	1	0	15.12	0.38-84.23
	Vulva	1	0	3.38	0.09-18.81
	Bladder	6	2	2.4	0.88-5.22

a Significant.

b Female only.

Table 5: Standardized incidence ratio (SIR) per indicator on developing a second primary cancer after EMPD.

Discussion

This study compiles a unique large number of patients diagnosed with EMPD using the data of the RARECARE database, enabling coverage of a mean population of 90,163,609 people over 13 years. Siesling et al. and Pierie et al. presented data on invasive EMPD as well EMPD in situ, reporting a distribution of 1:3.7 and 1:1.8 respectively.[7,18] We had to exclude the EMPD in situ for analyses as we have no information on how the different cancer CRs distinguished the EMPD in situ from invasive EMPD; some registries did not report any case of EMPD in situ, suggesting that those registries report the invasive EMPDs only. Cases of EMPD that were histologically confirmed were included. A much higher incidence in women than in men was revealed, which is consistent with previous literature describing the epidemiology of EMPD.[1,2,5,7] Pierie et al.[18] found a much greater predominance of EMPD in women than we did in our study, possibly due to the smaller sample size in his study. The preferred location in which most EMPD occurs is the anus and anal canal, extragenital skin, vulva in women and the male genitals (except penis), confirming findings in other studies.[2,5-7] The vulva and the male genital organs also includes the genital skin, as we were not able to differentiate for skin within these specific localisations.

Five-year relative survival in EMPD was higher in females than males, and almost the same for patients under the age of 65 and above. In this study, we found a difference in survival for people with EMPD between the different EU regions. This difference might be caused by the localisation of the EMPD. In the Northern EU region, a relatively high percentage of EMPD was located in the skin, in contrast to the UK and Ireland region. The opposite was found for the vulva, in which the Northern EU region had a relative low percentage of cases. Even more remarkable is the difference in survival between the patients included in the different levels of GDP and TNEH. In part this can be explained by the limitation that RARECARE presented GDP and TNEH as two separate indicators without making a correction for the difference in relative cost for healthcare per country. As this has never been described before, the relation between these results in survival needs further research.

The group with middle GDP and middle TNEH display almost similar 5-year survival rates, respectively based on 321 and 330 counts (95%CI: 82.7-96.8 and 95%CI: 81.8-95.9 respectively) (Table 4). EMPD is known as a slow growing disease with low mortality figures,[19] unfortunately we do not have any data on stage or extent of disease at the moment of diagnosis. Therefore retrieving stage at diagnosis and longer follow-up could probably of help to better explain our results.

Another finding in this study is the overall higher risk of developing a second primary tumour among people being diagnosed with EMPD compared to the standard population. Significant results of an increasing risk of developing a second primary tumour were found in patients aged 61-79 years old (SIR; 1.5 95%CI: 1.1-2.0). The part of the body most at risk of developing a second primary tumour after an EMPD is the female genital organs (SIR 15.1; 95%CI: 0.4-84.2) in contrast to the connective tissue, that has a strong decreased risk in comparison to the

standard population (SIR 0.13; 95%CI: 0.0-0.7). A twofold increased risk of developing a second primary tumour after an EMPD was found between the Northern EU region (SIR 1.1 95%CI: 0.7-1.7) and the Southern EU region (SIR 2.3 95%CI 1.5-3.5). The same is found between the Central EU region (SIR 1.1 95%CI: 0.6-2.2) and the Southern EU region. Unfortunately there are no other studies accessing EU data upon EMPD stratifying for the different EU regions to confirm our findings. As the number of cases used for analyses is very low, the difference group composition within the different EU regions can cause major effect in the results shown. The increased risk of developing a second primary tumour on the female genital organs after an EMPD was also found by Siesling et al.[7] Unfortunately we did not include data on histology type therefore we did not differentiate on morphology for the second primary tumours, it would be a good suggestion for future research to get more in detailed information on morphology even some pathological reviews for the secondary tumour is desirable.

All cancers included were histologically confirmed, a relative easy procedure for EMPD. Therefore, confusion with other diagnosis, such as Bowen's disease, superficial spreading melanoma and pagetoid spread of visceral carcinoma[20,21] is not expected. The only complexity that might occur is determining the original localisation of the tumour, as this requires specialised immunostaining techniques. Therefore we cannot exclude that bias might have occurred for the primary localisation of the EMPD used for analyses. For example we cannot rule out that metastases might have been included accidentally.

For EMPD we can state that differences between countries in incidence, survival and standardized incidence ratios can be seen. However, as we cannot rule out that the reliability of data may vary between cancer registry (CR) and regions, partly explains the reported differences. It is important to state that we need to be cautious giving and interpreting the results related to the different European regions.

Finally we analysed relative recent data with a limited follow-up period: we expect some patients to develop new primaries in over 15 years after initial treatment.[21] Nevertheless, the highest SIR in follow-up was found in the first year after diagnosing the EMPD, indicating that the existence of other primaries at the time the EMPD was diagnosed is very likely.

In conclusion, the risk of a new primary tumour after EMPD is increased compared to the standard population. Consequently, a thorough search for other tumours during the follow-up of EMPD patients should be considered. The risk of a second primary tumour is present mainly in women, predominantly affecting the genital tract, and most commonly presents within the first year of followup after being diagnosed with EMPD.

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Conflict of interest

None.

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Chapter 8

Summary, general discussion and future perspective

Summary

The widespread incidence and effects of cancer[1] have led to a growing development in cancer prevention in the form of screening and research programs and cancer registries. Because of the low number of patients with rare cancers this improvement is not applied to the same extent to all cancer patients. This thesis has operationalized the definition of rare cancer and the proposed list of cancers as presented by the RARECARE project. Using this definition and the RARECARE list of cancers we found that in Europe about half a million new patients are annually diagnosed with a rare cancer. Calculation of the complete prevalence indicated that over 4 million people who have been diagnosed with a rare type of cancer are still alive today.

With this thesis we aimed to estimate the burden of rare cancers in general as well as some specific tumours in particular. We defined the burden of these rare cancers in terms of their incidence, prevalence and disease specific rates of survival. Moreover, demonstrating the use of European data sets on very rare cancers, we determined the incidence and survival of invasive extra-mammary Paget's disease (EMPD) and calculated patients' risk of developing secondary tumours after EMPD.

Chapter 1 covers the introduction with the aims and outline of this thesis.

Part I Definition of rare cancer

In **chapter 2** the RARECARE definition of rare cancers (incidence <6 cases per 100,000 person-years) was applied to the RARECARE list of cancers. The observed annual incidence of all rare cancers in the EU was 541,000 new diagnoses, which is 22% of all cancers. In 2008 an estimated 4,300,000 patients were living with a diagnosis of a rare cancer in the EU, 24% of the total cancer prevalence. The five-year relative survival, which approximates disease-specific survival, was lower for rare cancers (47%) than for common cancers (65%). These estimates provide the first indication of the extent of the public health problem caused by rare cancers and constitute a useful basis for further research.

In **chapter 3** the new RARECARE definition of rare cancers was applied to the Dutch population in order to determine the usefulness of the definition in a single country and to estimate the particular incidence of rare cancers in the Netherlands. Data from 2004 through 2008 were extracted from the Netherlands Cancer Registry (NCR) and classified according to the RARECARE list of cancers. Crude and European-standardized incidence rates were calculated. Of the 260 tumour entities defined by RARECARE, 223 (86%) were rare according to the RARECARE definition, accounting annually for 14,000 cancers (17%). Over several years considerable fluctuations in crude rates were seen for the major group of cancers. Therefore, we recommend using a mean incidence over 5 years; this will give more solid insight into

the burden, eliminating the large fluctuations in time of most of the cancers. In addition, the population at risk should be better defined; the proposed RARECARE definition of rare cancers include the total population as population at risk, also for gender related cancer types.

Part II Tumour specific outcome and burden of disease

In **chapter 4** a total of 17,688 rare thoracic cancers cases were analysed. Mesothelioma was the most common tumour (19 cases per million person-years), followed by epithelial tumours of the trachea and thymus (1.3 and 1.7 cases per million person-years respectively). The age-standardised incidence rates of epithelial tumours of the trachea were twice as high in Eastern and Southern Europe as in the other European regions, 2 cases per million person-years. Epithelial tumours of the thymus had the lowest incidence in Northern and Eastern Europe, the UK and Ireland. The highest incidence of mesothelioma was seen in the UK and Ireland, and the lowest in Eastern Europe. Patients with tumours of the thymus had the best prognosis (1-year relative survival 85%, 5-year relative survival 66%). Five-year relative survival was lowest for the mesothelioma, 5% compared to 14% of patients with tumours of the trachea. Mesothelioma was the most prevalent rare cancer (12,000 cases). With these estimates, prevalence measures for these rare thoracic cancers are made available for the first time.

In **chapter 5** over 33,500 cases with a carcinoma of the endocrine organs were analysed. Incidence rates increased with age and were highest in patients of 65 years or older. In 2003, an estimated 315,000 patients were living in the EU with a past diagnosis of a carcinoma in the endocrine organs. The incidence of carcinoma of the pituitary gland equalled 4 cases per million person-years and showed the strongest decline in survival with increasing age. Thyroid gland carcinoma showed the highest crude incidence rate (40 cases per million person-years). Carcinoma of the parathyroid gland was the rarest endocrine entity (2 cases per ten million person-years). For carcinomas of the adrenal gland, the most remarkable observations showed a higher relative survival for women compared to men (40% compared to 32%, respectively). Overall more high-quality studies of rare cancers, e.g. with additional information on stage and therapeutic approach, are recommended and may be of help in explaining the observed variation in survival.

In **chapter 6** over 20,000 incidences of neuroendocrine tumour (NETs) were analysed and a specific data quality check of NETs was performed. The overall incidence rate for NETs was 25 cases per million person-years. Incidence was highest in patients diagnosed with well-differentiated endocrine carcinomas (non-functioning pancreatic and gastrointestinal tumours) aged 65 years and older (40 per million person-years). In 2003 an estimated 100,000 patients in the EU were living with a past diagnosis of NETs. Overall, NETs had a 5-year relative survival of 50%; survival was low (12%) for poorly differentiated endocrine carcinoma, and relatively high (64%) for well-differentiated carcinoma (non-functioning tumours of the pancreas and

digestive organs). Within NETs, medullar, and mixed medullar and follicular carcinoma of the thyroid gland had the best 5-year relative survival (82%). Because of the lack of knowledge and the high number of different disciplines involved with NETs (as they arise in many organs), a multidisciplinary approach performed in highly qualified reference centres and an international network between those centres is recommended.

In **chapter 7** the aim was to calculate and determine the incidence and survival of invasive extra-mammary Paget's disease (EMPD) within Europe and to describe the possible increased risk of developing secondary tumours after EMPD, since a possible association with other malignancies, before or after diagnosis of EMPD is known to exist.[2,3] The use of the RARECARE database made it possible to study 871 malignant EMPD cases for the period 1990-2002. Incidence was expressed in European standardized rates (ESR). Relative survival was calculated for the period 1995-1999, with a follow-up until December 31, 2003. Standardized incidence ratios (SIR) of second primary tumours were calculated to reveal possible increased risk for secondary primary tumours after EMPD. The ESR was 0.6 new cases per million person-years. Five-year relative survival was 91.2% , 8.6% of the EMPD patients developed other malignancies. The highest increased risk of developing a second primary tumour was found in EMPD patients living in the South European region (SIR:2.3) or being female (SIR:1.5). Female genital organs displayed the greatest increased risk of developing a second primary tumour after EMPD (SIR:15,1). Due to this increased risk a thorough search for other tumours during follow-up is recommended.

General discussion and future perspectives

Part I Definition of rare cancer

Incidence is a better indicator for rare cancers

The use of incidence as indicator for rarity is not self-evident, as in medicine most definitions for rarity are prevalence-based.[4,5] Prevalence is based on the number of newly diagnosed cases in relation to life expectancy, whereas incidence is calculated by the number of new cases per year as observed in the population at risk. In Europe a disease is defined as rare when the prevalence is <50 cases per 100,000 persons.[6] Applying this prevalence-based definition to the RARECARE list of cancers we found the second tier squamous cell carcinoma of the uterus and the cervix, and carcinoma of the thyroid gland, all cancers with a favourable life expectancy, not to be rare despite their low number of newly diagnosed cases per year. On the other hand, more frequently diagnosed tumours with an unfavourable life expectancy, like adenocarcinoma of the stomach, were considered rare based on prevalence, but not rare based on incidence.[7] These findings are related to the fact that life expectancy varies greatly between tumour entities, thus affecting prevalence: as mentioned prevalence is based on number of new cases and life expectancy. The main characteristic of rare cancers is their low frequency, which is independent of their life expectancy. For this reason the use of incidence may be a more useful indicator to define rare cancers; this is also in harmony with the sub-acute clinical course of most rare cancers. The decision to use incidence instead of prevalence to define rare cancers is supported by a study of Greenlee et al[8-10], and confirmed by the RARECARE project.[11]

According to the RARECARE project rare cancers are defined as those cancers with an incidence of <6 cases per 100,000 person-years, corresponding to <30,000 new cases per year in Europe for a single rare cancer type. For the European population it was estimated that over half a million people were newly diagnosed with a rare cancer each year from 1995 to 2002. This implies that about 22% of all newly diagnosed cancers are rare cancers. For the Dutch population the incidence-based definition of rare cancers corresponds to <1,000 new cases for a single rare cancer type in 2015.[12] In the Netherlands an annual average of 14,000 newly diagnosed people with a rare cancer, or 17% of all cancers diagnosed per year, was reported. Differences between the Dutch and European findings are partly related to the different definitions of the population at risk. The proposed RARECARE definition for rare cancers uses the total population to calculate incidence for all cancer types, while for instance for testicular cancer only the male population is at risk. As incidence is calculated using the population at risk, we suggest changing the threshold of <6 new cases per 100,000 person-years to <12 new cases per 100,000 person-years to define rarity for gender-specific cancer types. Assuming the male to female ratio to be 1:1 in the total population, this change results in the same absolute number of new cases yearly, taking into account the population at risk.

Any threshold for rarity is arbitrary

The threshold of <6 new cancer cases per 100,000 person-years was selected by the RARECARE project to draw a line between frequent and rare conditions. Also an incidence threshold of <3 cases per 100,000 person-years was discussed during an expert consensus meeting held in Treviso (Italy).[11] During this meeting experts, including patient advocacy groups, reached a consensus that the threshold of <3 cases per 100,000 person-years does not adequately reflect rarity, as cancers with an incidence between 3 and 6 new cases per 100,000 person-years present the same organisational and clinical difficulties as cancers with an incidence of <3 cases per 100,000 person-years.[11] Overall, the RARECARE project developed a definition for rare cancers that is straightforward and easy to use; nevertheless, any threshold for rarity should be considered as indicative and must be used in the perspective of all complexities faced by rare-cancer patients and clinicians.[13]

To identify the difficulties faced by patients and clinicians due to the rarity of the cancer, the RARECARE project linked the incidence-based threshold to a 3-tier hierarchical list of cancers. This list included 59 first tier tumour groupings and 201 second tier tumour entities, of which a total of 186 entities were rare according to the threshold of <6 new cancer cases per 100,000 person-years. When a first-tier tumour grouping meets the threshold for rarity, the main problems faced by clinicians and patients are related to the referral pattern and organization of healthcare. For these low volume families of cancers it is challenging to develop the necessary expertise to reach a timely and correct diagnosis. It is also challenging to acquire skills in rarely used treatment modalities, as patients and knowledge are spread across different hospitals. When a clinically defined second-tier tumour entity meets the threshold of rarity, among the problems faced by clinicians and patients is a lack of knowledge, as the quality of available evidence tends to be limited; for example, patient volume is necessary to conduct a clinical trial. The third tier includes the separate tumour entities[7] used to construct the first and second tier, and does not represent any rare-cancer related difficulty (see chapter 2 Table 1).

The incidence based definition of rare cancers has important implications

Use of the incidence-based instead of the prevalence-based definition for rare cancers has several consequences. Organisations have developed their strategies based on prevalence. The European Agency for the Evaluation of Medical Products (EMA) promotes orphan drug development for rare diseases based on a prevalence of <50 cases per 100,000 persons. For diseases measuring up to this prevalence-based definition the EMA provides longer market exclusivity, protocol assistance, fee reductions and special funds to support research.[14] The use of a prevalence-based definition for rarity is in line with the chronic course of most rare non-neoplastic diseases, but out of line with the subacute clinical course of most rare cancers. Consequently, cancer types considered rare according to the incidence-based definition but not meeting the prevalence-based definition for rarity cannot make use of the privileges provided by the EMA for rare diseases. For this reason it is vital that the newly developed incidence-

based definition for rare cancers be acknowledged and implemented by organisations like the EMA. To achieve this the leading European clinical societies, like the European SocieTy for Radiotherapy and Oncology (ESTRO), European Society of Pathology (ESP), European Society of Surgical Oncology (ESSO) and the European Society for Medical Oncology (ESMO) should actively support the new definition of rare cancer.

Another implication of using the incidence-based definition of rare cancers is associated with the RARECARE list of cancers. This list is based on historically defined histopathological appearances as described in the most up-to-date ICD-O-3.[15] Increasingly, prognostic and predictive molecular markers are used to better characterize cancer types.[16,17] These recent developments in profiling cancers are expected to provide new understanding of tumour response to therapy and be useful for future classification of cancer. This increased knowledge is expected mainly to affect clinical therapeutic decision-making, which is related to the second-tier tumour entities.[18,19] For example, a more common tumour can become regarded as rare due to a new sub-classification based on recent developments in profiling cancers. Therefore, regularly reassessing and updating of the RARECARE list of cancers, with additional clinically applicable information on genetic and molecular profiles, could support a better tumour characterization and lead to the identification of new second-tier tumour entities.

Part II Tumour-specific outcome and burden of disease

High-quality cancer registry data are important to estimate the burden of rare cancers Population-based cancer registries (CRs) are important for cancer epidemiologists since they are able to provide information on the distribution of cancer in well-defined populations.[20] Moreover, to study rare cancers these population-based CRs provide one of the few possibilities to describe tumour and patient characteristics, interventions and outcomes based on large scale data for rare- cancer patients.[17] The use of CR data makes it possible to interpret some causal relations between observations, as for example the relation between inhaling asbestos and the increased risk of developing mesothelioma; however, these causal relations are always linked with the quality of the items retrospectively collected within the scope of the particular CR (e.g. cancer surveillance, evaluation of cancer control programs, etc.[20]). To improve the data quality of CRs in Europe the European Network of Cancer Registries (ENCR) was founded in 1989.[20] The ENCR contributed to the improvement of CR data by providing generally accepted quality criteria for CRs. For example, percentages of “death certificate only”, “autopsy”, “microscopic verification” and “censoring before 5 years” are now generally used as indicators to make CR data more transparent. A European study conducted by Gatta et al. showed that data for rare cancers were less complete than those for common cancers.[21]

To improve the data quality of all the participating CRs in the RARECARE project, data were checked with special focus on abnormal topography and morphology combinations.[22]

This data check has improved data quality and comparability among CRs, resulting in more reliable study outcomes, as presented in this thesis. Still, these thorough checks do not guarantee that all data are correct, as each CR is dependent on the information available in pathology and hospital records. The standardization and development of electronic pathology records is expected to improve the completeness of tumour information and could prevent inconsistencies. For instance, pre-programmed selection options have progressively increased the ability of pathologists to accurately interpret pathology reports. The risk of using pre-programmed selection options is, however, that exceptions to the majority, like rare cancers, are not well programmed due to lack of knowledge. Together with centralizing standardized and automated data-quality checks implemented in the CRs, databases will support the future data completeness and quality of the CRs, making it possible to study rare cancers more effectively. The future use of electronic hospital records, which could even provide patients with secure access to their own medical files, could also empower patients to take control of their own care process. Moreover, patients could actively include on the electronic file information on, for example, their quality of life. This information could then be used to better support the patients' needs. Including all this information in CRs or providing linkages between CRs and other databases containing detailed patient information is expected to support data quality and enlarge research possibilities.

The RARECARE project is an example of how CR registry data and international collaboration between researchers, clinicians, patients' advocacy groups and policymakers can evolve to an effectively functioning European information network on rare cancers. Fortunately, although the RARECARE project was only a four-year funded initiative, a sequel called RARECARENet was put into place and funded by the European Union (EU) to run the project for four more years. The RARECARENet project maintains and updates the website and the RARECARE list of cancers. Moreover, the RARECARENet project aims to establish an information network for rare cancers, identifying quality criteria for centres and networks of expertise by conducting high resolution studies to collect more detailed CR information. Still, the continuation of activities initiated by both projects is threatened by lack of sustainable funding. Different funding structures must be found to maintain these activities.

Rare cancer diagnosis and treatment require expert insights

The knowledge of rare cancers is limited both among the general public and healthcare professionals.[23] This impedes accurate and timely diagnosis, effective treatment modalities and evidence-based guidelines with the result that patients with a rare cancer often do not receive optimal healthcare. In this thesis we found a less favourable 5-year life expectancy in the group of rare cancer patients (47%) than in the group with common cancers (65%). More specifically, our findings in chapter 4-7 show differences between European regions in relative survival, suggesting inequalities in tumour-specific expertise throughout Europe. For example in chapter 5, Table 4 shows inequalities in survival for patients with epithelial tumours of the

trachea and epithelial tumours of the thymus. Similar results were found for other rare cancers included in the Annex of the technical report of the RARECARE project.[24] To overcome these inequalities it is necessary to establish centres of expertise for rare cancers and international information networks between centres across the EU. This would help to bring about the organisational structure needed to improve accuracy and standardisation of diagnosis, support the development of multidisciplinary healthcare pathways, create critical mass for carrying out clinical trials, and develop alternative study designs and methodological approaches to clinical experimentation for rare-cancer patients.

To support the development of these centres of expertise and international information networks more detailed information is needed. The RARECARE studies provide general information on indicators like incidence, prevalence, survival and mortality. To identify the availability of expertise in the field of rare cancers more (cancer-specific) items are fundamental for the diagnosis, treatment and follow up of patients with rare cancers.[25] This is in line with the aim of the RARECARENet project to build an information network to provide comprehensive information on rare cancers to the community at large (oncologists, general practitioners, researchers, health authorities, patients and their families). More specifically, the RARECARENet will identify and publish qualification criteria of rare cancers for centres of expertise.

Rare cancers give opportunities to develop new research methods

Back in the 17th century William Harvey already noticed the importance of rare diseases. He stated that 'Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease.'[26] Yet all. studies included in this thesis emphasise that only a limited amount of research is available to confirm and discuss the results. Moreover, only a few rare cancers can be treated by therapies proven by randomized clinical trials.[27,28]

The number of large prospective, controlled, randomised trials for rare cancers is low. Because of low patient volume and the scarcity of international initiatives, clinical research into rare cancers is limited, resulting in a negative effect on patients. To overcome the volume-related challenges the scientific field is developing new methodological options to study rare cancers.[29] An overview by Billingham et al.[17] presents several methods applicable to trials for rare cancers, methods that could change clinical practice. One example was to maximise trial duration, as longer follow-up is likely to capture more events per participant.[30,31] Another example was to maximise efficiency, as high quality data and complete follow-up are expected to increase statistical efficiency.[32] Another method, involving use of the Bayesian framework, would allow using a limited population in a randomised clinical trial to test the hypothesis on treatment-

effect size;[30-34] this was a method advocated in reviews as promising for clinical practice in rare cancer settings.[17] To find innovative approaches to research and develop new treatment modalities it could be helpful to share knowledge; such sharing can be supported by information networks between universities responsible for training future scientists. Education is important because our future scientists are the people who will have to continue to overcome challenges and use opportunities to study rare cancers.

Centres of expertise on rare cancers are necessary

It is challenging to make a correct diagnosis and start the best treatment modality for a rare-cancer patient. Different initiatives like The Stichting Oncologische Samenwerking (SONCOS) in the Netherlands[35] and the guidelines to become a European Neuroendocrine Tumor Society (ENETS) centre of excellence for neuroendocrine tumours (NET)[36] have defined the minimum patient volume needed to identify expertise. Especially with respect to gaining skills in less frequently used treatment modalities a higher hospital volume has been associated with better outcome.[37,38] To understand this phenomenon Luft et al already tried to understand the causality between volume and outcome in 1979 and introduced two principles: 'practice makes perfect' and 'selective referral pattern'.[39] The first principle assumes a positive relationship between the frequency of doing something and the development of expertise. The second principle assumes a positive relationship between effective treatment results and attracting new patients. Within these perspectives volume should be considered representative of underlying conditions related to better outcome.[40] Another approach to identify expertise, not using the direct causality between patient volume and expertise, is proposed by the European Union Committee of Experts on Rare Disease (EUCERD). Their recommendations focus mainly on the organisational role which a centre of expertise should fulfil in the field of a rare disease, for example bringing together multidisciplinary and research teams that serve the specific medical rehabilitation and palliative needs of rare-disease patients.[41]

The centralisation of care could be related to the willingness of patients to travel to a centre of expertise. Nevertheless, an English study showed that 53% of the 1,720 respondents included were willing to travel over 2 hours to receive cancer treatment if they thought it would increase their survival outcome.[42] However, this attitude of patients may differ per country. For example the difference in patients' contribution to coverage of treatment costs was not included in this study and could affect a patient's decision to go to a centre of expertise. For the future, possibilities offered by e-health applications are expected to decrease the need of physical traveling to contact expert clinicians.[43] However, for optimal use of e-health applications a thoughtful implementation plan is required. This plan should support both patient and clinician in using these tools. The financial consequences of using e-health applications, as for example the reimbursement of a video consult, should be considered. Moreover, an international approach is required, as for rare cancers the centralisation of care is not restricted to national borders.

Networks of expertise for rare cancers should be developed

Centralising care by identifying centres of expertise for rare cancers may not be enough to overcome the difficulties faced by clinicians and rare-cancer patients. Centralising rare cancers towards the first tier following the RARECARE list of cancers would seem logical, as this tumour grouping is based on the organisational challenges faced by clinicians and patients. The development of dedicated multidisciplinary teams involving all related disciplines for a first-tier group of rare tumours would increase the expertise needed to make correct diagnoses and select the best possible treatment modality. Nevertheless, cancer is a complicated disease and can occur and spread throughout the whole body. It is therefore important to understand who will finally oversee the complete picture and be able to treat rare cancers presenting in more than one specialised area.[44] Centres of expertise should thus be embedded within a network of hospitals covering all the expertise needed for the structures in which a cancer can occur.

The group of very rare cancers face the most severe organisational challenges for centres of expertise. For this group it is desirable to have only a few centres of expertise in the whole of Europe, where patients can be treated within a network of expertise. This network of expertise can be structured according to different levels of expertise, or echelons. The different levels of expertise available in this network give the opportunity to treat a patient with a very rare cancer close to home when possible and far away when needed. For example, a patient with a very rare tumour may undergo surgery at a highly specialised centre of expertise, possibly abroad, but for the follow-up treatment be referred to the local university hospital near where he or she lives. In this perspective centres of expertise should be embedded not only within a national but also an international network of hospitals covering the total patient clinical pathway to guarantee early diagnose, correct treatment and adequate follow-up.

The introduction of international networks of expertise implies the need for patients to go to another country to receive the best treatment available. The Directive 2011/24/EU on the application of patients' rights to cross-border healthcare was adopted in March 2011[45]; it described the right of European citizens to access to and reimbursement of safe and high quality treatment across EU borders. This directive provides a basis for the establishment of European Reference Networks (ERNs) between the different centres to offer the best possible quality of treatment.[23] Such international networks are obligated to harmonize care and improve the quality of care throughout Europe following the patients' clinical pathway. The implication is that, if needed, the patient may travel within Europe to seek for a second opinion, specialised therapies, surgical interventions or to be included in clinical trials not available in his or her own country, all without facing an administrative, legal and medical battle to travel abroad for these purposes. This approach will stimulate the transfer of knowledge from a central network of expertise to associated peripheral centres to offer the patient the best quality of treatment in his local environment.[23]

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Samenvatting

Het grote aantal nieuwe gevallen en de negatieve effecten van kanker[1] hebben geleid tot steeds meer nieuwe ontwikkelingen in screening, onderzoeksprojecten en kankerregistraties. Door de lage aantallen hebben deze ontwikkelingen in mindere mate betrekking op patiënten met een zeldzame vorm van kanker. Dit proefschrift gaat verder in op de door het RARECARE-project nieuw geformuleerde definitie van zeldzame kanker en bijbehorende lijst met de verschillende vormen van kanker. Het toepassen van deze definitie laat zien dat er jaarlijks een half miljoen nieuwe patiënten met een zeldzame vorm kanker in Europa bijkomt. Kijken we naar de prevalentie van zeldzame vormen van kanker, dan blijken er momenteel meer dan vier miljoen Europeanen te zijn die een zeldzame kanker hebben of hebben gehad en leven met de gevolgen daarvan.

Dit proefschrift heeft als doel om de ziektelast van zeldzame kanker in het algemeen en voor een aantal specifieke vormen van zeldzame kanker te beschrijven; zeldzame vormen van kanker in het thoracale gebied, carcinomen van de endocriene organen en neuro-endocriene tumoren. Waar ziektelast een breed begrip is, wordt het in dit proefschrift gedefinieerd in termen van incidentie, prevalentie en overleving. Met de beschikbare Europese data vanuit de RARECARE-database was het tevens mogelijk om de zeer zeldzame extra-mammaire vorm van de ziekte van Paget (EMPD) te bestuderen. Dit proefschrift laat daarmee zien dat door internationale samenwerking en het gebruik van Europese data onderzoek naar zeer zeldzame vormen van kanker mogelijk is.

Hoofdstuk 1 bevat de introductie met de doelstellingen en de opzet van dit proefschrift.

Deel I De definitie van zeldzame kanker

In **hoofdstuk 2** is de nieuwe definitie van zeldzame kanker (incidentie van <6 gevallen per 100.000 persoonsjaren) toegepast op de door RARECARE beschikbaar gestelde lijst met de verschillende vormen van kanker. Als resultaat werden er jaarlijks gemiddeld 541.000 nieuw gediagnosticeerde patiënten met een zeldzame kanker in Europa geobserveerd. Dit is 22% van alle jaarlijkse nieuwe diagnoses. Voor het jaar 2008 schatten we dat 4,3 miljoen Europeanen die ooit gediagnosticeerd zijn met een zeldzame vorm van kanker, nog steeds leven met de gevolgen daarvan. Dit is 24% van de totale prevalentie van kanker. Daarnaast is de 5-jaars relatieve overleving voor patiënten met een zeldzame vorm van kanker minder goed (47%) dan voor patiënten met een veel voorkomende vorm van kanker (65%). Deze bevindingen geven voor het eerst de omvang van het probleem rond zeldzame kanker aan en vormen daarmee een basis voor vervolgonderzoek.

In **hoofdstuk 3** is de door RARECARE nieuw geformuleerde definitie van zeldzame kanker toegepast op de Nederlandse populatie. Hiermee is de incidentie van zeldzame kanker in Nederland berekend en is onderzocht of deze nieuwe definitie ook op een individueel land toepasbaar is. Voor dit onderzoek is data uit de Nederlandse Kankerregistratie (NKR) van de jaren 2004-2008 gebruikt. Om de Nederlandse data met andere landen en de RARECARE-uitkomsten te kunnen vergelijken, is zowel de ongecorrigeerde incidentie als de Europese gestandaardiseerde incidentie uitgerekend. Als resultaat vonden de auteurs dat van de 260 door RARECARE gedefinieerde vormen van kanker er 223 (86%) zeldzaam zijn in Nederland. Dit resulteert in jaarlijks 14.000 nieuwe gevallen van zeldzame kanker, 17% van de totale incidentie in Nederland.

Door de jaren heen worden er voor de meeste vormen van kanker fluctuaties in incidentie geobserveerd. Het wordt dan ook aanbevolen om het gemiddelde van de incidentie over vijf jaar te nemen om zeldzame vormen van kanker te identificeren. Daarnaast adviseren de auteurs om de door RARECARE voorgestelde definitie van zeldzame kanker aan te passen voor geslacht-specifieke vormen van kanker.

Deel II Tumorspecifieke uitkomsten en bijbehorende ziektelast

Hoofdstuk 4 beschrijft middels een analyse 17.688 tumoren de incidentie, prevalentie, overleving en Europese verschillen voor zeldzame vormen van kanker in het thoracale gebied; mesotheliomen, epitheliale kanker van de luchtpijp en epitheliale kanker van de thymus. Binnen deze groep is het mesothelioom de meest voorkomende vorm van kanker (19 nieuwe gevallen per miljoen persoonsjaren), opgevolgd door de epitheliale kanker van de luchtpijp en thymus (1,3 en 1,7 nieuwe gevallen per miljoen persoonsjaren). De leeftijd-gestandaardiseerde incidentie van de epitheliale kanker van de luchtpijp is twee keer zo hoog in Oost- en Zuid-Europa als in de twee andere Europese regio's: twee nieuwe gevallen per miljoen persoonsjaren. Epitheliale kanker van de thymus heeft de laagste incidentie in Noord- en Oost-Europa en het Verenigd Koninkrijk en Ierland. De hoogste incidentie voor het mesothelioom is geobserveerd in het Verenigd Koninkrijk en Ierland en het laagste in Oost-Europa. Patiënten die gediagnostiseerd zijn met een tumor van de thymus hebben de beste overlevingskansen (1-jaarsoverleving van 85% en 66% na 5 jaar). De 5-jaarsoverleving is het laagst voor patiënten gediagnosticeerd met een mesothelioom: 5% in vergelijking met 14% voor patiënten met een tumor van de luchtpijp. Het mesothelioom is de meest prevalente vorm van kanker (12.000 gevallen). Met deze studie komt voor het eerst de prevalentie voor zeldzame vormen van thoracale kanker beschikbaar.

In **hoofdstuk 5** worden meer dan 33.500 carcinomen van de endocriene organen geanalyseerd. De incidentie van deze zeldzame vorm van kanker neemt met de leeftijd toe en is het hoogst in de groep mensen die 65 jaar of ouder zijn. Voor 2003 schatten de onderzoekers dat er 325.000 Europeanen zijn, die ooit gediagnosticeerd zijn met een carcinoom van de endocriene

organen, en nog steeds leven met de gevolgen daarvan. De incidentie voor patiënten met een carcinoom van de hypofyse is 4 nieuwe gevallen per miljoen persoonsjaren en laat de sterkste afname in overleving zien bij toename in leeftijd. Het carcinoom van de schildklier heeft de hoogste ongecorrigeerde incidentie (40 nieuwe gevallen per miljoen persoonsjaren). Het carcinoom van de bijschildklier is de meest zeldzame vorm van kanker (2 nieuwe gevallen per 10 miljoen persoonsjaren). Voor het carcinoom van de bijnieren is de meest opmerkelijke bevinding de betere overleving voor vrouwen in vergelijking tot mannen (40% tegenover 32%). Concluderend wordt de aanbeveling gedaan om meer studies van hoge kwaliteit te doen voor deze zeldzame vormen van kanker. Het breed verzamelen van meer informatie op het gebied van bijvoorbeeld stadiëring en gegeven therapieën wordt aanbevolen.

In **hoofdstuk 6** zijn meer dan 20.000 nieuwe patiënten met een neuro-endocriene tumor (NET) geïncludeerd voor analyse. De totale incidentie voor deze zeldzame vorm van kanker is 25 nieuwe gevallen per miljoen persoonsjaren. De incidentie is het hoogst voor patiënten van 65 jaar of ouder gediagnosticeerd met een goed gedifferentieerd (niet-functionerende pancreas en gastro-intestinaal) endocrien carcinoom (40 per miljoen persoonsjaren). Voor 2003 schatten de onderzoekers dat 100.000 Europeanen die ooit gediagnosticeerd zijn met een zeldzame NET nog steeds leven met de gevolgen ervan. De 5-jaars relatieve overleving voor NET (50%) is relatief ongunstig voor patiënten met een slecht gedifferentieerd endocrien carcinoom (12%) en relatief gunstig voor patiënten met een goed gedifferentieerd (niet-functionerende pancreas en gastro-intestinaal) carcinoom (64%). De beste 5-jaars relatieve overleving is gevonden voor het carcinoom van de schildklier (82%). Gezien de complexiteit en de vele disciplines die betrokken zijn bij het diagnosticeren en behandelen van NET (ze komen in vele organen voor) bevelen de betrokken onderzoekers aan om deze zeldzame vorm van kanker multidisciplinair te benaderen en te behandelen in gekwalificeerde expertisenetwerken. Ook zouden deze centra een informatienetwerk moeten ontwikkelen.

De doelstelling van **hoofdstuk 7** was het berekenen van de incidentie en overleving van de extra-mammaire vorm van de ziekte van Paget (EMPD). In dit hoofdstuk is ook het – in de literatuur aangegeven[2,3] - mogelijk verhoogde risico op het krijgen van een tweede primaire tumor na EMPD geanalyseerd. Dit onderzoek is tevens een voorbeeld van de bijdrage die grote datasets kunnen leveren aan meer gedetailleerd epidemiologisch onderzoek naar zeer zeldzame vormen van kanker. Met gebruik van de RARECARE-database zijn 871 gevallen van EMPD in 1990-2002 in Europa bestudeerd. Incidentie is uitgedrukt in Europese gestandaardiseerde ratio's (ESR). Relatieve overleving is berekend voor de periode 1995-1999 met een follow-up tot 31 december 2003. Gestandaardiseerde incidentieratio's (SIR) zijn berekend om het risico op tweede primaire tumoren na EMPD te achterhalen. De ESR voor EMPD is 0,6 nieuwe gevallen per miljoen persoonsjaren. De 5-jaars relatieve overleving is 91,2 en 8,6% van de EMPD-patiënten ontwikkelde nieuwe tumoren. Het hoogste risico op het ontwikkelen van een tweede primaire tumor na EMPD is gevonden voor de Zuid-Europese regio's en bij vrouwen.

Tweede primaire tumoren in de vrouwelijke genitalia kwamen het meest voor na EMPD. In lijn met de literatuur[2,3] wordt op basis van deze bevindingen aanbevolen om patiënten die gediagnosticeerd zijn met EMPD in de gaten te houden en in follow-up te houden om tweede primaire tumoren na EMPD tijdig waar te kunnen nemen.

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Curriculum Vitae

Johannes Martinus van der Zwan (Jan Maarten) werd op 8 juli 1981 geboren in Amsterdam. Tot zijn negende woonde Jan Maarten in Abcoude, in 1990 verhuisde hij naar Maarssen. Na in 1999 zijn havo-diploma te hebben behaald aan het Niftarlake College te Maarssen is hij begonnen aan de studie fysiotherapie aan de Hogeschool van Amsterdam. Na het succesvol afronden van deze studie koos Jan Maarten er in 2004 voor om als fysiotherapeut in het 'Wasso Hospital' bij de Masaï en Sonjo stam in Tanzania te gaan werken. Deze buitenlandervaring heeft Jan Maarten doen besluiten gezondheidswetenschappen te studeren aan de Vrije Universiteit van Amsterdam. In 2007 werd de master International Public Health afgerond met een eindstage op het hoofdkwartier van de Wereldgezondheidsorganisatie (WHO) in Genève (Zwitserland). Aansluitend op deze studie is Jan Maarten in Enschede bij Integraal Kankercentrum Noord-Oost (IKNO), later Integraal Kankercentrum Nederland (IKNL), begonnen aan het Europese 'RARECARE'-project over zeldzame tumoren. Tevens heeft Jan Maarten naast zijn werkzaamheden als onderzoeker van 2012 tot2015 als IKNL-adviseur en projectleider een inhoudelijke bijdrage geleverd aan de fusie van de afdelingen oncologie van het Scheper Ziekenhuis in Emmen, Ziekenhuis Bethesda in Hoogeveen en het Refaja Ziekenhuis in Stadskanaal. Naast alle inhoudelijke werkzaamheden heeft Jan Maarten van 2012 tot mei 2015 in de ondernemingsraad van IKNL gezeten. Momenteel werkt hij aan het RARECARENet-project. Dit is een vervolg op het RARECARE-project gericht op het identificeren van Europese expertisecentra voor zeldzame tumoren.

Johannes Martinus van der Zwan (Jan Maarten) was born in Amsterdam on the 8th of July 1981. Until his ninth Jan Maarten lived in Abcoude, in 1990 he moved to Maarssen. After completing his secondary education at the Niftarlake College in Maarssen he started his study physical therapy at the University of Applied Sciences (HvA) in Amsterdam in 1999. In 2004, he successfully completed his study and choose to explore new horizons and worked in Tanzania as physical therapist at the 'Wasso Hospital', serving the Massaï and Sonjo tribes. This experience made Jan Maarten to decide to study Health Sciences at the VU University Amsterdam. In 2007 he finished his masters International Public Health doing his final internship at the World Health Organization (WHO) Headquarter in Geneva, Switzerland. Adjacent to his study Jan Maarten joined the 'RARECARE' project studying rare cancers at the Comprehensive Cancer Organisation North-East Netherlands (IKNO), later called Comprehensive Cancer Organisation the Netherlands (IKNL). Besides his activities as researcher Jan Maarten was involved as IKNL consultant and project leader to facilitate the merge of the oncology departments of the Scheper Hospital in Emmen, Hospital Bethesda in Hoogeveen and the Refaja Hospital in Stadskanaal, all in the Netherlands. Jan Maarten had a position at the IKNL Employees Council for the period 2012 until 2015. At the moment he is joining the RARECARENet project, which is a sequel of the RARECARE project focussing on the identification of European centres of expertise for rare cancers.

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