Epidemiology of uncommon male genital cancers

Studies with regional, national and international cancer registry data

Rob Verhoeven

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Epidemiology of Uncommon Male Genital Cancers

Studies with regional, national and international cancer registry data

Epidemiologie van de zeldzame tumoren van de mannelijke genitaliën

Studies met regionale, nationale en internationale kankerregistratie-data

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Contents

Chapter 1

Introduction

In this thesis, I provide detailed information on the epidemic of testicular cancer by presenting age-, stage- and histology-specific trends of incidence, primary treatment, relative survival, and mortality from testicular cancer. In addition, I present descriptive epidemiological studies on two rare urogenital cancers: penile cancer and scrotal cancer. For the latter, I also evaluate whether occupational exposures are still the main risk factor in an era of modern occupational hygiene.

Male genital cancers

The male genital organs

The male genital organs consist of the scrotum, testes, epididymides, ductus deferens, prostate, seminal vesicles, urethra, and the penis (Figure 1). The scrotum is a cutaneous fibromuscular sac that contains the testes and associated structures. The testes produce hormones, principally testosterone, and sperm. The produced sperm is stored in the epididymides. During ejaculation the sperm is moved trough the ductus deferens to the prostate. A thick fluid that mixes with the sperm is secreted by the seminal vesicles. Further on, prostatic fluid is added by the prostate. With an ejaculation the semen leaves the body through the urethra.

Cancer can essentially develop in any part of the human body, so also in any part of the male genital system. With the exception of prostate cancer, cancer in the male genital organs is rather uncommon.

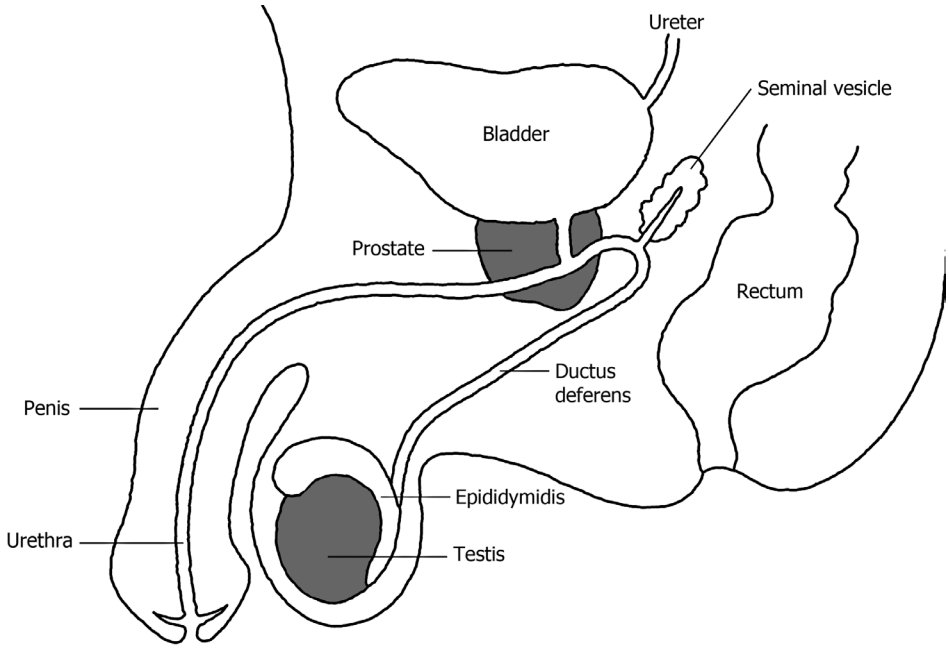

Figure 1. Anatomy of the male genital system

Male genital cancers in the Netherlands

Prostate cancer is the most frequent cancer in Dutch males 21% of the diagnosed tumors in men in 2009 were prostate tumors.[1] The proportions of testicular cancers and penile cancers of all diagnosed tumors in males were only 1.4% and 0.3%, respectively. A total of 10,992 tumors were diagnosed in the male genital organs in the Netherlands in 2009, 10,166 (92%) prostate cancers, 667 (6.1%) testicular cancers, 142 (1.3%) penile cancers and 17 (0.2%) cancers of non-specified or other parts of the male genitals (including the scrotum). The risk for Dutch men of being diagnosed with a prostate tumor is before the age of 85 11.3%; the lifetime risk of being diagnosed with a testicular or penile tumor is 0.6% and 0.1%, respectively.

Testicular cancer

Incidence and prevalence

Although testicular cancer is relatively uncommon, it is the most common malignancy among young men (aged 20-39 years) in the Netherlands.[1] The European age-standardized incidence rate increased from 4.1 per 100,000 person-years in 1989 to 8.5 per 100,000 in 2009. Similar increases have been observed in most Western countries in the last decades. [2, 3] There is also a considerable geographic variation in the incidence of testicular cancer, with high rates in Western countries and much lower rates in most non-Western countries (Figure 2).[4] On January 1st 2010 there were 9071 males living in the Netherlands with a diagnosis of testicular cancer in the past 20 years.

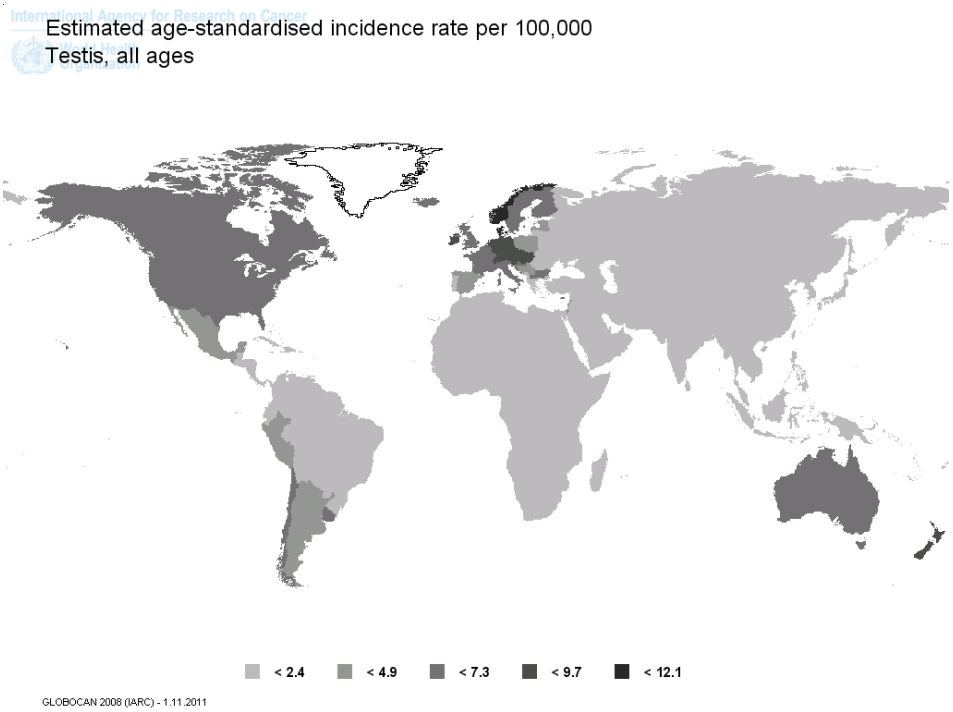

Figure 2. A map of the estimated world age-standardized incidence of testicular cancer in the world (downloaded from http://globocan.iarc.fr)[4]

Risk factors

The etiology of testicular cancer is not well understood. Cryptorchidism, a family history of testicular cancer and a previous history of testicular cancer are well-established risk factors for testicular. These risk factors are however only responsible for a small proportion of the testicular cancer cases and the underlying reasons for the increasing incidence remain elusive.[5] *In utero* or perinatal factors, such as exposure to endocrine disrupters (exogenous estrogens and antiandrogens), high birth weight, low gestational age, low birth order, small sibship size and both younger and older maternal age. It is suggested that a relative excess of estrogens during early pregnancy might be an important cause of testicular cancer.[6] Possible testicular cancer risk factors such as being the first-born and maternal are factors that are related to increased maternal estrogen levels. These factors are in fact thus indicators of exposure to a risk factor for testicular cancer and not risk factors on their own. Although a lot of factors have been studied, the etiology of testicular cancer remains poorly understood.[5, 7]

Treatment

For testicular cancer patients the treatment starts with an orchidectomy, i.e. surgical removal of the testis, which is a diagnostic procedure at the same time. Only in situations where a tumor in the testicles is not palpable and not visible with imaging, and the diagnosis is based on serum markers, the testicles are left *in situ*. Based on histology (seminoma or non-seminoma) and disease stage the further treatment consists of active surveillance, radiotherapy and/or chemotherapy. Patients with a primary seminoma and with affected regional lymph nodes usually receive radiotherapy at the para-aortic lymph nodes. All other patients with regional or distant metastases receive chemotherapy. Effective cisplatin based chemotherapy was introduced in the 1970s. Until the late 1980s most patients received the PVB-regime, which includes cisplatin, vinblastine, and bleomycin, since that time the BEP-regime was used in which the vinblastine was replaced by etoposide.[8]

Survival

Survival of testicular cancer has increased markedly by the introduction of cisplatin-based chemotherapy in the mid 1970s.[8, 9] This resulted in a 5-year relative survival of 96% for adult testicular cancer patients in the Netherlands diagnosed in the period 2004-2008.[1] Due to the effective chemotherapy even patients with the highest TNM-stage (stage III) had a 85% 5-year relative survival in the period 2003-2008.[1] Although survival from testicular cancer is high for most patients, it seems to be lower for patients aged 55 years and older at diagnosis than for younger patients.[10] The exact pattern in which the survival decreases by age is however unknown. One of the aims of this thesis is therefore to evaluate at what age relative survival of testicular cancer became poorer and whether the differences in survival between age groups have become smaller over time.

Penile cancer

Incidence and prevalence

Penile cancer is a rare neoplasm in the Western world with an age-standardized incidence rate of 0.5 to 1.0 per 100,000 men.[11] There is a worldwide geographic variation in incidence that is caused by differences in socio-economic status, hygiene/infections, religious and cultural conditions (circumcision). For example, the incidence of penile cancers is low (0.1

per 100,000 men) in the Jewish population of Israel and high (3 to 4 per 100,000 men) in non-Western countries such as Brazil, Uganda, and Thailand.[11] Although the exact pathogenesis is still largely unknown, inflammation may represent an important component in penile tumor development and progression, as many penile cancers arise at sites of infection, chronic irritation or injury.[12, 13]
On 01-01-2010 there were 955 men alive in the Netherlands who had been diagnosed with penile cancer in the previous 20 years.[1]

Treatment

The standard treatment for an invasive penile tumor is a partial or total penectomy (surgical removal of the penis).[14] Small tumors limited to the foreskin can be treated with a circumcision with a clear tumor-free margin.[15] Laser ablation or radiotherapy has also been used as an alternative for partial amputation in patients with small tumors.[15] Patients with positive lymph nodes usually undergo a radical inguinal lymph node dissection. The management of patients with clinically negative lymph nodes, however, poses a clinical problem. Around 20-25% of these patients might have occult inguinal metastases. Retrospective studies have shown that early removal of these nodes provides a survival benefit compared to removal of the nodes when they become clinically apparent.[16] However an elective inguinal lymph node dissection in all clinical-node negative patients would lead to substantial unnecessary morbidity such as lymph edema and infections.[17]

Survival

For patients with penile cancer the overall 5-year relative survival in the Netherlands was 76% in the period 2004-2008.[1] However, patients with stage III or stage IV disease at diagnosis in the period 2003-2008 (together about 18% of all penile cancer patients) had a 5-year relative survival of only 54% and 20%, respectively.[1] Most available scientific publications on survival of penile cancer are based on patients treated in a single-institution or provide population-based survival estimates without much detail. It is therefore not clear whether the survival of penile cancer at population-level has improved over the last decades.

Scrotal cancer

Incidence and risk factors

The age-standardized incidence rate in the U.S.A. is around 0.1 per 100,000 males and it seems to be slightly increasing.[18] Incidence rates for European countries are unfortunately not available.
In 1775 Pott described a high incidence of scrotal cancer among chimney sweepers.[19] Later, scrotal cancer has also been linked to other occupations, e.g. men who worked with the distillates of coal or mineral oils.[20] Due to improvements in working conditions since the 1960s and 1970s scrotal cancer has become a very rare tumor.[20] Due to a lack of etiologic studies on scrotal cancer since the 1980s, it is uncertain whether occupational exposures are still the most important risk factors for the currently diagnosed scrotal cancers. Therefore one of the aims of this thesis was to study the current risk factors of scrotal cancer.

Treatment

Wide local excision is the primary treatment for patients with a scrotal tumor.[21] For patients with clinically negative nodes there is the same clinical problem as with penile cancer patients with clinically negative nodes. A lymph node dissection might be useful for the removal of occult metastases that occur in some patients, but it might also cause serious morbidity. Scrotal cancer patients with clinically palpable lymph nodes should first receive antibiotics to treat enlarged lymph nodes due to infections. If the nodes remain palpable, an ilioinguinal lymph node dissection is performed.[21]

Survival

There are no useful studies published on population-based relative survival of scrotal cancer. Due to the lack of population-based information on the incidence and survival of scrotal cancer, it is difficult to estimate the burden of scrotal cancer in the present-day world. We therefore aimed to provide detailed population-based information on the incidence, age-, stage-, and histological-distribution, and relative survival of scrotal cancer in the Netherlands.

Cancer registries

For the studies in this thesis data of the Eindhoven Cancer Registry, the Netherlands Cancer Registry, and several international population-based databases have been used.

Eindhoven Cancer Registry

The Eindhoven Cancer Registry (ECR) started in 1955 as part of a program for nation-wide cancer registration. Data on all new cancer patients were collected directly from pathology reports and medical records, sometimes through emerging hospital discharge registries. The registry started in three hospitals in Eindhoven and gradually expanded to include the southeastern part of the province of North Brabant, the northern part of the province of Limburg (since 1970) and the middle and southwestern part of North Brabant since 1986 (except for a small most western part) (Figure 3). The region is characterized by good access to medical care without financial obstacles. The distance to a hospital for all inhabitants has always been less than 30 kilometers. The population in the area is markedly aging due to longer life expectancy and a decreasing number of births since 1970. This results in an increased proportion of elderly people.

The area of the population-based ECR now covers 2.4 million inhabitants, 10 general hospitals at 16 locations, 6 regional pathology laboratories, two large radiotherapy institutes and one neurosurgical center.[22]

Netherlands Cancer Registry

The regional registries, other than the ECR, had discontinued their activities, until a new nationwide program was established in 1984 following the ECR example in terms of data collection. Since 1989 the whole Dutch population is covered by nine regional cancer registries, which established the Netherlands Cancer Registry (NCR), governed by the Association of Comprehensive Cancer Centers. In 2011 there are still two left, the Comprehensive Cancer Centre Netherlands (IKNL) and South (IKZ), of which the latter hosts the ECR. The Dutch cancer registries get notifications of all newly diagnosed malignancies by the automated national pathology archive (PALGA). Additional sources are the national registry of hospital discharge,

hematology departments and laboratories and radiotherapy institutes. Completeness is estimated to be at least 95%.[23] Trained registration clerks actively collect data on diagnosis, topography, histology, stage and information about primary treatment (delivered within 6 months from diagnosis) from hospital records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status.[24] Information on the vital status of the patients was initially obtained from the municipal registries and since 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all deceased citizens of the Netherlands.

Figure 3. The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre South

Outline

The main objectives of the studies described in this thesis were:

1. To give detailed information on the epidemic of testicular cancer by studying age-, stage- and histology-specific trends of incidence, primary treatment, relative survival, and mortality from testicular cancer in the Netherlands and also in larger international population-based settings.
2. To provide information on the epidemiology of penile and scrotal cancer by studying the incidence, relative survival of and mortality from penile and scrotal cancer in the Netherlands.
3. To explore whether occupational exposures are still the main risk factor for developing scrotal cancer.

The nationwide trends in age-, stage- and histology-specific incidence, treatment and relative survival of patients with testicular cancer are presented in **chapter 2.1**. In **chapter 2.2** the long-term trends of testicular cancer since 1970 in incidence and mortality and the effect of birth-cohorts on the incidence are described. Trends in treatment and relative survival from newly diagnosed patients with seminoma and non-seminoma testicular cancer and their effect on mortality since 1970 are presented in **chapter 2.3.** Age- and histology-specific 5-year relative survival of newly diagnosed patients with testicular cancer in Europe and the USA since 1993 is studied in detail in **chapter 2.4**.
In **chapter 3.1** an overview is given of the incidence, stage distribution, relative survival and mortality of penile squamous cell carcinomas in the Netherlands. Variation in the 5-year relative survival of newly diagnosed patients with penile cancer across Europe and between Europe and the USA is presented in **chapter 3.2**.
An overview of the descriptive epidemiology of scrotal cancer in the Netherlands since 1989 is presented in **chapter 4.1**. In **chapter 4.2** a nationwide case-control study on the effects of different occupational and non-occupational exposures on the risk of scrotal cancer is presented. With the aid of data of the Nordic Occupation Cancer project the risk of scrotal cancer for different types of occupations in the Nordic countries is presented in **chapter 4.3**.
The general discussion (**chapter 5)** discusses the main results of the studies presented in this thesis as well as the perspectives for research and clinical management of testicular, penile, and scrotal cancer.

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Chapter 2

Epidemiology of testicular cancer

Chapter 2.1

Markedly increased incidence and improved survival of testicular cancer in the Netherlands

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Submitted for publication

Abstract

Background

Worldwide marked changes have been observed in the incidence and survival of testicular cancer (TC) during the last decades. We conducted a study on trends in TC incidence, treatment, survival, and mortality in the Netherlands during the period 1989-2009 with specific focus on trends according to age, histology and stage of disease.

Methods

Data from the Netherlands Cancer Registry and Statistics Netherlands was used. Three-year moving average age-adjusted incidence and mortality rates and 5-year relative survival were calculated. Incidence and survival rates were assessed according to calendar period, age, histology and stage. Treatment was categorized into five major groups and analyzed by period, histology and stage.

Results

TC incidence showed a substantial annual increase of 3.9% in the period 1989-2009. The incidence increased for all stages of both seminoma and non-seminoma TC. Stage distribution for the non-seminoma patients shifted towards more localized tumors. Most patients received primary treatment according to the guidelines. Five-year relative survival improved for most groups of stage and histology. A clinically significant improvement of 15% (from 73% to 88%) was found for seminoma TC patients with distant metastases. TC mortality dropped sharply in the 1970s and 1980s and remained relatively stable (around 0.3 per 100,000 person-years) thereafter.

Conclusion

This study shows that incidence of TC has increased sharply in the Netherlands. Relative survival is high and improved in most disease stages. There is a growing demand for medical care of newly diagnosed TC patients and for the rapidly increasing number of prevalent TC.

Introduction

Testicular cancer (TC) is the most commonly diagnosed cancer among men aged 20 to 39 years in the Netherlands, accounting for 32% of all newly diagnosed tumors in men of that age category.[1] Ninety-five percent of all TCs are germ cell tumors, which can further be divided into seminomas and non-seminomas.[2]

The etiology of TC is only partly understood. Cryptorchidism, a contralateral TC and a family history of TC are the best established risk factors.[2] These factors can not however explain the increase in TC incidence that has been observed in most developed countries during the past 50 years.[3-7]

Besides an increased incidence, survival of TC also improved. A study in the Southern part of the Netherlands showed that 10-year relative survival of seminoma and non-seminoma patients increased from 81% and 54%, respectively, in the 1970s to over 90% in the 1990s for both histologies.[8] This was similar to the 5-year relative survival in the Nordic countries, which increased from 60% to 70% in the early of 1970s to over 90% in the mid 1990s.[9] This improvement in survival is mainly due to the introduction of cisplatin-based chemotherapy in the late 1970s.[8, 10] This also resulted in a steep decrease in mortality in most European countries since the 1970s.[7] Although there have been clear treatment guidelines for TC for several years, there is still a considerable variation in survival of TC across Europe, with lower rates in Eastern European countries, probably due to suboptimal treatment or poor access to health care.[11, 12]

In 1997 the International Germ Cell Consensus Classification was introduced, to classify metastasized germ cell cancers into good, intermediate and poor prognosis groups.[13] The Dutch guideline states that a hospital should treat at least 5 good prognosis patients a year and that all intermediate or poor prognosis patients should be referred to specialized centers.[14] Because most hospitals adhere to this guideline, the treatment of TC patients with metastasized disease is fairly centralized in the Netherlands.

To evaluate recent progress against TC in the Netherlands we conducted a study on trends in TC incidence, mortality, disease stage, treatment and survival during the period 1989-2009 with specific interest in trends per calendar period according to age, histology and stage.

Methods

Population-based data from 1989 onwards were used from the nationwide Netherlands Cancer Registry (NCR), specific details of the registration methods of the NCR have been described elsewhere.[15] Data of the Eindhoven Cancer Registry (ECR) was used to investigate trends between 1970 and 1989. This cancer registry was started in the 1950s and is considered to be complete since 1970, covering about 7% of the Dutch population in the period 1970-1989.[8, 16, 17] For the overall incidence rates of TC and for the incidence rates of the seminomas and non-seminomas, data of the ECR (1970-1989) was added to the data of the NCR. National mortality data for the period 1970-2009 was obtained from the causes of death registry of Statistics Netherlands.

All patients with invasive primary TC (ICD-O-3 topography code C62) diagnosed during the period 1989-2009 in the Netherlands were included in the analyses. Hematological tumors of the testis (e.g. lymphomas) were excluded (n=521). Age was divided into five groups (<15, 15-29, 30-44, 45-59, and ≥60 years). The study period was divided into four periods: 1989-1993, 1994-1998, 1999-2003, and 2004-2009. The tumors were grouped according

to histological origin, as described in ICD-O-3[18]: seminomas (ICD-O-3 codes: 9060-9064), non-seminomas (9065-9085,9100-9102,9105) or other (including: Leydig and Sertoli cell tumors, sarcomas, and not otherwise specified tumors). Although the Royal Marsden stage classification of TC is included in the NCR, this was only documented for 60% of the TC patients included in this study. Therefore, the postoperative TNM (pTNM) stage was used. For cases in which pN (90%) and/or pM (38%) were unknown, cN and/or cM were used. The stage grouping of the TNM-classifications of TC changed in such a way over time that it became impossible to compare the different stage groups over time. Therefore, stage in this article is grouped as localized (T1-4, N0/Nx, M0/Mx or TX, N0, M0), regional lymph nodes (any T, N+, M0/Mx), distant metastases (any T, any N, M1) and stage unknown (Tx, N0, Mx or Tx, Nx, M0 or Tx, Nx, Mx). Patients with stage unknown (*n*=196, 1.9%) were excluded from analyses according to stage.
Patients younger than 15 years (*n*=77) were excluded from survival analysis, as well as cases diagnosed by autopsy (*n*=2). The younger patients were excluded because there were not enough patients in each period to calculate relative survival according to period for this age group.

Statistical analyses

Three-year moving average incidence and mortality rates for the period 1989-2009 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardized to the European standard population (European Standardized Rates (ESR)). Changes in incidence were evaluated by calculating the estimated annual percentage change (EAPC) with corresponding 95% confidence interval. To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. y=ax + b where y = ln(rate) and x = calendar year then EAPC = 100 * (ea – 1)).
Primary treatment of TC was divided into the following groups: surgery alone, surgery and radiotherapy, surgery and chemotherapy, surgery, radiotherapy and chemotherapy and no surgery (with or without radiotherapy or chemotherapy). Surgery includes all types of surgery (e.g. orchidectomy, retroperitoneal lymph node dissection (RPLND), resection of residual masses). Other types of treatments were not analyzed. Treatment is given as percentages per period according to histology and stage. The Cochran-Armitage trend test was used to test for differences in treatment over time.
Survival was calculated as the time from diagnosis to death, emigration or December 31, 2009. Traditional cohort-based relative survival analysis was used to calculate 5-year relative survival. For the 5-year survival estimates of the last period (2004-2009) only the patients diagnosed in 2004 had 5-year follow-up. Recent changes in survival might therefore not be accurately represented by standard cohort 5-year survival estimates. Period-based relative survival analysis should provide the most up-to-date estimates for recent time periods.[19] A sensitivity-analysis was performed to check whether the cohort-based survival estimates were similar to the period-based relative survival estimates for the most recent period. The 5-year cohort-based relative survival estimates for the four time periods were used in a Poisson model to test the significance of increases or decreases over time. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

Results

Incidence and mortality

Between 1989 and 2009, 10,384 cases of TC were newly diagnosed in the Netherlands. The annual number of cases doubled from 336 in 1989 to 667 in 2009. The age-standardized incidence rate of TC in the south of the Netherlands remained relatively stable during the 1970s and 1980s (Figure 1). From 1989 onwards there was a sharp increase in TC incidence with an EAPC of 3.9% (95% Confidence Interval (95% CI): 3.6%-4.3%) from 1989 to 2009. From 1992 onwards the incidence rates of the ECR and NCR were similar (data not shown). The incidence of both seminomas and non-seminomas showed similar increases from 1989 onwards with EAPCs of 3.7% (95% CI: 3.2%-4.2%) and 4.3% (95%CI: 3.8%-4.8%), respectively. The age-standardized mortality rate of TC dropped from 1.4 per 100,000 person-years in 1970 to around 0.3 per 100,000 in the mid 1990s and remained relatively stable thereafter.

Age-specific incidence

In figure 2 age-specific incidence rates according to histology are presented. For both histologies the age-groups of 15 to 29 and 30 to 44 show the largest increases in incidence, with EAPCs varying between 4.4% and 5.1%. The incidence rates among men aged 44 to 59 years old also exhibited a significant increase for both seminoma (EAPC=1.9%, 95% CI: 0.6%-3.2%) and non-seminoma (EAPC=2.7%, 95% CI: 0.1%-5.22%) patients. The EAPC of the incidence of non-seminoma patients of 14 years and younger showed a significant decrease (EAPC= -6.3%, 95% CI: -10.7%- -1.8%), but this was only based on only 50 patients.

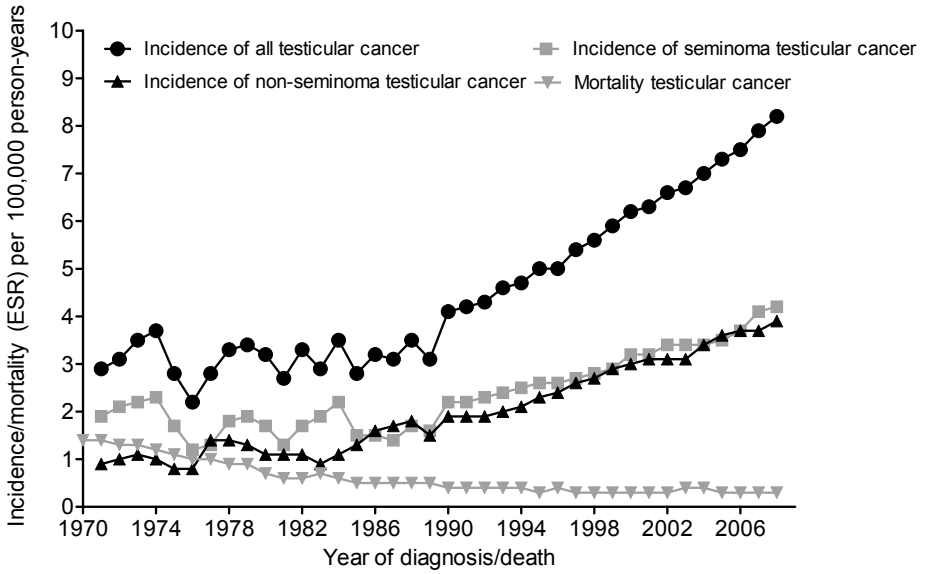

Figure 1. Three-year moving average European standardized (ESR) incidence and mortality rates for testicular cancer in the Netherlands 1970-2009 per 100,000 person-years.
(Incidence rates 1970-1989: data from the Eindhoven Cancer Registry; Incidence rates 1990-2009: data from the Netherlands Cancer Registry; mortality rates 1970-2009: Statistics Netherlands).

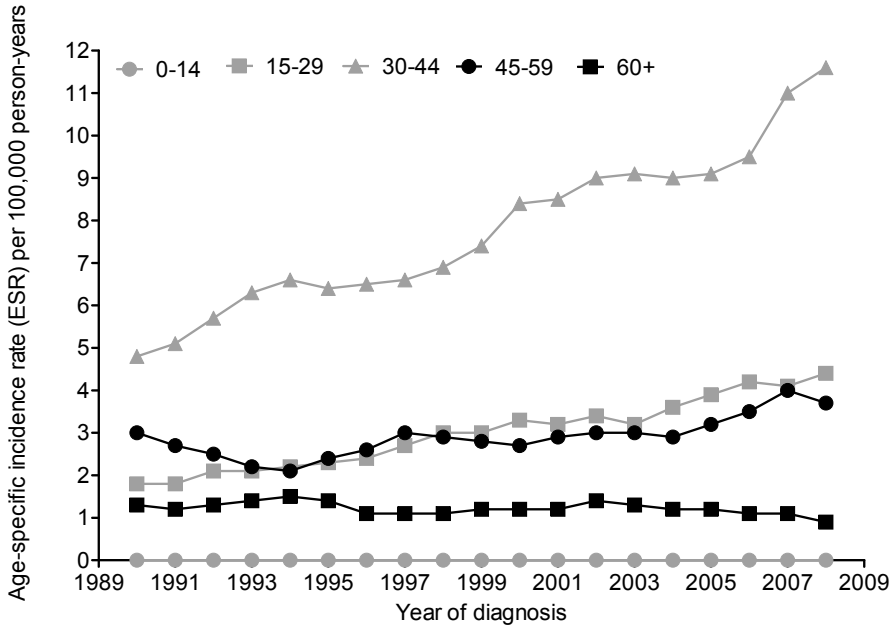

Figure 2A

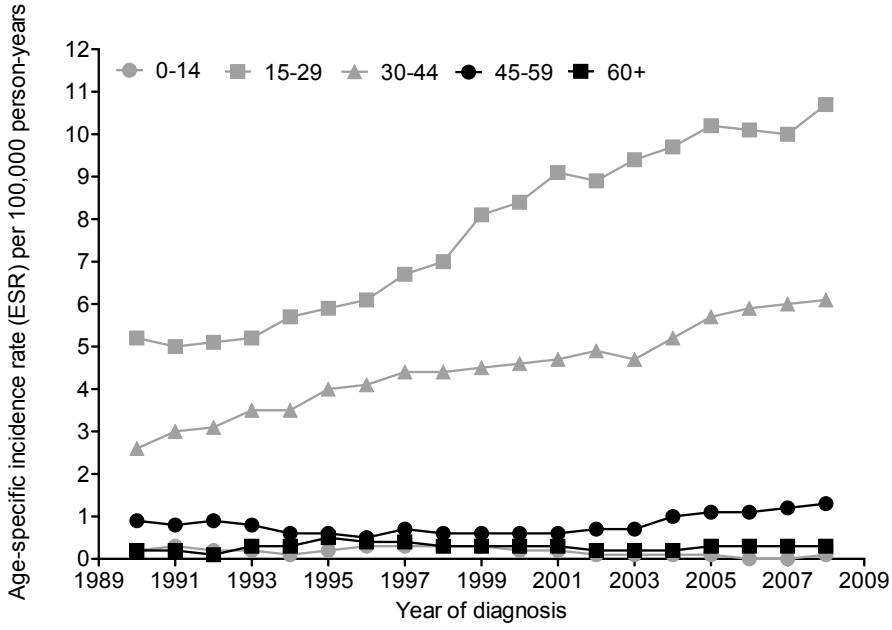

Figure 2B

Figure 2. Three-year moving average of age-specific European standardized (ESR) incidence rates of seminoma (Figure 2a) and non-seminoma (Figure 2b) in the Netherlands.

Stage-specific incidence of seminomas

In the period 1989-1993, 78% of the seminoma patients were diagnosed with localized disease, 15% with regional lymph node involvement, 5% with distant metastases, and 1.8% with an unknown stage. In the period 2004-2009, these percentages were 81%, 14%, 5%, and 0.2%, respectively. The incidence of localized seminomas increased from 1.7 per 100,000 person-years in 1989 to 3.4 in 2009 (EAPC=3.9%, 95% CI: 3.4%-4.5%) (Fig. 3a). There was a somewhat smaller increase in seminomas with positive regional lymph nodes (EAPC=2.9%, 95%CI: 1.9%-4.0%). The incidence rate for seminoma patients with distant metastases at diagnosis increased from 0.1 per 100,000 person-years in 1989 to 0.2 in 2009 (EAPC=4.5, 95%CI: 0.8%-8.3%).

Stage-specific incidence of non-seminomas

From the first to the last period the percentage of patients with localized (clinical stage I) non-seminoma increased from 57% to 64%, the percentage of regional lymph nodes decreased from 22% to 19%; distant metastases decreased from 21% to 17% and the percentage with an unknown stage decreased from 0.8% to 0.3%. The incidence of localized non-seminomas increased from 1.0 per 100,000 person-years in 1989 to 2.6 in 2009, with an EAPC of 5.2% (95%CI: 4.6%-5.8%) (Fig. 3b). The incidence rates for patients with positive regional lymph nodes and patients with distant metastases also increased significantly, with EAPCs of 3.3% and 2.7%, respectively.

Treatment of seminoma

Treatment of localized seminoma TC varied over time, but without a clear trend (Fig. 4). The percentage of patients who underwent surgery alone varied between 15% and 21%, while the percentage of patients who received surgery and radiotherapy decreased from 78% in the period 1989-1993 to 71% in the period 2004-2009 ($p<0.0001$). The percentage of patients who received surgery and chemotherapy increased from 1.5% in the first period to 7.9% in the last period ($p<0.001$). Almost all seminoma TC patients with regional lymph nodes underwent either surgery and radiotherapy (varied between 36% and 46%) or surgery and chemotherapy (47% to 55%), with no significant changes over time. A small proportion of the patients received both radiotherapy and chemotherapy (2% to 6%). The percentage of seminoma TC patients with distant metastases at diagnosis who received surgery and chemotherapy increased over time, albeit not significantly from 80% to 91% ($p=0.15$) and fewer underwent no surgery (decreased from 9% to 5%).

Treatment of non-seminoma

Of the patients with localized non-seminoma, 86% to 89% received only surgery. Most of the remaining patients underwent surgery and chemotherapy, without any significant changes over time. More than 91% of the non-seminoma TC patients with regional lymph nodes received surgery and chemotherapy, while most of the other patients were treated with surgery alone. Patients with distant metastases at diagnosis usually underwent surgery and chemotherapy (varying between 92% and 95%).

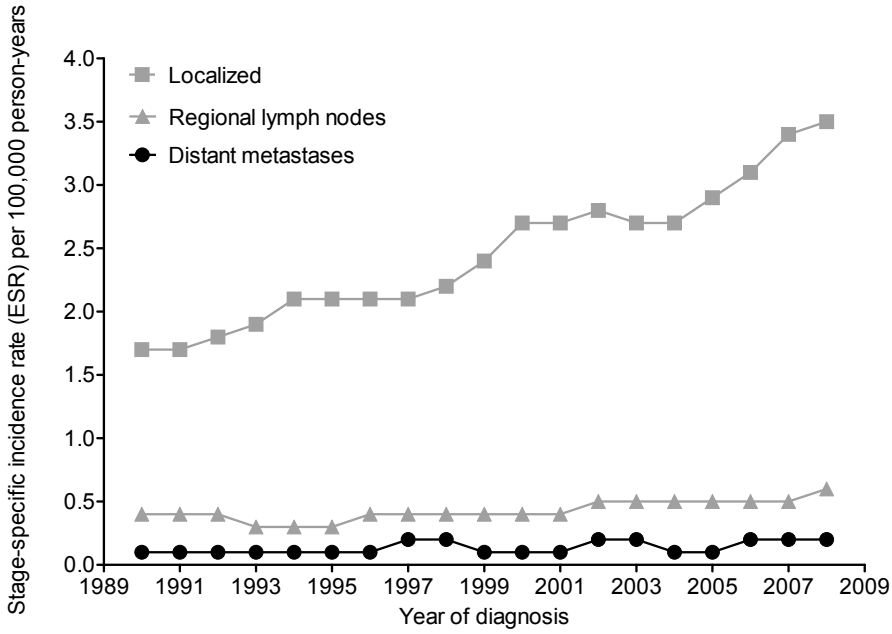

Figure 3A

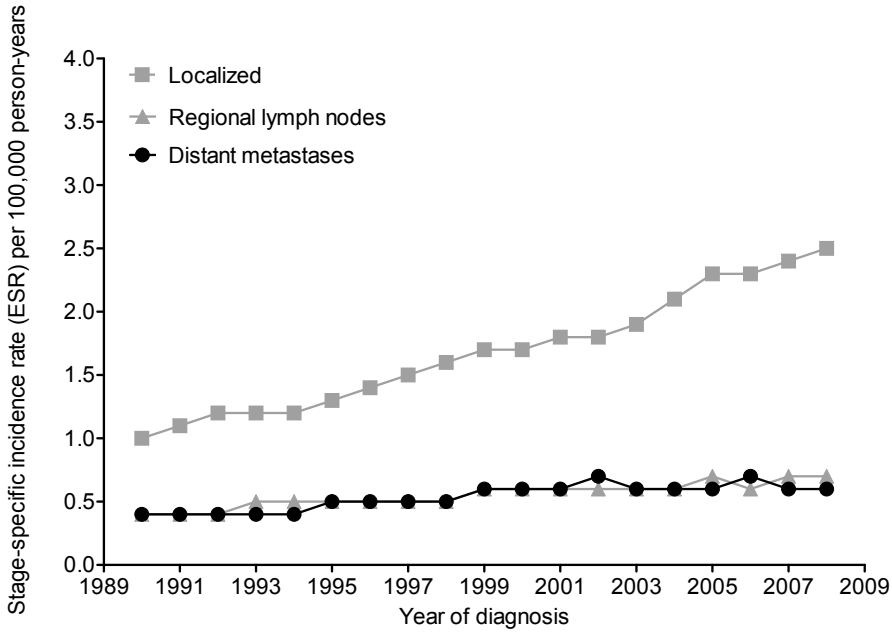

Figure 3B

Figure 3. Three-year moving average stage-specific European standardized (ESR) incidence rates per 100,000 person-years for seminoma (Figure 3a) and non-seminoma (Figure 3b) testicular cancer in the Netherlands 1989-2009.

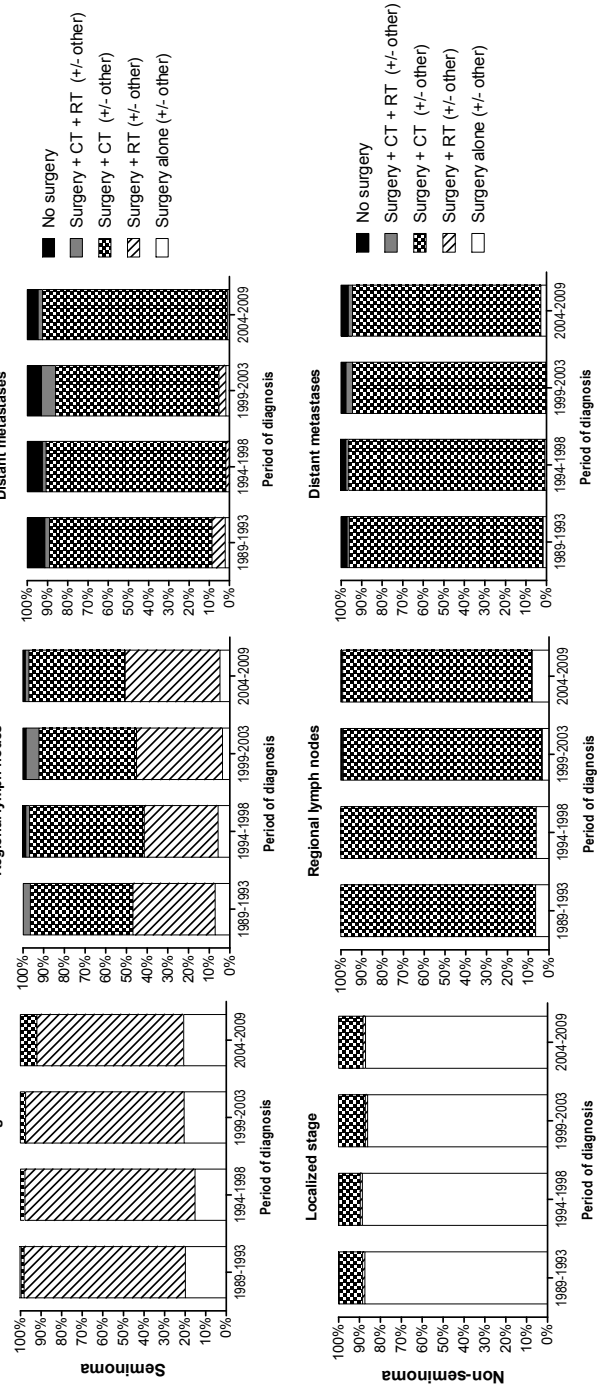

Figure 4. Treatment of testicular cancer in the Netherlands, according to period of diagnosis, histology and stage
RT=Radiotherapy; CT=Chemotherapy

Survival

The overall 5-year relative survival of TC improved from 95% in 1989-1993 to 98% in 2004-2009 ($p<0.0001$) (Table 1). The survival of patients aged 15 to 29 years also improved significantly from 95% to 98%, for the age group 30-44 survival increased from 96% to 98% ($p=0.02$). Survival of the oldest two age groups also increased over time, but not significantly. Patients ≥ 60 years even exhibited the largest improvement in survival, from 85% to 96% in the period 2004-2009.

Survival of seminoma

Patients with a localized seminoma TC had a high 5-year relative survival throughout the whole study period (99% to 101%) (Table 1). Survival of seminoma TC patients with regional lymph nodes at diagnosis improved significantly from 93% to 100%. Five-year relative survival of patients with distant metastases improved from 73% to 88% ($p=0.07$).

Survival of non-seminoma

The 5-year survival for patients with a localized tumor was 98% to 99% throughout the whole study period (Table 1). Survival of non-seminoma TC patients with regional lymph nodes at diagnosis varied between 94% and 98% over time, with no significant trend. Five-year relative survival of patients with distant metastases improved from 78% in the first period to 85% in the last period ($p=0.05$).

Comparison of cohort- and period-based survival analysis

Cohort- and period-based 5-year relative survival estimates were compared for the period 2004-2009. Only the survival estimates of patients aged 60 years and older showed differences larger than two percentage points between the cohort- and period-based 5-year relative survival estimates. The estimate of the cohort-based analyses was 95.7% (Standard Error (SE)=5.5%), while the period-based survival estimate was 91.6% (SE=4.3%). We chose to present cohort-based survival estimates in all other analyses for the period 2004-2009, so that all relative survival estimates for all periods are cohort-based and therefore are comparable.

Discussion

There was a marked and continuing increase in TC incidence in the Netherlands during the period 1989-2009, the largest increases were seen for patients with localized disease. There was little variation over time in the treatment patterns for the different histologies and stages of TC. Relative survival of most stages improved slowly over time. The largest survival improvement was found among seminoma TC patients with distant metastases.

The incidence of TC as well as the increase in incidence in the Netherlands is similar to that in other industrialized countries.[3, 4, 6, 7] While, in other industrialized countries, the incidence started to increase during the 1960s-1970s, it was not until the late 1980s that it started in the Netherlands.[3, 4, 6, 7] This may have been caused by calendar differences in the onset of exposure to yet unknown risk factors. This trend difference may thereby help to identify risk factors.

Table 1. Five-year relative survival with 95% confidence intervals for patients with testicular cancer in the Netherlands according to period of diagnosis, age and histology and stage groups

		1989-1993	1994-1998	1999-2003	2004-2009	*p*-value trend
Total		95 (94-96)	95 (94-96)	96 (95-97)	98 (97-98)	<0.0001
Age (years)	15-29	95 (93-97)	95 (93-96)	96 (95-97)	98 (96-98)	<0.01
	30-44	96 (94-97)	97 (95-98)	97 (96-98)	98 (97-99)	0.02
	45-59	94 (89-97)	93 (89-96)	96 (93-99)	96 (92-98)	0.05
	≥60	85 (72-96)	89 (77-99)	87 (76-96)	96 (82-104)	0.86
Seminoma stage	Localized	99 (97-100)	99 (97-100)	99 (98-100)	101(100-101)	0.09
	Regional lymph nodes	93 (87-97)	96 (91-99)	96 (92-98)	100 (97-101)	0.01
	Distant metastases	73 (57-84)	83 (69-92)	87 (74-95)	88 (75-94)	0.07
Non-seminoma stage	Localized	99 (97-100)	99 (97-100)	98 (96-99)	99 (98-100)	0.91
	Regional lymph nodes	97 (93-99)	94 (90-97)	98 (95-99)	94 (89-97)	0.54
	Distant metastases	78 (71-83)	81 (75-85)	82 (77-86)	85 (80-90)	0.05

A possible explanation for this time difference might be that in the Netherlands, in contrast to other Western countries, the emancipation of women (increase in age at first birth, the decrease in the number of children per woman and the increasing use of alcohol and tobacco by women, etc.) started relatively late and some factors associated with the emancipation, such as sibship size and maternal age, are possibly related to TC.[20]

An important established risk factor for TC is cryptorchidism, although it is unclear whether this predisposes to TC or whether it shares common risk factors with TC.[20] The testicular dysgenesis syndrome (TDS) hypothesis suggests that four conditions (cryptorchidism, hypospadias, impaired spermatogenesis and TC) might be associated with each other as different manifestations of disturbed prenatal testicular development.[21] It is suggested that developmental arrest of fetal germ cell differentiation is the core pathogenic event leading to persistence of gonocytes, which would develop into carcinoma *in situ* and subsequently into TC.[22] Development of TDS is multi-factorial, in which both genetic and exogenous exposures play a role. *In utero* or perinatal exposure to endocrine disrupters (exogenous estrogens and anti-androgens) is the presumed exogenous exposure for the development of TDS.[21, 22] However, if the TDS hypothesis is true, then it would be expected that the different conditions which are associated with this syndrome would exhibit similar trends in incidence. While it is clear that the incidence of TC has been increasing in most developed countries, it is not clear whether the incidence of cryptorchidism and hypospadias has increased similary.[23] Because of the complexity of the pathogenic and epidemiologic features of each component of the TDS it will probably take a while before this hypothesis is finally proven or disproven. Other important established determinants of TC are familial occurrence and a contralateral testicular tumor.[2, 20, 24, 25] Because the genetic make-up of a stable population cannot change very rapidly and most TCs are still detected in men without a history of TC, these risk factors cannot have caused the large and rapid increase in TC incidence. Other factors that might be associated with the risk of TC are low birth weight, low gestational age, low birth order, small sibship size, low and high maternal age, increased adult height and high dairy food consumption.[20] Although a considerable amount of etiological research has been performed, the underlying reasons for the increase in TC incidence in the Western countries remain poorly understood.[2, 24, 25]

Several other studies also observed an increase in incidence of TC that was more marked for localized than for disseminated stages or an increasing percentage of localized stages was found over time.[26-29] A shift towards more localized disease could be due to several reasons. Improved education and awareness of TC and cancer in general among patients and general practitioners could result in earlier detection of the tumor. A recent Irish study showed that awareness and knowledge of TC and knowledge about symptoms of TC has indeed increased among men.[30] However this should also result in a decrease in incidence of advanced stage tumors, which is in contrast to our findings.
It could also be due to an increase in localized tumors due to changes in case-finding practices of general practitioners and urologists or the use of more sensitive imaging modalities. Although there seems to be an increase in the utilization of echo imaging for scrotal complaints, it is unlikely that this alone could cause the large increase in TC incidence.

The introduction of a new risk factor for TC could also have played a role, if this risk factor would result in more slower growing tumors than in the past. Because of the limited knowledge of the etiology of TC, it is impossible to test this hypothesis.
It is not unlikely that a combination of the above-mentioned explanations is responsible for the increased incidence of localized tumors.

The primary treatment for testicular cancer has been rather clear for some time and is well described in Dutch and European guidelines.[31-33] Orchidectomy is the start of treatment for all stages of TC. For stage I seminoma TC there are three treatment options after orchidectomy, i.e. surveillance, adjuvant radiotherapy of retroperitoneal para-aortic lymph nodes or one cycle of adjuvant carboplatin.[31] For stage I non-seminoma TC the standard option in the Netherlands is surveillance, although until recently some hospitals performed a RPLND after orchidectomy routinely.[31] Seminoma TC patients with stage IIA/IIB (regional lymph nodes up to 5 cm) usually undergo radiotherapy to the para-aortic and ipsilateral iliac lymph nodes.[32] All other patients with disseminated seminoma or non-seminoma TC should receive BEP (bleomycin, etoposide and cisplatin) chemotherapy.[32]
The large majority (71% to 83%) of the patients with a localized seminoma underwent surgery and adjuvant radiotherapy. This resulted in a 5-year relative survival of 99% to 101% for the total group of localized seminoma patients, similar to seminoma patients with a comparable stage diagnosed between 1988 and 2001 in 12 SEER (Surveillance, Epidemiology, and End Results) registries in the USA.[34]
More than 86% of the patients with a localized non-seminoma underwent surgery only. We found a 98% to 99% 5-year relative survival, which is similar to the survival rates in the USA.[34] Since we could not stratify the group of patients with regional lymph nodes according to the size of the lymph nodes, we found two large treatment groups for seminoma patients with nodal involvement. About 36% to 46% of these patients underwent surgery and radiotherapy and 47% to 57% of the patients underwent surgery and chemotherapy. Five-year relative survival of the whole group improved from 93% to 100%, likely due to more accurate staging thanks to better imaging, which was similar to the survival of American men with a comparable disease stage (96%).[34]
Non-seminoma patients with positive regional lymph nodes had a 96% 5-year relative survival in the USA, which is between the 94% and 98% in the current study.[34] More than 91% of these patients received chemotherapy, while 3% to 8% of the patients underwent only surgery, probably consisting of orchidectomy and RPLND.
Of the seminoma patients with distant metastases 80% to 91% received surgery and chemotherapy. For the non-seminoma patients this varied between 92% and 95%. The 5-year relative survival of seminoma TC patients with distant metastasis improved from 73% to 88% in the latest period (p=0.07), while the survival of a similar group of American patients, diagnosed between 1988 and 2001, was 79%. [34] For patients with distant metastases of non-seminomas survival in this study improved from 78% to 85% (p=0.05), while survival in American patients was 72%.[34] The improvement of the survival is likely due to improved chemotherapy and the referral of patients with metastasized TC to specialized centers. The somewhat lower survival in USA for the distant metastases might be explained by the disparities in stage distribution and relative survival that exist between different racial/ethnic groups in the USA. Which might be affected by differences in socioeconomic status, cultural

and lifestyle factors, health insurance coverage, and health care access and usage.[35] Most of these factors are more homogeneous in the Netherlands and almost every Dutch citizen has health insurance and an almost excellent access to health care, which could explain the better survival in the Netherlands.

Up to 2004 patients aged ≥60 years had a lower survival than younger patients. This could have been caused by several factors, such as a less favorable stage distribution, delayed diagnosis, different biologic behavior of the tumor, lower tolerance for specific therapeutic modalities such as chemotherapy, and/or suboptimal treatment.[36] Lower tolerance to chemotherapy seems to be the most important factor. All three main chemotherapeutic agents for testicular cancer have been associated with increased toxicity in the elderly and especially bleomycin is known for its lung toxicity in patients aged over 40.[37-39] Older patients might therefore have received dose reductions due to (expected) toxicity, which could have affected their long-term survival or they could have died due to the toxicity.

Mortality due TC in the Netherlands decreased in the 1970s and 1980s from 1.4 to around 0.3 per 100,000 person-years and remained relatively stable thereafter. This decrease in mortality is most likely due to the introduction of cisplatin chemotherapy in the late 1970s.[10] The fact that mortality has remained stable since the 1990s, despite the large increase in TC incidence since that time, is due to the high survival rates and the majority of localized tumors.

A limitation of our study is that the cohort-survival estimate for the relative 5-year survival of the period 2004-2009 is largely dependent on the patients diagnosed in 2004. However, the cohort- and period-based 5-year relative survival estimates exhibited relatively small differences. We therefore can expect that the true 5-year relative survival in this time period resemble to estimates reported in this study.

Conclusions

Incidence of TC has increased sharply in the Netherlands over time, with the largest increase in localized tumors, relative survival remains high and mortality is low. There is a growing demand for medical care for newly diagnosed TC patients and the rapidly increasing number of prevalent TC patients who require a long active follow-up and might experience long-term side-effects of the radiotherapy and chemotherapy treatment.

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Chapter 2.2

Testicular cancer: Marked birth cohort effects on incidence and a decline in mortality in southern Netherlands since 1970

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Abstract

The aim of this study was to interpret the changing incidence, and to describe the mortality of patients with testicular cancer in the south of the Netherlands between 1970 and 2004.
Based on data from the Eindhoven Cancer Registry and Statistics Netherlands five-year moving average standardized incidence and mortality rates were calculated. An Age-Period-Cohort (APC) Poisson regression analysis was performed to disentangle time and birth cohort effects on incidence.
The incidence rate remained stable for all ages at about 3 per 100,000 person-years until 1989 but increased annually thereafter by 4% to 6 in 2004. This increase can almost completely be attributed to an increase in localized tumors. The largest increase was found for seminoma TC patients aged 35-39 and non-seminoma TC patients aged 20-24 years. Relatively more localized tumors and tumors with lymph node metastases were detected in the later periods. APC analysis showed the best fit with an age-cohort model. An increase in incidence of TC was found for birth cohorts since 1950. The mortality rate dropped from 1.0 per 100,000 person-years in 1970 to 0.3 in 2005, with a steep annual decline of 12% in the period 1979-1986. In conclusion, the increase in incidence of TC was strongly correlated with birth cohorts since 1945. The increase in incidence is possibly caused by *in utero* or early life exposure to a yet unknown risk factor. There was a steep decline in mortality in the period 1979-1986.

Introduction

Testicular cancer (TC) is a rare neoplasm, accounting for 0.8% of all male cancers worldwide,[1] but it is the most common malignancy among men aged 15 to 44 in developed countries. Of all TCs, 95% are germ cell tumors which are grouped histologically into seminomas and non-seminomas.[2] The latter have an age-specific incidence peak 10 years earlier (20-35 years) than seminomas (30-45 years).[2] The non-seminoma TC group has multiple histologies, including tumors with mixed histology containing seminoma tissue.

Incidence rates across Europe ranged from 2 per 100,000 person-years in Spain to 10 in Denmark in the period 1993-1997.[3] Trends in incidence in almost all European countries are characterized by steep increases in the past few decades, particularly among adolescents and young adults. The smallest increase over a period of 20 years was found for Switzerland (28%, from 5.1 to 6.5 per 100.000), the largest for France (126%, from 3.5 to 7.9 per 100,000).[3] Incidence in the Netherlands has also increased, but it is not clear when the incidence started to rise.[4] In contrast to incidence, TC mortality has dropped by about 70% in the USA and Western Europe since the 1970s.[5] The pace of the decrease was different among countries, depending on the ability of the health care system to give specialized care to TC patients. This decrease in mortality is attributed to the introduction of cisplatin chemotherapy, which has proven to be the most effective treatment for non-seminoma TC.[6]

It has been reported consistently in northern and middle European countries that the period of birth affects the incidence of TC.[7-11] Birth cohorts from around 1930 and later exhibited a higher incidence of TC; some countries had an attenuation in the increasing trend TC incidence in the birth cohorts from 1930 until 1945. The trend in incidence has been described by both an age-cohort model and an age-period-cohort model in many different western populations.[7, 8, 10-13] An age-cohort model suggest that age and time of birth affect the incidence of TC, while an age-period-cohort suggests that the incidence is also influenced by the time period of TC diagnosis.

Analytical studies of possible risk factors (mainly those occurring early in life) have shown that cryptorchidism, a hypotrophic (< 12 ml) or atrophic testis, Klinefelter's syndrome, and a family history of testicular tumors among first-degree relatives are associated with TC among Caucasians.[14] Subfertility, maternal *in utero* exposure to cigarette smoke and hormones, early age at puberty, decreased levels of androgen and high intake of dairy products have been associated with an increased risk of TC, but the relevance of these risk factors remains unclear.[14]

The aim of this study was to detect trends in incidence and mortality of TC in the South of the Netherlands from 1970 to 2004. In addition we aimed to clarify whether the trend in TC incidence follows an age-cohort pattern or an age-period-cohort pattern.

Methods

Patients

The Eindhoven Cancer Registry (ECR) has collected data on all patients with newly diagnosed cancer in the southern part of the Netherlands since 1955.[15] Until 1988, only patients diagnosed in the eastern part of the area were registered, this was a population based coverage of 1.0 million inhabitants. Thereafter, also patients living in the middle and western parts were registered. Nowadays, the registry covers a population of 2.4 million inhabitants. The area offers good access to specialized medical care in 9 general hospitals and two large

radiotherapy institutes. Information on diagnosis, staging and treatment was extracted from the medical records by trained registrars after notification by pathology laboratories and the medical records departments of the hospitals.
All patients diagnosed with testicular cancer between 1970 and 2004 were included in the study. The tumors are grouped according to histological origin, as described in the third revision of the International Classification of Diseases for Oncology (ICD-O)[16] seminomas (ICD-O codes: 9060-9064), non-seminomas (ICD-O codes: 9065-9085, 9100-1902, 9105) or other. The stage grouping of the TNM-classifications of TC changed over time in such a way that it became impossible to compare the different stage groups over time. We have therefore chosen to categorize the extent of the disease as: localized (any T, N=0 and M=0), lymph node metastases (any T, N>0 and M=0), distant metastases (any T, any N and M>0) and stage unknown. Patients with stage unknown (*n*=23) were excluded from analyses that were stratified by stage.

Incidence

Five-year moving average age-standardized incidence rates were calculated per 100,000 person-years for the total group of TC and for seminomas and non-seminomas separately. The total incidence of TC was compared to the total incidence of TC in the Netherlands, which was available for the period 1989-2003.[17] Standardization was performed according to the European standard population. Moreover, stage and age-specific incidence rates were computed. Because stage was recorded reliably from 1980 onwards, only patients diagnosed in 1980 and later were included in the stage distribution analysis.
Evaluation of the trend in incidence was performed by calculating the estimated annual percentage changes (EAPC) for different time periods.

Age-Period-Cohort (APC) models

For the Age-Period-Cohort (APC) models, patients aged <15 (1.0% of all cases) and ≥60 (7.2% of all cases) were excluded because of the small number of cases in these age groups. The population was divided into 5-year age groups (15-19, ..., 54-59), 5-year calendar periods (1970-1974, ..., 2000-2004) and matching 10-year birth cohorts (1915-1924, ..., 1980-1989), which means that each cohort overlaps the next cohort by exactly 5 years. Birth cohorts will be denoted by the central birth year, for example the 1915-1924 birth cohort is denoted by 1920. The GENMOD procedure of the SAS package was used to fit a series of Poisson regression models, to estimate the separate effects of age, time of diagnosis and birth cohort on the trend in incidence, according to the methods described by Clayton and Schifflers.[18, 19] To test the goodness-of-fit of the models with the observed incidence rates and to test the models against one another, deviances and differences between the deviances with appropriate degrees of freedom were used.[18, 19] The terms preceding the word model indicate which variables are used to describe the data. So an age-cohort (AC) model means that the incidence data is described by both the age and cohort variables. The age-drift (AD) model means that the incidence data is described by the age variable and a drift parameter.
Birth cohorts with data for less than 3 diagnostic periods will not be presented.

Mortality

Mortality data were available from Statistics Netherlands for the period 1970-2005. Five-year moving average European standardized mortality rates per 100,000 person-years were calculated and were compared to the Dutch mortality rates.[20] In addition, trend EAPC analysis was performed for different time periods. For the period 1970-1988 the Dutch mortality rates were only available as crude mortality rates.

Results

Incidence

In total, 1,165 patients were diagnosed with TC between 1970 and 2004 (53% seminoma, 45% non-seminoma and 2% other). The age-standardized 5-year moving average incidence rate increased from 2.9 per 100,000 males in 1970 to 6.1 in 2004 (Figure 1). Incidence rates of 3.3 and 6.0 per 100,000 males in the ECR-region, for the years 1988 and 2003, were similar to such rates of 4.1 and 6.5 per 100,000 males in these same years in the whole Netherlands (data not shown). Because the largest increase seemed to take place in the period 1988-2004, an EAPC was calculated over this period. Which was 4.4% (95% confidence interval (CI) 3.0% to 5.8%) in this period, while this was –0.2% (95% CI -3.1% to 2.7%) for the period 1970-1987. This means that there was a significant annual increase of the incidence of 4.4% in the period 1988-2004 but no increase of incidence in the period 1970-1987. An incidence analysis of only the eastern part of the ECR region showed a similar TC incidence over time as that of the whole ECR region.

In the period 2000-2004, the highest age-specific incidence rate for seminomas was found for the 35-39 year age group (6.8 per 100,000 person-years) and for non-seminomas for the 20-24 year age group (6.7 per 100,000 person-years).

The 5-year moving average incidence rates according to stage are presented in figure 2, which shows that almost the total increase in incidence can be attributed to the increase in local tumors. This increase was almost equally distributed over the seminoma and non-seminoma TCs. The annual increase over the period 1980-2004 in localized tumors of seminoma TC was 4.4% (95% CI 2.3% to 6.5%) and 6.2% (95% CI 4.4% to 8.0%) for non-seminoma TCs. For the tumors with lymph node metastases this was 3.7% (95% CI 1.0% to 6.4%) for the seminoma TCs and 4.3% (95% CI 1.8% to 6.8%) for the non-seminoma TCs.

APC models

The fits of the different models are presented in table 1. The AD model and the age-period (AP) model gave a poor fit, with a *p*-value for the goodness-of-fit test of <0.001 for both (a small *p*-value indicates that the model is significantly different from the observed incidence data). The age-cohort model (p=0.12) and APC model (p=0.10) both showed a good fit.

The AC model was significantly better than the AD model (p<0.001), while the AP-model did not differ significantly from the AD model (p=0.05). The APC model did not describe the data much better than the AC model (p=0.46). We therefore concluded that the AC model provided the most parsimonious description of the data.

The birth cohort effect in the AC model is presented in Figure 3. Men who were born around 1975 had a 3 times (95% CI 2.2-4.2) higher risk of developing TC than those in the reference 1950 birth cohort.

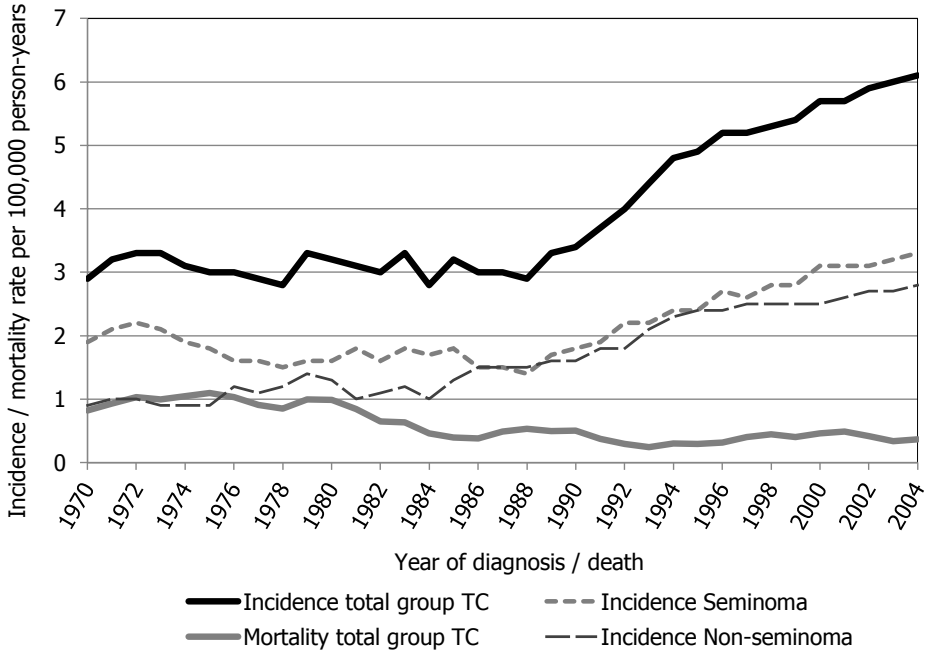

Figure 1. Five-year moving average European standardized testicular cancer incidence and mortality rates per 100,000 person-years

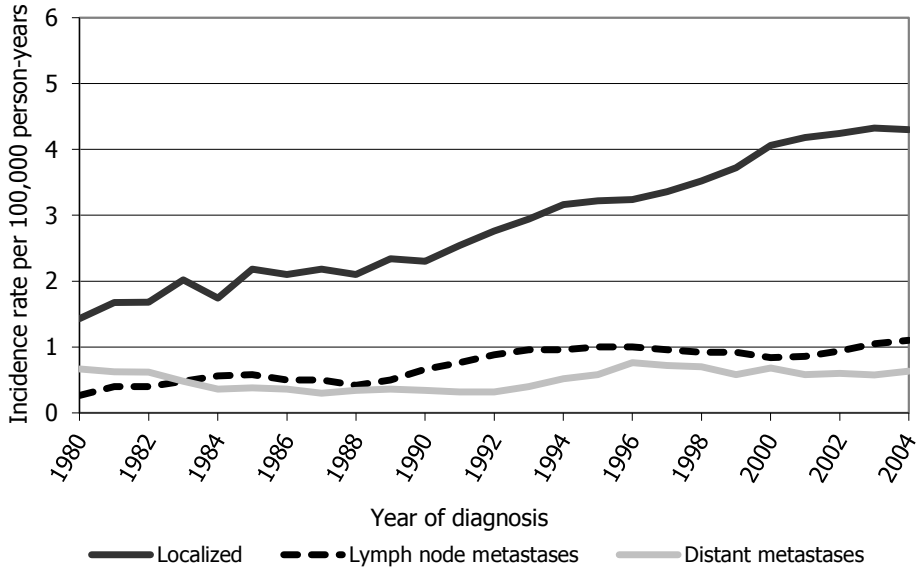

Figure 2. Five-year moving average European standardized testicular cancer incidence rates per 100,000 person-years according to stage

Table 1. The goodness-of-fit for the different models

Model	Deviance	DF	*P*-value
Age	179.7	54	<0.001
Age-drift	98.3	53	<0.001
Age-period	87.3	48	<0.001
Age-cohort	50.5	40	0.12
Age-period-cohort	45.8	35	0.10

A small p-value indicates that the model is significantly different from the observed data

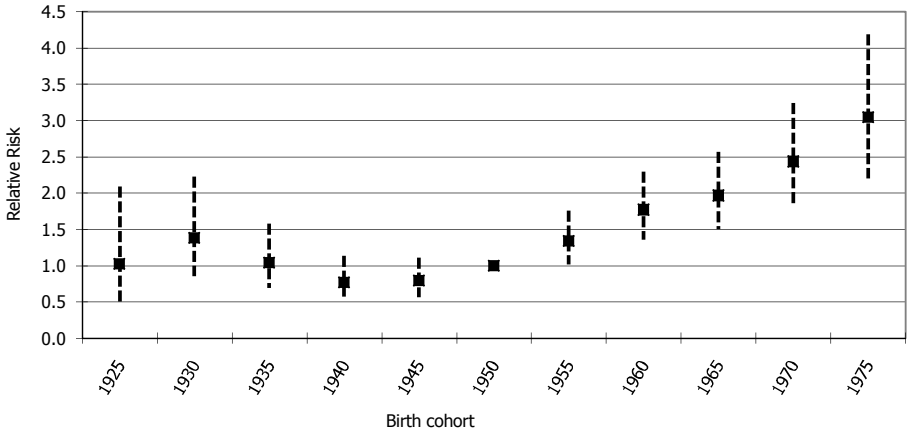

Figure 3. Relative risk of testicular cancer incidence per birth cohort with 95% Wald confidence limits, based on age-cohort model (birth cohort 1950 is the reference cohort)

Mortality

The 5-year moving average mortality rate increased in the period 1970-1978 (Figure 1) and declined steeply in the period 1979-1986 (from 1.0 per 100,000 to 0.4 per 100,000, with an EAPC value of –12.0% (p=0.07)). In the period 1987-2005 the mortality rate fluctuated around a level of 0.4 per 100,000 and being similar to that of the entire Netherlands during the period of 1970 until 2005 (data not shown).

Discussion

A marked increase in incidence of TC has occurred since 1989 in the southern part of the Netherlands, which correlates with increasing risks for birth cohorts since 1945. There has been a marked decrease in mortality since 1979.

TNM testicular cancer stage classification changed several times between 1970 and 2004. To prevent misclassification of the tumors we have made our own stage classification, in which all tumors are classified in the same way. But through this stage classification it becomes more difficult to compare the study results with other studies.
The changes in histological classification over the years have no meaningful influences on our histological classification into seminoma and non-seminoma TC.

Unfortunately, the Eindhoven Cancer Registry does not have access to death certificates. The registry partly solve the problem of potential incompleteness by active registration based on a national computerized archive of pathological diagnosis (PALGA) and on clinical diagnosis derived from a computerized national hospital discharges system (LMR).

Incidence and APC models

The incidence of TC increased by 110% in the period 1970-2004: seminoma TC started to increase in 1990 and non-seminoma TC some years earlier. This increase can be attributed almost entirely to the increase in localized TC tumors. As a result of the increasing incidence and the decreasing mortality, the prevalence of TC in the Netherlands increased from 37 per 100,000 person-years in 1990 to 64 per 100,000 in 2002 and the prognosis is that the prevalence in 2010 will be 132 per 100,000.[21] As a consequence the claim for medical care in the Netherlands will rise markedly, since active follow-up for localized TC seems to be efficacious (unlike the situation in many other tumor sites).[22, 23]

The fact that the rate of the incidence increase in the eastern part of the ECR region was comparable to the incidence increase of the whole ECR region indicates that the expansion of the ECR region in 1988 did not introduce a bias in the TC incidence.

The incidence of non-germ cell TC was low and relatively constant during the whole study period and did not influence the overall TC incidence.

The fact that the incidence of both seminoma and non-seminoma TC is increasing suggests that one or more mutual risk factors, probably introduced by changes in environment and lifestyle, might be responsible for the increase in incidence. Because the age-cohort model gave the most efficient fit of all APC models, and the increased risks of incidence for birth cohorts since 1950 also suggest that the risk factor exerts its effect *in utero* and/or early in life. When the risk factor would exerts its effect later in life, it would probably affect boys and men of different ages. An increased incidence would then be more attributable to period effects then to birth cohort effects as is found in this study.

The result of our age-cohort model is comparable to that of two other studies, which analyzed multiple European populations and found the best fit to be an age-cohort model for most populations.[7, 11] A study in the United States found the best fit with an age-period-cohort model, but the birth cohort effect was dominant.[12] All 3 studies found an increase in risk with successive birth cohorts, which is comparable to the results of our study.

There are several hypotheses explaining the increase of TC incidence. One of them suggests that there is an increase in incidence of several testicular diseases (for example cryptorchidism and TC) through changes in genetic and/or environmental factors, including endocrine disrupters.[24] Another hypothesis suggests that lifestyle changes such as an increase in maternal age and an increase in the number of first-born children causes the increase of TC incidence.[25] In the Netherlands, the average age of the mother at birth of her first-born child increased from 24.9 years in the 1960s to 26.4 years in the 1980s and the average number of children per mother decreased from 3.0 to 1.5. This resulted in an increase in the percentage of first-born children from 35% in the 1960s to 45% in the 1980s. Although these changes are in the same period as the increase in relative risk of birth cohorts on TC, we cannot verify this hypothesis in our data because these possible risk factors of TC were not registered in the ECR.

The risk factors that are responsible for the increase in incidence may initiate or promote the development of both histologies, *in utero* and/or early in life, but apparently have a shorter latency time for non-seminomas than for seminomas, explaining the difference in the age-peaks of seminoma and non-seminoma TC.
The incidence of TC has been increasing for many decades in most European countries, but with a varying start.[3, 7] A study of TC in Scotland found that the increase in incidence was more pronounced in the age-group <40 than in the age-group ≥40.[26] The rise in incidence seems to have started later in the ECR-region, compared to most other European countries, but the absolute incidence and the age-distribution of the incidence have become similar to those of other European countries.
We also found a small non-significant decrease in the relative risk for birth cohorts 1935 and 1940, as was found in Denmark, France, Norway, Italy, Slovenia, Spain and Sweden.[7, 10, 11] Through the relative small population in this study it was not possible to perform a more detailed APC-analysis for example smaller period and cohort groups or separate analysis for seminoma and non-seminoma groups.

Mortality

The mortality rate dropped from around 1 per 100,000 person-years in the mid 1970s to 0.4 in 1986 and fluctuated thereafter between 0.2 and 0.5. However in this last period the numbers became very small. This pattern of decrease is comparable to the mortality rates found in the populations of the United States and the European Union. The steep decrease is probably related to improved TC survival in that time.[26-29] There was a small and non-significant annual decrease of -1.2% (p=0.61) in mortality in the area of the ECR in the period 1987-2005. And in almost the same period (1987-2004) the incidence increased by 4.2% (p=<0.001). Thus although the incidence was rising, mortality did not rise. This can be attributed to the higher percentage of less-aggressive tumors, which have higher survival rate than more aggressive tumors, and increased survival rates for TC in the ECR region.[29] These increased survival rates can be attributed to the introduction of cisplatin-containing chemotherapy in the 1970s.[6]

Conclusion

A marked increase in incidence of TC was observed in the south of the Netherlands, predominantly for tumors with lower aggressiveness and for both the seminoma and non-seminoma TCs. This occurred predominantly in birth cohorts since 1945; *in utero* and/or early life influences seem likely. The marked decrease in mortality since the 1970s was most likely caused by improved treatment.
Future investigations should focus on factors that influence the development of testicular tumors.

Acknowledgements

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The Comprehensive Cancer Centre South enabled this study.

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Chapter 2.3

Testicular cancer: Trends in mortality are well explained by changes in treatment and survival in the southern Netherlands since 1970

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Abstract

The aim of this study was to interpret changes in mortality from testicular cancer (TC) against the background of changes in treatment and survival in the south of the Netherlands.
Five-year moving average standardized mortality rates were calculated. Primary treatment and relative survival were analyzed according to histology, stage and year of diagnosis.
The mortality rate dropped in the period 1979-1986 and then flattened out. The types of treatment that patients received did not change significantly over time and were according to the guidelines. Ten-year relative survival for seminoma TC patients improved from 81% (67%-91%) in 1970-1979 to 95% (88%-100%) in 2000-2002; for non-seminoma TC patients these rates were 54% (38%-68%) and 92% (85%-99%), respectively. Conditional 5-year relative survival for seminoma and non-seminoma TC patients 5 years after diagnosis was 99% and 96%, respectively.
In conclusion, there was an enormous increase in relative survival and a significant decrease in mortality.

Introduction

Although testicular cancer (TC) only accounts for 0.8% of all male cancers,[1] it is the most common malignancy among men aged 15 to 44 in developed countries. Of all TCs, 95% are germ cell tumors which are grouped histologically into seminomas and non-seminomas.[2] The majority of the seminoma TCs are diagnosed among men in the age group of 30 to 45 years, while most of the non-seminoma TC patients are between the ages of 20 and 35 years.[2] The incidence of TC is increasing throughout Europe, but there are large variations in the incidence rates and in the speed at which incidence increases across the European countries.[3] Relative survival of TC has increased during the last 40 years to an average 5-year rate of 93% in Europe, [4-7] but with substantial variations across Europe.[6] In addition to stage at diagnosis,[8] age at diagnosis matters, younger patients exhibiting better survival than older patients.[8, 9] Most of the increase in survival is primarily attributed to the introduction of effective cisplatin-containing chemotherapy for advanced disease in the 1970s.[4, 10] Mortality has dropped by about 70% in the USA and Europe since the 1970s, but at a lower pace in Eastern Europe than in the European Union and the USA.[11] The aim of this study was to detect trends in treatment, survival and mortality of TC in the south of the Netherlands from 1970 to 2004, where the management of TC was decentralized.

Methods

Patients

The Eindhoven Cancer Registry (ECR) has collected data on all patients with newly diagnosed cancer in the southern part of the Netherlands since 1955.[12] Until 1988, only patients diagnosed in the eastern part of the area were registered, but since that year patients diagnosed in the middle and western part of North Brabant are also included. Nowadays, the registry serves a population of 2.4 million inhabitants. The area offers good access to specialized medical care in 9 general hospitals and two large radiotherapy institutes. Information on diagnosis, staging and treatment was extracted from the medical records by trained registrars.

All testis cancer patients diagnosed between 1970 and 2004 were included in the study. The tumors are grouped according to histological origin, as described in the third revision of the International Classification of Diseases for Oncology (ICD-O)[13]: seminomas (ICD-O codes: 9060-9064), non-seminomas (ICD-O codes: 9065-9085, 9100-1902, 9105) or other. The stage grouping of the TNM-classifications of TC has changed over time in such a way that it became impossible to compare the different stage groups over time. We have therefore chosen to categorize the extent of the disease as: localized (any T, N=0 and M=0), lymph node metastasis (any T, N>0 and M=0), distant metastasis (any T, any N and M>0) and unknown. Patients with stage unknown were left out of the stage-specific analysis. Stage was recorded reliably from 1980 onwards, so only patients diagnosed since then were included in the stage-specific analyses.

Treatment

Five major subgroups were considered for primary treatment: surgery only, surgery and radiotherapy, surgery and systemic therapy, unknown, and other/none. The specific type of therapy was not registered, therefore it was not possible to identify whether a patient received cisplatin-containing chemotherapy or another type of chemotherapy.

A fisher-exact test was used to test whether there was an overall change in administered treatment over time. This was done according to histology and stage.

Relative survival

Data on vital status (available until January 1, 2005) were obtained from the hospital records and the mortality register of the Central Bureau for Genealogy (an institution that registers all deaths in the Netherlands via the municipal population registries). Data on vital status were only available for patients diagnosed in or before 2002.

Relative survival is an estimation of the disease-specific survival. It is calculated as the absolute survival among cancer patients divided by the expected survival for the general population with the same sex and age structure.[14] Relative survival was computed with the traditional cohort-analysis for periods with complete 5 and 10-year follow-up. Period analysis was used to estimate the relative survival for the most recent periods with incomplete 5 or 10-year follow-up.[15] Survival analyses were carried out according to histology and stage.

Conditional survival was computed with period analysis for patients diagnosed between 1970-2002, and was performed according to histology. Five-year relative survival was computed for every additional year survived, conditional on being alive at that moment. Since patients who have already survived for some years are older than at diagnosis, conditional relative survival rates were also adjusted for survival in the general population with the same age distribution as patients at that time. A conditional 5-year relative survival at year *x* is the 5-year relative survival for patients who are still alive *x* years after diagnosis of TC.

Mortality

Mortality data were obtained from Statistics Netherlands for the period 1970-2005. Five-year moving average European standardized mortality rates per 100,000 person-years were calculated and compared to the Dutch testicular cancer mortality.[16] In addition, trend EAPC analysis was performed for different time periods. For the period 1970-1988 the Dutch mortality rates were only available as crude mortality rates.

Results

Treatment

In total, 966 patients were included for treatment analysis (54% seminoma and 46% non-seminoma).

The overall treatment of the localized seminoma TC patients changed significantly ($p < 0.0001$) over time (Fig. 1a), the surgery alone treatment was lower in the period 1990–1999 than in the other two periods. While the percentage of patients who received surgery and radiotherapy was higher in the period 1990–1999 (93%) in contrast to the periods 1980–1989 (82%) and 2000–2004 (85%). The treatment in the group of seminoma TC patients with lymph node metastasis

changed significantly ($p < 0.001$), the percentage of patients who received surgery and radiotherapy decreased from 58% in the 1980s to 32% in the period 2000–2004, while the percentage of patients who received surgery and systemic therapy increased from 33% to 64% in the same period. The distant metastases seminoma TC patients exhibited no significant differences in treatment over time, the number of patients in this group was small (n=22).

In the non-seminoma treatment group there was a significant difference ($p < 0.0001$) in the treatment of patients with localized disease over time (Fig. 1b). The percentages of localized non-seminoma TC patients who received only surgery and who received surgery and systemic therapy fluctuated over time. The treatment of non-seminoma TC patients with lymph node metastasis changed significantly over time
($p< 0.0001$). Patients more frequently received surgery and systemic therapy in the period 2000–2004 (96%) than in the period 1980–1989 (68%). The changes of treatment of non-seminoma TC patients with distant metastases ($p < 0.01$) are contributable to an increase in the other/none category. Most of the patients in the other/none treatment group received systemic therapy with or without other treatments.

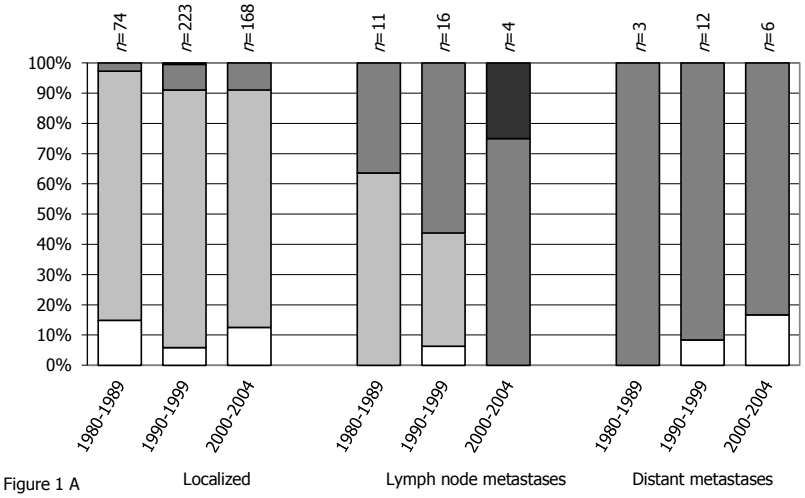

Figure 1 A

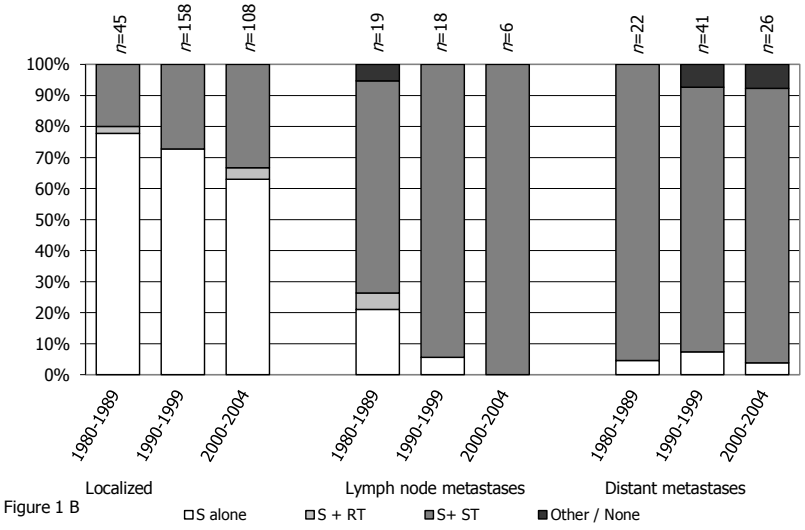

Figure 1 B

Figure 1. Primary treatment of seminoma (Figure 1A) and non-seminoma (Figure 1B) testicular cancer according to histology, stage and time. (S=surgery; RT=radiotherapy; ST=systemic therapy)

Survival

During a mean follow-up of 10 years, 167 patients died (87 seminoma and 68 non-seminoma). For seminoma TC, 10-year relative survival improved from 81% (95% Confidence Interval 67%-91%) in 1970-1979 to 94% (83%-100%) in the period 1980-1989 while remaining relatively stable in the next decade (Figure 2 A). For non-seminoma TC patients these rates increased from 54% (38%-68%) in 1970-1979 to 87% (76%-93%) in the period 1980-1989 and to 92% (85%-99%) in the 1990s (Figure 2 B). The greatest improvement in survival took place in the second half of the 1970s and the early 1980s.

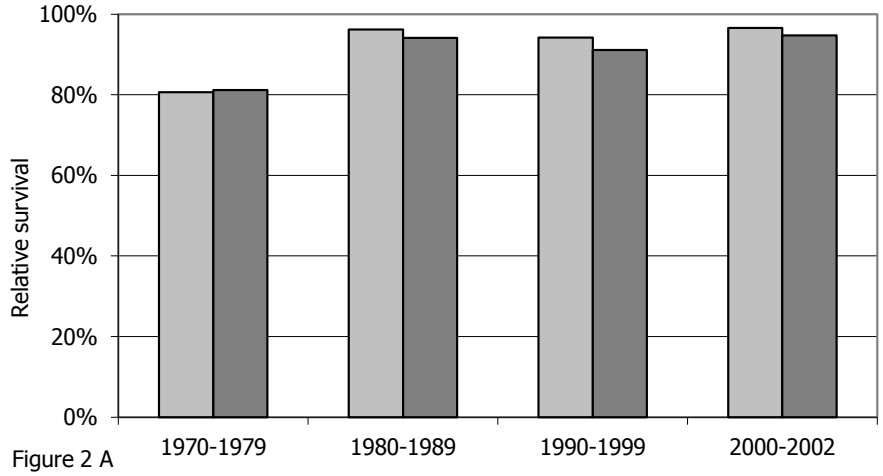

Figure 2 A

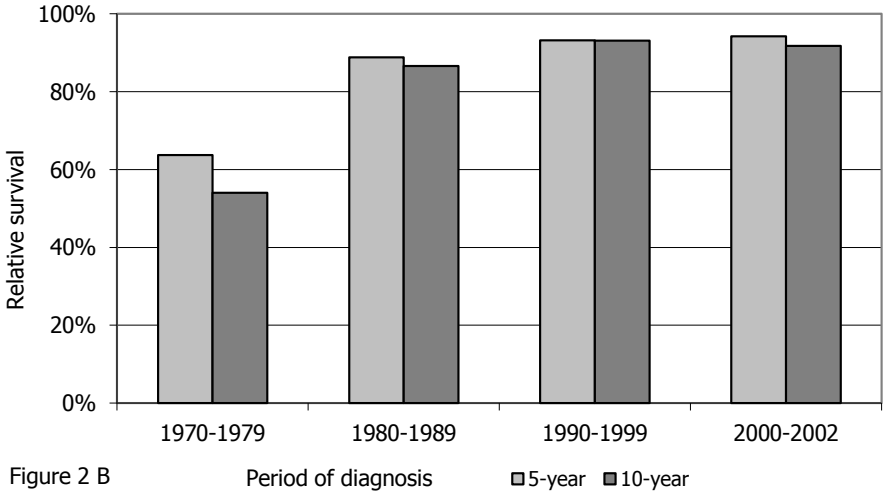

Figure 2 B

Figure 2. Five- and 10-year relative survival of patients with seminoma (Figure 2 A) and non-seminoma (Figure 2 B) testicular cancer in the south of the Netherlands.
The 10-year survival of the period 1990-1999 and the 5- and 10-year relative survival of the period 2000-2002 were calculated by means of period-analysis.

Ten-year relative survival in the period 1990-2002 was high for patients with both localized seminoma (92%; 86%-96%) and localized non-seminoma TC (97%; 92%-99%) (Figure 3). The ten-year relative survival of seminoma TC patients with lymph node metastasis was slightly lower that to that of the localized seminoma TC patients (88% versus 92%). Non-seminoma TC patients with lymph node metastasis also had a worse 10-year survival than localized non-seminoma TC patients (93% versus 97%). Three-year survival for the seminoma TC patients with distant metastases was 63%. For the non-seminoma TC patients with distant metastasis 10-year survival was 75%.
Relative survival of patients with TC younger than 50 years was slightly higher than that for those ≥50. Only the 1-year relative survival was significantly different: 99% (98%-100%) versus 93% (84%-98%).

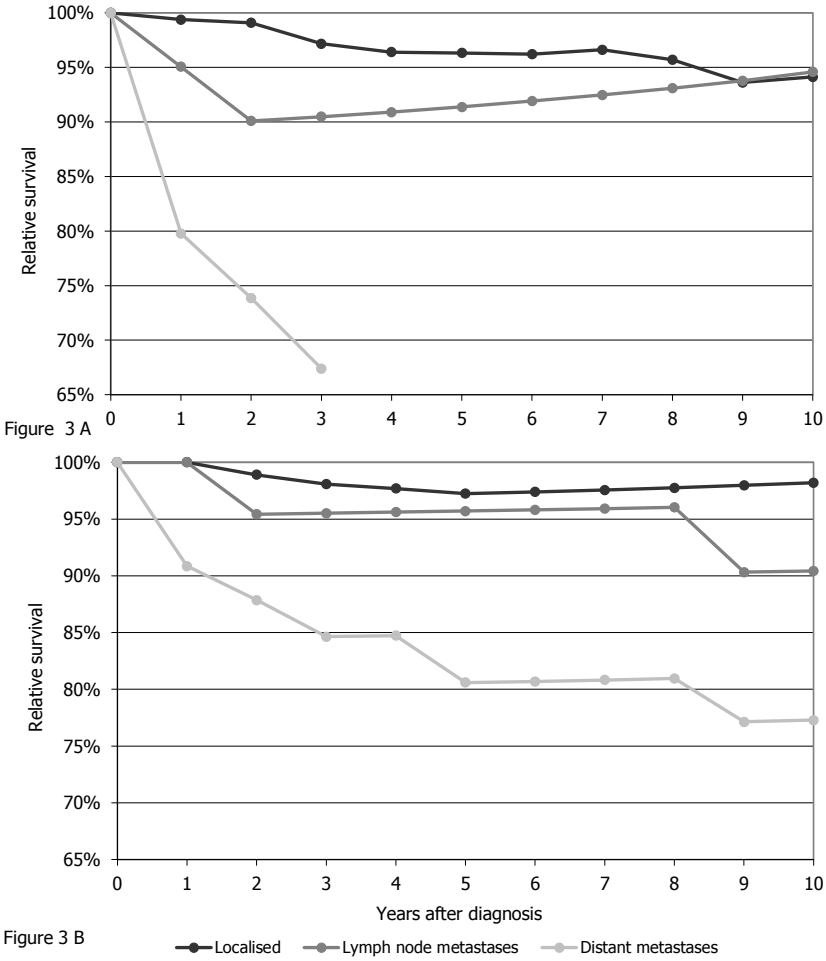

Figure 3. Relative 10-year survival curve according to stage for seminoma (Figure 3 A) and non-seminoma (Figure 3 B) testicular cancer patients diagnosed in the south of the Netherlands during 1990-2002.

Figure 4 shows the relative survival curve at diagnosis for both histologies, as well as the conditional 5-year relative survival rate for each additional year survived. For non-seminoma TC patients the conditional 5-year relative survival was 96% after 5 years and for seminoma TC patients it was 98%. The conditional 10-year relative survival was 98% and 100%, respectively.

Mortality

After a slight increase in mortality from 0.8 to 1.0 in the period 1970-1978 (Figure 5), the 5-year moving average mortality rate decreased from around 1.0 per 100,000 person-years in 1979 to 0.4 in 1986, the average annual change being -12% (p=0.07). In the latest period, 1987-2005, the mortality rate fluctuated between 0.2 and 0.5, being similar to the trend for the entire Netherlands.

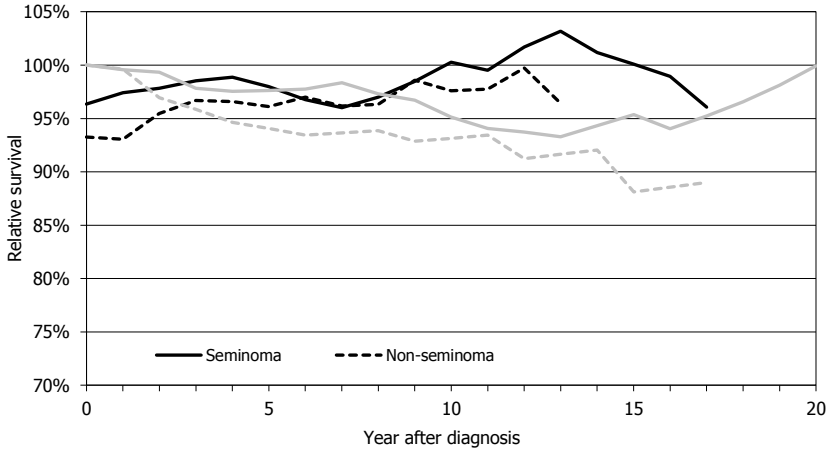

Figure 4. Actuarial and conditional survival for patients with seminoma and non-seminoma testicular cancer. Black lines are conditional 5-year survival rates; grey lines are relative survival rates at diagnosis.

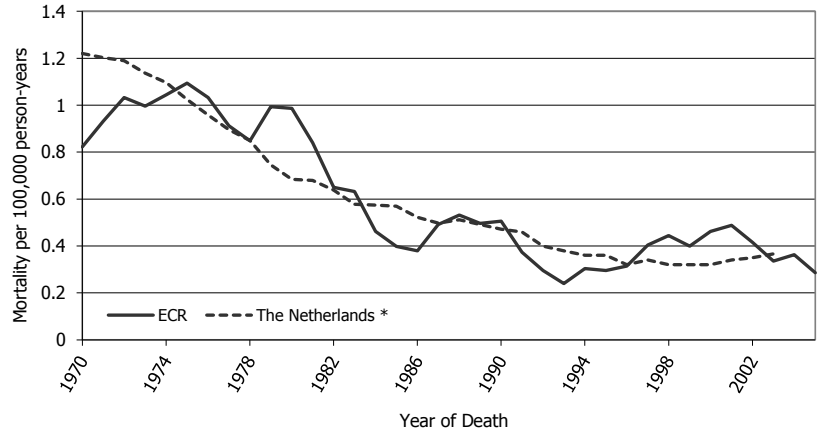

Figure 5. 5-year moving average testicular cancer European standardized mortality rates per 100,000 person-years (ECR= Eindhoven Cancer Registry)

** For the period 1970-1988, non-standardized rates were used to calculate the 5-year moving average*

Discussion

This study shows a marked increase in survival of TC, especially for non-seminoma TC, in the south of the Netherlands since the mid 1970s accompanied by a significant decrease in mortality. These changes started in the late 1970s and continued to change until the end of the 1980s. Since 1990 the survival and mortality have remained relatively steady.

Treatment

Almost all (99.9%) of the patients who received surgery underwent an orchidectomy, while only 22 lymph node dissections were registered, 17 of which were carried out in the period 2000-2004. The fact that this number of lymph node dissections is lower than expected is because we only registered primary treatment within 6 months of diagnosis. Most secondary lymph node dissections were probably performed more than 6 months after diagnosis.

National and international guidelines [17-20] recommend surgery and radiotherapy for patients with localized seminomas. In our study, 82% of these patients received this combined treatment in the 1980s increasing to 93% in the period 1990-1999 and decreased to 85% in the period 2000-2004. Seminoma TC patients with lymph node metastasis were advised to undergo surgery and radiotherapy or systemic therapy depending on the size of the lymph node metastases. Ninety-five percent of these patients received one of these treatment combinations. The number of patients who underwent surgery and systemic therapy appears to be increasing. Eighty-six percent of the seminoma TC patients with distant metastasis underwent surgery and systemic therapy as indicated in the guidelines.

Surgery only or surgery and systemic therapy has been advised for patients with localized non-seminomas, and 98% received either one of these 2 treatment combinations. Surgery with systemic therapy is the preferred treatment for non-seminoma TC patients with lymph node and distant metastasis, 90% and 89% of these patients received this combined treatment, respectively.

In total there were 9 patients in the other/none treatment category, 1 of whom received no therapy; the other 6 patients underwent systemic treatment with or without other treatments.

The beneficial effect of centralization of treatment of TC patients with distant metastases, which has been described repeatedly, arises from the complexities of staging, supportive care during aggressive systemic treatment and dedicated surveillance.[21] However, in our region clinical management of TC has remained relatively decentralized, only 60% of patients with distant metastatic tumors have been treated in larger hospitals, with little change over time. In the 1990s survival from TC in the south of the Netherlands was similar to that of the Northwest region of the country, where treatment is concentrated in 3 major cancer centres.[22]

Survival

Relative survival of patients with seminomas and non-seminomas increased substantially over time to a 5-year survival of 97% for seminomas and 94% for non-seminomas in the period 2000-2002, similar to the North west region of the Netherlands (98% and 95%, respectively)[22], England and Wales (5-year survival of TC improved from 70% in 1971-1975 to 95% in 1991-1993)[4] and Sweden (5-year survival of seminoma and non-seminoma TC improved from about 87% and 47% in the mid 1960s to 97% and 96% in the mid 1990s, respectively)[5].

Survival analyses according to stage and histology showed better survival for localized disease and lymph node metastasis compared to distant metastasis of both seminoma and non-seminoma TC, similar to the results for most of the countries in the EUROCARE study, which covered the diagnostic period 1987-1992.[8]
American TC patients younger than 50 years exhibited significantly better survival for almost all histological and stage subgroups than TC patients of 50 years and older,[9] as in the EUROCARE study.[8] We also found higher survival rates for patients below the age of 50, but only 1-year survival was significantly different.
A group of patients can be considered cured when the conditional 5-year relative survival approaches 100%. Survival for this group of patients is then similar to that for the general population with the same age structure. Under these conditions seminoma TC patients are cured after 3 years and non-seminoma TC patients after 9 years.

Mortality

Mortality dropped from around 1 per 100,000 person-years to 0.3 in 2005, with the greatest decrease in the period 1979-1986. This pattern of steep decrease is similar to what was found for male populations of the United States and the European Union and is generally (in the absence of any other reasonable explanation) attributed to better systemic therapy.[4, 23, 24] The fluctuations in the period 1986-2005 are most likely due to random variation around a general trend of mortality and a rising incidence, mainly for localized TC, in the south of the Netherlands.[25]

Conclusion

Although the treatment combinations prescribed for these patients did not vary over time and the treatments administered followed national and international guidelines, there was a substantial improvement in TC survival over time, resulting in a marked decrease in mortality since the 1970s, which has been sustained in the last 15 years despite a marked increase in incidence.

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Chapter 2.4

Testicular cancer in Europe and the USA: Survival still rising among older patients

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Abstract

Introduction

Despite high curability, some testicular cancer patient groups may have increased mortality. We provide a detailed age- and histology-specific comparison of population-based relative survival of testicular cancer patients in Europe and the USA.

Methods

Using data from 12 European cancer registries and the USA SEER 9 database, we report survival trends for patients diagnosed with testicular seminomas and non-seminomas between 1993-1997 and 2003-2007. Additionally, a model based analysis was used to compare survival trends and relative excess risk of death (RER) between Europe and the USA adjusting for differences in age and histology.

Results

In 2003-2007, the 5-year relative survival of patients with testicular seminoma was at least 98% among those aged <50, while the survival of patients with non-seminoma remained 3-6% units lower.

Although relative survival of non-seminoma patients aged ≥50 years improved by 13-18% units between 1993-1997 and 2003-2007, it was still markedly poorer in the last period than the survival of seminoma patients of the same age group. Overall, RER was significantly increased for older (30+ years) compared to younger patients (<30 years), particularly for those aged 55+ years (RER=6.5), was strongly decreased for seminomas compared to non-seminomas (RER=0.28), and slightly higher in Europe compared to the USA (RER=1.20).

Conclusions

There remains little room for survival improvement among testicular seminoma patients, especially for those aged <50 years, while patients with non-seminoma continue to have a lower survival in all age groups compared to patients with seminomas. The lower survival of older TC patients seems mainly attributable to the lower survival of the non-seminoma patients.

Introduction

Testicular cancer (TC) is one of the most curable cancers nowadays, mainly due to the effective cisplatin-based chemotherapy for advanced disease that was introduced in the 1970s.[1, 2] Although the majority of the TC patients are 15 to 44 years old at the time of diagnosis, 18% of the patients are aged over 45 years at the time the TC is diagnosed and 7% are aged over 55 years.[2] Histopathologically, testicular germ cell tumors are divided into two major groups: seminomas and non-seminomas. Seminomas tend to grow more slowly and have a better prognosis than non-seminomas.[3] The age-specific incidence of non-seminomas peaks earlier, around the age of 25 years, than that of the seminomas, in which the incidence peaks about 10 years later.[3, 4] In TC patients aged over 40 years, the vast majority of the tumors are seminomas.[5] Both histology and stage are important factors for choice of treatment and prognosis.[6, 7]

Relative survival has been increasing for both histologies of TC since the 1970s, although more pronounced for the non-seminomas than for the seminomas.[8] In the period 1988-2001, 5-year relative survival of American seminoma and non-seminoma patients was 98% and 93%, respectively. This is quite comparable to Dutch survival estimates in the same period.[8, 9] Survival of TC patients over 50 years of age has been shown to be lower than that of younger patients.[2, 10] This could be due to suboptimal treatment, co-morbidities, a lower tolerance to chemotherapy, a different biological behavior of the tumor or a less favorable stage distribution in the elderly.[2, 10-12] However, the exact pattern in which the survival decreases by age is unknown, and recent detailed international comparisons of trends in TC survival are not available.

The aim of this study was to estimate and compare the trends in population-based relative survival of TC between Europe and the USA and to present age- and histology-specific relative survival for both continents.

Methods

Data

For Europe, the database of the European Network for Indicators on Cancer (EUNICE) Survival Cooperation was used, which includes information on the incidence and follow-up of cancer cases from 12 European population-based cancer registries from 1985 onwards. General inclusion criteria and data preparation procedures were described in detail in a previous publication.[13] For the USA, the Surveillance, Epidemiology and End Results (SEER) 9 limited-use database was used, with the same selection and inclusion criteria.[14]

We have included all TC cases aged 15-84 who were diagnosed in 1988-2007 from both the EUNICE and the SEER 9 database, along with corresponding age, sex, race (USA only), and calendar period-specific life tables to enable calculation of relative survival estimates. Cancer cases that were notified by death certificate or autopsy only were excluded.
For all analyses, patients from the European registries as well as the SEER9 registries were considered together. Patients aged 85 years or older at diagnosis were excluded from this study due to very small numbers in this age group and possible problems with follow-up of vital status.

Survival analyses

Five-year relative survival estimates were calculated separately for the European and American registries. Relative survival estimates were derived as ratios of the observed survival of the TC patients and the expected survival of the underlying general population with a similar sex and age distribution.[15] The survival estimates were calculated according to the Ederer II method.[16] All survival estimates were period estimates, which are exclusively based on the survival experience of patients during the specific calendar period for which they were derived.[17] This method has been shown to closely predict survival later observed for patients diagnosed in that period.[18-20]

First, 5-year period-based relative survival estimates were calculated for the calendar periods 1993-1997, 1998-2002, and 2003-2007, using a period-specific saturated Poisson regression model for relative survival.[21] To derive a test for survival trends, the periods 1993-1997, 1998-2002, and 2003-2007 were additionally included as numerical terms. In instances where registries had data available on incident cases until 2005 or 2006, but follow-up of vital status until 2007, hybrid analysis was used. This method enables estimation of up-to-date survival for situations where follow-up data are available for more recent years than incidence.[22, 23] Standard errors of the survival estimates were calculated with the delta method. Alpha=0.05 was used as a level of significance for the different tests.

Age and histology specific trend analyses

For the detailed age specific analysis, the age groups 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-64, and 65-84 years were considered. For analyses according to histology, the tumors were grouped into seminomas (ICD-O-3 morphology codes: 9060-9064) and non-seminomas (ICD-O-3 morphology codes: 9065-9085, 9100-9102, 9105). Tumors that could not be grouped as seminoma or non-seminoma were excluded from analyses according to histology (EUNICE: *n*=559, SEER: *n*=217). The age groups 15-29, 30-49 and 50+ were considered.

Modeling

In order to examine and compare survival trends between registries from Europe and the USA over time while adjusting for histology and age, we extended the previously described survival model, to include period of diagnosis (numerical variable, 1=1993-1997, 2=1998-2002, 3= 2003-2007), age (categorical variable, 4 age groups (15-29, 30-39, 40-54, 55-84)), histology (seminoma or non-seminoma) and continent (dichotomous variables). The output of this relative survival multiple regression analysis were fully adjusted relative excess risks (RER) of death with a 95% Wald confidence intervals (95% CI).

Results

Overall, data from 15,559 and 14,435 TC patients were selected from the EUNICE and SEER 9 databases, respectively, for this study (table 1). In Europe the number of cases contributed by each cancer registry varied between 275 (Estonia) and 4,373 (Norway), in the USA this varied between 573 (Hawaii) and 2,590 (Seattle).

Detailed age-specific 5-year relative survival of TC patients from the EUNICE and SEER databases in the period 2003-2007 is presented in table 2. For both the European and the American patients the 5-year relative survival was high, i.e. mostly 96% or higher for the age-groups up to 54 years. For those aged 55-64, 5-year relative survival seemed to be somewhat lower compared to the patients aged 54 years or less, while 5-year relative survival was markedly poorer for the small group of patients aged 65 years or older in both Europe and the USA, with survival estimates of 72% and 83%, respectively.

Table 1. Cancer registries, underlying populations, national coverage percentage, number of testicular cancer cases

Registry	Country	Registry underlying population (millions)	National coverage (%)	Number of testicular cancers (1988-2007)
Cracow	Poland	0.8	1.9	303
Estonia	Estonia	1.4	100	275*
Lithuania	Lithuania	3.4	100	576*
Slovenia	Slovenia	1.9	100	1,461
Turin	Italy	1.0	1.8	432*
Tuscany	Italy	1.2	2.1	421*
Eindhoven	The Netherlands	1.0	6.6	1,134
Scotland	U.K.	5.1	100	3,703
Finland	Finland	5.2	100	1,702
Norway	Norway	4.5	100	4,373
Geneva	Switzerland	0.4	5.3	314
Saarland	Germany	1.0	1.3	865
Total EUNICE		**26.9**	**4.5†**	**15,559**
Atlanta	USA	2.9	1.0	1,153
Connecticut	USA	3.4	1.2	1,907
Detroit	USA	4.0	1.4	2,058
Hawaii	USA	1.2	0.4	573
Iowa	USA	2.9	1.0	1,632
New Mexico	USA	1.8	0.6	923
San-Francisco-Oakland	USA	4.1	1.5	2,277
Seattle-Puget Sound	USA	4.0	1.4	2,590
Utah	USA	2.2	0.8	1,322
Total SEER 9	**USA**	**26.7**	**9.5**	**14,435**

** For Estonia and Tuscany, data were available up to 2005, for Turin up to 2006, while for Lithuania, data were available since 1990.*

† As percentage of Europe (not including Russia, Turkey, Kazakhstan, Azerbaijan, Armenia and Georgia)

The histological distribution of testicular cancer is presented in table 3. In both populations, there was a clear age specific pattern in the proportion of seminomas and non-seminomas, with the proportion of patients with non-seminoma making up the majority in the age-group 15-29 years, while in the two older age groups 65 to 83% of the cases had a seminoma. The proportion of patients with seminoma was marginally higher in each age group and period in the USA. While the proportion of seminomas may have increased slightly among patients aged 15-29 in Europe, proportions were rather stable in the other age groups as well as the USA.

Table 2. Age-specific five-year relative survival of testicular cancer patients from the EUNICE and SEER 9 registries in the period 2003-2007

Age-groups	5-year relative survival EUNICE			5-year relative survival SEER 9		
	n	PE	SE	*n*	PE	SE
15-19 years	143	96.2	1.6	177	94.0	1.9
20-24 years	518	96.0	0.9	493	96.3	0.9
25-29 years	789	96.0	0.7	683	97.2	0.7
30-34 years	853	95.8	0.7	718	96.4	0.8
35-39 years	796	97.5	0.6	605	97.0	0.8
40-44 years	576	97.1	0.8	513	98.1	0.8
45-49 years	343	93.1	1.6	341	95.7	1.4
50-54 years	209	96.1	1.7	198	97.4	1.5
55-64 years	195	93.2	2.4	143	89.8	2.9
65-84 years	120	72.3	5.4	62	82.6	7.0
Total	**4,542**	**95.7**	**0.4**	**3,933**	**96.6**	**0.4**

PE = point estimate; SE = standard error

Table 3. Histological distribution of testicular cancer from the EUNICE and SEER 9 registries by age groups

	Histology	1993-1997		1998-2002		2003-2007	
		n	%	*n*	%	*n*	%
EUNICE							
15-29 years	Seminoma	377	31	463	33	486	35
	Non-seminoma	848	69	940	67	896	65
30-49 years	Seminoma	1,204	65	1,600	68	1,662	67
	Non-seminoma	646	35	747	32	813	33
50-84 years	Seminoma	316	80	334	78	374	79
	Non-seminoma	77	20	92	22	97	21
SEER 9							
15-29 years	Seminoma	421	39	465	39	493	37
	Non-seminoma	670	61	722	61	843	63
30-49 years	Seminoma	1,424	70	1,637	71	1,476	69
	Non-seminoma	599	30	656	29	672	31
50-84 years	Seminoma	207	82	238	82	307	83
	Non-seminoma	45	18	51	18	64	17

The 5-year relative survival of seminoma patients in the age groups 15-29 and 30-49 years was generally very high in both the USA and Europe (table 4) in all 3 periods, and by 2003-2007, estimates reached at least 98.6% both populations. A significant improvement was seen among European seminoma patients for the age groups 15-29 and 30-49. While no significant improvement was found for the USA patients, in which the already very high survival in the first period left little scope for further improvement.
The survival for non-seminoma patients in the age groups 15-29 and 30-49 years varied between 90% and 95%, with little change over time and very little difference between Europe and the USA. For the age groups 15-29 and 30-49, the 5-year relative survival of non-seminoma patients was consistently between 2% to 6% units lower than that of the seminoma patients within the same age group in all 3 periods of diagnosis.
In both Europe and the USA, the largest percentage units change in 5-year relative survival was seen in the age group 50-84, for whom a significant increase in survival over time was seen in Europe for seminoma patients and in the US for non-seminoma patients. The survival of American patients was slightly higher than that of patients in the EUNICE registries in all 3 examined periods for both histology groups, except for non-seminoma patients in 1998-2002. Among patients aged 50 years or older, the 5-year relative survival of non-seminoma patients was 8 to 10% units lower than that of seminoma patients in the period of 2003-2007, a larger difference than seen for younger age groups, but smaller than seen in previous periods.

The relative survival multiple regression model for testicular cancer is presented in table 5. The model confirms, after adjusting for age and histology, a statistically significant reduction in excess mortality over time, an increasing excess mortality with for older (≥30 years) compared to younger patients (<30 years), and a highly increased excess mortality for those aged ≥55 years. A much lower excess mortality was found for seminomas compared to non-seminomas (RER=0.28, $p<0.01$). Overall, a statistically significantly increased RER of 1.20 was found for the EUNICE registries in comparison to the SEER registries.

Table 5. Multiple relative survival regression analyses for patients with testicular cancer

	Relative excess risk of death	**95% Wald Confidence limit**	***P*-value**
Period of diagnosis*	0.79	0.73-0.86	<0.01
Age group			
15-29 years	1.00		
30-39 years	1.22	1.02-1.45	0.03
40-54 years	1.76	1.44-2.15	<0.01
55-84 years	6.50	5.14-8.23	<0.01
Histology			
Non-seminoma	1.00		
Seminoma	0.28	0.24-0.33	<0.01
Registries			
SEER 9	1.00		
EUNICE	1.20	1.04-1.39	0.01

** Period of diagnosis was included as a numerical variable (1=1993-1997, 2=1998-2002, 3=2003-2007)*

Table 4. Trends in model-based 5-year relative survival by age and histology of testicular cancer patients from the EUNICE and SEER 9 registries

	Histology	1993-1997		1998-2002		2003-2007		Change[a]	*P*-value for trend
		PE	SE	PE	SE	PE	SE		
EUNICE									
15-29 years	Seminoma	95.4	1.1	96.4	1.0	99.0	0.5	3.6	<0.01
	Non-seminoma	93.4	0.9	94.7	0.8	94.8	0.8	1.4	0.41
30-49 years	Seminoma	96.6	0.6	98.0	0.5	98.6	0.4	2.0	<0.01
	Non-seminoma	90.6	1.3	93.7	1.0	93.0	1.0	2.4	0.11
50-84 years	Seminoma	87.1	2.6	91.1	2.2	93.7	1.7	6.6	0.02
	Non-seminoma	70.2	6.6	84.7	4.8	83.5	4.3	13.3	0.07
SEER									
15-29 years	Seminoma	98.1	0.8	99.0	0.5	99.0	0.6	0.9	0.34
	Non-seminoma	94.7	0.9	94.8	0.9	95.5	0.8	0.8	0.55
30-49 years	Seminoma	97.6	0.5	98.1	0.4	98.6	0.4	1.0	0.04
	Non-seminoma	92.5	1.2	92.2	1.1	93.7	1.0	1.2	0.30
50-84 years	Seminoma	94.3	2.6	94.7	1.8	96.8	1.6	2.5	0.22
	Non-seminoma	70.7	7.7	77.7	6.5	88.9	4.6	18.2	0.048

PE = point estimate; SE = standard error

[a] *Change in the 5-year relative survival between 1990-1994 and 2000-2004, in % units*

Discussion

Our analysis of recent trends in testicular cancer survival in Europe and the USA found consistently higher 5-year relative survival for seminoma patients compared to non-seminoma patients, with the biggest differences among these groups seen among patients in the oldest age group (50-84 years). Despite considerable rises in the relative survival in the oldest age group, the multiple regression analysis showed that relative survival of the patients aged 55 years and older was still considerably poorer than that of younger patients. The analysis suggests that mainly patients with non-seminoma testicular cancer remain at an increased risk for mortality in all age groups.

Five-year relative survival estimates for TC patients for the age groups <45, 45-54, 55-64 and 65-74 years have been published for both European (EUROCARE-4 data) and American (SEER) patients for the period 1995-1999/2000.[2, 24] Both studies showed that survival of the patients aged 45-54 years was only 1% or 2% units lower than that of the patients younger than 45 years. Survival of patients aged 55 to 64 years was 4% to 9% units poorer than that of patients aged <45 years, while survival of patients aged 65 to 74 was at least 13% units lower than that of the youngest age group. This pattern of the decrease of survival with age is rather similar to our survival estimates presented in table 2 and the results of our multiple regression analyses which showed that patients of 55 years of age and older had the worst survival.

The results of this study indicate that among TC patients, mainly non-seminoma patients remain at increased risk of mortality. It should to be noted however, that results of a previous high resolution study[11] suggest that the large difference in survival between the two histology groups is mainly explained by the greater propensity of the non-seminomas to metastasize. The survival differences between seminomas and non-seminomas that have been found in this study are rather consistent with previously reported survival differences between these two histologies.[8-10] Due to more rapid growth and more aggressive behavior non-seminomas tend to have a less favorable stage distribution than seminomas and within the group of metastasized patients they also have a poorer prognosis than seminomas.[9, 25] It is therefore not unexpected that the non-seminoma patients have a somewhat lower relative survival than seminoma patients.

Based on the high relative survival of seminoma patients aged 50 to 84 years, it seems that the poorer survival of TC patients aged ≥55 years that was found in the multiple regression analysis is mainly attributable to the non-seminoma patients in that age group. The rather large rises in the survival of patients aged 50-84 in the recent decade suggests that increasing effectiveness of therapy was achieved among these patients in these years.
The however remaining poorer survival for older TC patients could have been caused by a less favorable stage distribution, possibly due to delayed diagnosis, less tolerability to specific therapy modalities such as chemotherapy, co morbidities and/or suboptimal treatment.[10] A previous study based on SEER data showed that, except for the localized seminomas, the worse survival for TC patients over 50 years of age was still present after stratification for histology and stage (localized vs. metastasized).[10] Less favorable stage or histology distributions can thus not solely explain the worse survival in older TC patients. The main three chemotherapeutic agents for TC (cisplatin, etoposide, and bleomycin) have been

associated with increased toxicity in the elderly.[26] One of the most important toxicities is bleomycin related pulmonary toxicity, which can be fatal. Several studies have reported that bleomycin related (fatal) pulmonary toxicity is increased in patients over the age of 40 and in patients with poor renal function.[27, 28] Older TC patients might have received dose reductions due to (expected) toxicities, which could have affected their long-term survival or they could have died due to the toxicity. In addition, there is a general tendency to assume that tolerance to chemotherapy is lower in older people, which may result in under-treatment of elderly cancer patients for fear of excessive toxicity.[26] However, a reduction of the doses of chemotherapy is generally not recommended for elderly cancer patients. [26, 29]

A limitation to this study was the lack of availability of data on stage and treatment of patients, which could have been used to further investigate the causes of the lower survival in the older patients. Because we only used data of certain regions of Europe and the USA, the results of this study may not be entirely representative for the whole of Europe and the USA.

Conclusions

The trends in relative survival of TC patients do not seem to differ between Europe and the USA. Survival for seminoma patients, particularly for the age groups 15-49, has come extremely close to the maximum possible by 2003-2007, representing an essentially total lack of cancer specific mortality among these patients, and leaving very little if any further room for further improvement of survival in these patients.
Survival of non-seminoma patients was consistently lower than that of seminoma patients. Although the largest improvement of survival of non-seminoma patients was noted in patients aged 50 years and older, the non-seminoma patients in this age group still have the largest survival difference compared to seminoma patients. Future research into the lower survival of older TC patients should thus focus on these patients, to firstly establish why they have poorer survival and secondly address the problem of the causes of the lower survival, so that these patients can also benefit fully from the excellent opportunities that are available to cure TC.

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Chapter 3

Epidemiology of penile cancer

Chapter 3.1

Incidence trends and survival of penile squamous cell carcinoma in the Netherlands

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Abstract

We examined trends in the incidence and mortality, and described the survival of patients with penile squamous cell carcinoma in the Netherlands between 1989 and 2006. On the basis of nation-wide population-based data, three-year moving average European age-standardized incidence and ten-year relative survival estimates were calculated. Penile squamous cell carcinomas were categorized according to stage grouping based upon the TNM classification. In the 17-year study period, 2000 primary penile cancers were diagnosed in the Netherlands of which 1883 (94%) were squamous cell carcinomas. Median age at diagnosis was 68 years. The majority of patients (57%) were diagnosed with localized tumors (stage 0 or stage I). The percentage of missing disease characteristics increased with increasing age. The three-year moving average incidence rate of patients with penile squamous cell carcinoma increased significantly from 1.4 per 100,000 person-years in 1989 to 1.5 in 2006 with an estimated annual percentage of change of 1.3%. Ten-year relative survival of patients according to the different stage groups was 93% for stage 0, 89% for stage I, 81% for stage II, the nine-year survival was 50% for patients with stage III disease and a two-year survival of 21% for patients was found for stage IV disease. The present study shows that the incidence rate of penile squamous cell carcinoma in the Netherlands has increased slightly, especially the incidence of carcinomas *in situ*. Patients with stage III and IV tumors have poor survival.

Introduction

Primary penile cancer is a relatively rare neoplasm in the Western world with an age-adjusted incidence rate of around 1 per 100.000 men.[1] More than 95% of these tumors are squamous cell carcinomas.[2] Causative risk factors for penile cancer include phimosis,[3] tobacco use,[4] and infection with human papillomavirus (HPV),[5-7] while neonatal circumcision is suggested to have a protective effect.[8] There is a worldwide geographic variation in incidence that could be caused by differences in socio-economic status, hygiene, religious and cultural conditions.[1, 9] For example, the incidence of penile cancers ranges from 0.04 per 100,000 men in Jewish populations in Israel (high incidence of circumcision) to 3 – 4 per 100,000 men in non-Western countries, such as Brazil, India, and Southern Africa.[1] Although the exact pathogenesis is largely unknown,[5] inflammation may represent a critical component in tumor development or progression as many penile cancers arise at sites of infection, chronic irritation or injury.[3] Prognosis is affected by tumor stage, grade and especially presence of lymph node involvement at diagnosis.[10, 11]

In recent years, the overall incidence of penile cancer has decreased in the United States.[12, 13] However, reported incidence rates varied by race/ethnicity being higher in Hispanic and Afro-American men.[1, 12-14] Trends of incidence of penile carcinoma in the Netherlands (with a large majority of Caucasian inhabitants) could therefore differ from those reported in the United States. We conducted a study of the trends in incidence and survival in the Netherlands in the period 1989-2006. Although a short overview is given of all penile malignancies, the main focus of the present study is on penile squamous cell carcinomas.

Material and methods

Data on primary malignant penile cancers diagnosed in the Netherlands from 1989 to 2006 were obtained from the nation-wide population-based Netherlands Cancer Registry (NCR) covering 14.8 million inhabitants in 1989 to 16.3 million inhabitants in 2006. The NCR combines the data of the eight Dutch regional cancer registries since 1989. These eight regional cancer registries receive lists of newly diagnosed cancer patients on a regular basis from the pathology departments of the hospitals, all participating in a nation-wide network (PALGA). In addition, the medical records departments of hospitals provide lists of diagnoses of outpatients and hospitalized cancer patients. Following these notifications, trained registrars extract patient and tumor characteristics (topography, histology, stage, date of diagnosis) data from the medical records.

All penile malignancies were classified according to the International Classification of Diseases for Oncology.[15] If patients had 2 or more invasive penile squamous cell carcinomas, only the first tumor was included in the survival analyses. A new primary tumor was defined as an invasive tumor more than 3 months after an *in situ* tumor diagnosis (n = 10), or a difference in subtype compared with the former penile tumor (n = 1). For patients with 2 invasive tumors (n = 3) the second tumor was excluded for all analyses of this study due the high chance that the second tumor was a recurrence. For patients with a non-invasive tumor following a previous invasive tumor diagnosis, only the invasive tumor was included in the survival analyses. To characterize the stage of the disease all the available pathological data of the first three months of diagnosis were used. If (parts of) the pathological stage was unknown or missing, (parts of) the clinical stage was used to determine the stage of the penile neoplasm. To analyze changes in stage distribution the chi-square test was used.

Penile squamous cell carcinomas were categorized according to stage grouping based upon the 6th TNM classification, that is stage 0 (Tis/Ta N0/Nx M0/Mx or Tx Nx Mx and registered as tumor *in situ*), stage I (T1 N0/Nx M0/Mx), stage II (T1 N1 M0/Mx, T2 N0-1 M0/Mx), stage III (T1-2 N2 M0/Mx, T3 N0-2 M0/Mx) and stage IV (T4, any N, any M, or any T, N3, any M, or any T, any N, M1), respectively.[16] Stage was categorized as missing if the T-stage was categorized as 0 or X and the tumor was registered as invasive. Tumors were graded as well differentiated (G1), intermediately differentiated (G2), poorly differentiated (G3), undifferentiated (G4) or unknown (Gx).
Mortality data were retrieved from the website of the NCR.[17] Three-year moving average age-standardized incidence and mortality rates were calculated per 100.000 person-years. Standardization was performed according to the European standard population. Evaluation of the trend in incidence and mortality rates were performed by calculating the estimated annual percentage changes (EAPC) with the Joinpoint program.[18]

Data on vital status (available until 1st January 2008) were obtained from the hospital records and the mortality register of the Central Office for Genealogy (an institution that registers all deaths in The Netherlands via the municipal population registries). Because the cause of death is not supplied by the Central Office for Genealogy, it is unknown in the NCR database. Hence, we calculated relative survival estimates for patients with penile squamous cell carcinomas. Relative survival is an estimation of the disease-specific survival. It is calculated as the absolute survival amongst cancer patients divided by the expected survival for the general population with the same sex and age structure.[19] For patients with an i*n situ* tumor before occurrence of an invasive tumor follow-up was calculated from the incidence date of the invasive tumor. Follow-up on vital status was available for patients diagnosed since 1995 only. Hence, patients diagnosed with penile carcinoma before 1995 were excluded from the survival analyses (n = 502). Vital status is missing for 7% (n = 96) of the 1368 patients with squamous cell carcinomas diagnosed since 1995. Patient older than 95 years (n = 10) were excluded from the survival analyses resulting in the inclusion of 1262 patients with squamous cell carcinoma of the penis for the relative survival estimates, that is 67% of the total number of patients diagnoses with squamous cell carcinoma of the penis between 1989 and 2006. For evaluation of possible independent prognostic factors, a multivariate survival analysis was performed according to the Cox proportional hazards model. Because the cause of death was unknown in the NCR database, we used overall survival for this analysis.

Results

Between 1989 and 2006, 2000 primary penile cancers were diagnosed in the Netherlands in 1986 men. Squamous cell carcinomas were the most common histological subtype comprising of 94% of the reported malignancies. Other penile tumors were melanoma (2%), Pagets disease (<1%), basal cell carcinoma (<1%), adenocarcinoma (<1%) and a group of other histologies (3%). There was little variation in the histological distribution over time. Focusing on the squamous cell carcinomas, the median age at diagnosis was 68 years. The incidence of these penile tumors however increased with age. The highest age-specific incidence rates of non-invasive en invasive penile carcinoma were found in men between 80 to 84 years old (1.7 per 100,000) and men of 85 years and older (17 per 100,000), respectively.

An overview of the tumor characteristics at diagnosis according to age is shown in table 1. Nineteen percent of the squamous cell carcinomas were carcinoma *in situ* (*n* = 353) and 81% (*n* = 1530) were invasive. The majority of tumors were staged T1 (42%), well differentiated (29%) and diagnosed at a localized stage (58%, stage 0 and I). The percentage of invasive tumors was lower in the age-category 20-39 years (49%). The percentage of patients with missing primary tumor stage, regional lymph node involvement and disease stage tend to increase with higher age of the patients. Twenty-one percent of the patients aged 80 years had a missing primary tumor stage en 31% of these patients had missing regional nodal involvement status, while these percentages were only 6% and 11%, respectively, in patients aged 20 to 39 years. Of the patients with primary invasive penile tumors and known regional involvement (*n* = 1162), staging of the lymph nodes was clinically in 63% (*n* = 728) and surgically in 37% (*n* = 434), respectively.

The three-year moving average overall European age-standardized incidence rate of penile squamous cell carcinoma increased from 1.4 per 100,000 person-years in 1989 to 1.5 in 2006 (figure 1), with EAPC of 1.3% (95% confidence interval (95% CI): 0.1% – 2.6%) over the whole study period. The three-year moving average European age-standardized incidence rate of non-invasive carcinomas increased significantly from 0.1 in 1989 to 0.3 per 100,000 person-years, with an EAPC of 4.5% (95% CI: 2.0% – 6.9%). The incidence rate of the invasive tumors was relatively stable and varied between the 0.9 and 1.3 per 100,000 person-years (EAPC=0.9%, 95%CI: -0.6% – 2.4%).The three-year moving average of the mortality rate of all penile cancers is also shown in figure 1 and varied between the 0.2 and 0.4 per 100,000 person-years in the Netherlands. The decreasing trend of the mortality was near significant (EAPC = -2.4%, 95%CI: -4.8% – 0.1%).

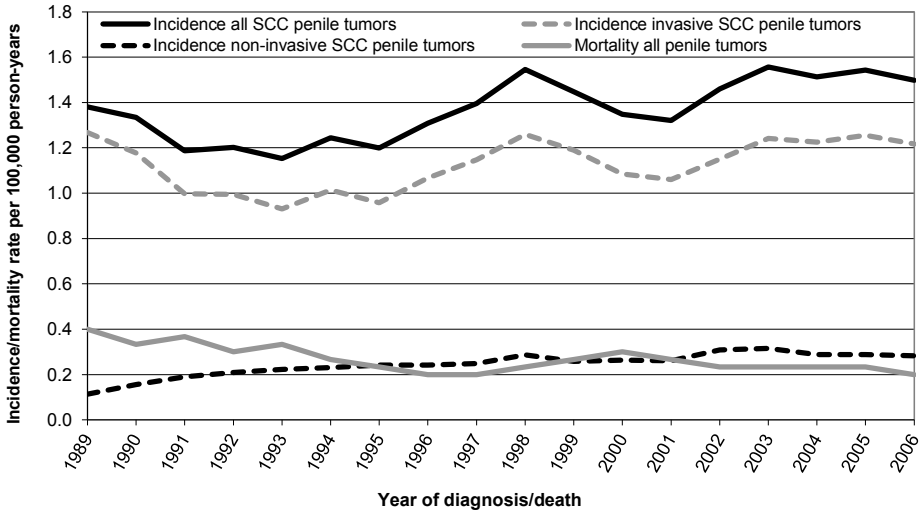

Figure 1. Three-year moving average European age-standardized penile squamous cell carcinoma incidence rates and three-year moving average European age-standardized of all penile cancer mortality rate per 100,000 person-years in the Netherlands

Table 1. Overview of penile squamous cell carcinoma characteristics at diagnosis in the Netherlands between 1989-2006

	Age at diagnosis				Total
	20-39 yrs *n* **(%)**	**40-59 yrs** *n* **(%)**	**60-79 yrs** *n* **(%)**	**≥ 80 yrs** *n* **(%)**	**(*n* = 1883)** *n* **(%)**
Penile tumor[1]					
Non-invasive tumor	46 (51%)	133 (25%)	135 (15%)	39 (11%)	353 (19%)
Invasive tumor	44 (49%)	390 (75%)	781 (85%)	315 (89%)	1530 (81%)
T-stage					
T0	0	0	2 (<1%)	0	2 (<1%)
Tis	43 (48%)	128 (25%)	128 (25%)	128 (25%)	128 (25%)
Ta	1 (1%)	3 (<1%)	3 (<1%)	3 (<1%)	3 (<1%)
T1	24 (27%)	200 (38%)	200 (38%)	200 (38%)	200 (38%)
T2	14 (16%)	98 (19%)	98 (19%)	98 (19%)	98 (19%)
T3	3 (3%)	20 (4%)	20 (4%)	20 (4%)	20 (4%)
T4	0	4 (<1%)	4 (<1%)	4 (<1%)	4 (<1%)
Tx	5 (6%)	70 (14%)	131 (14%)	71 (21%)	277 (15%)
Histological grade of invasive tumors					
Well	15 (34%)	125 (32%)	214 (27%)	91 (29%)	445 (29%)
Intermediate	16 (36%)	146 (37%)	265 (34%)	103 (33%)	530 (35%)
Poor	4 (9%)	41 (11%)	101 (13%)	49 (16%)	195 (13%)
Undifferentiated	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Missing	9 (20%)	78 (20%)	200 (26%)	71 (23%)	358 (23%)
N-stage of invasive tumors[2]					
N0	29 (66%)	247 (63%)	468 (60%)	171 (54%)	915 (60%)
N+	10 (23%)	77 (20%)	124 (16%)	36 (11%)	247 (16%)
N1	7 (16%)	25 (6%)	45 (6%)	16 (5%)	93 (6%)
N2	3 (7%)	43 (11%)	58 (7%)	13 (4%)	117 (8%)
N3	0	9 (2%)	21 (3%)	7 (2%)	37 (2%)
Nx	5 (11%)	66 (17%)	189 (24%)	108 (34%)	368 (24%)
M-stage of invasive tumors[2]					
M0	30 (68%)	286 (73%)	558 (71%)	215 (68%)	1089 (71%)
M1	0	2 (<1%)	11 (1%)	3 (1%)	16 (1%)
Mx	14 (32%)	102 (26%)	212 (27%)	97 (31%)	425 (28%)
Disease stage					
Stage 0	46 (51%)	133 (25%)	135 (15%)	39 (11%)	353 (19%)
Stage I	21 (23%)	184 (35%)	374 (41%)	146 (41%)	725 (39%)
Stage II	15 (17%)	76 (15%)	173 (19%)	65 (18%)	329 (17%)
Stage III	6 (7%)	56 (11%)	76 (8%)	28 (8%)	166 (9%)
Stage IV	0	15 (3%)	36 (4%)	11 (3%)	62 (3%)
Missing stage	2 (2%)	59 (11%)	122 (13%)	65 (18%)	248 (13%)

[1] *Non-invasive tumors included all T0, Tis, Ta and some of the Tx tumors, while the invasive tumors included the T1-T4 tumors and most of the Tx tumors.*

[2] *All non-invasive tumours were staged N0 or Nx and M0 or Mx.*

Focusing on disease stage at diagnosis, the percentage of men with stage 0 tumors increased from 16% in the period 1989-1994 to 20% in the period 2000-2006 ($p = 0.13$) (figure 2). There was little variation over time in the percentage of stage I, II and III tumors. Stage IV tumors decreased from 5% in the first period to 2% in the second period and increased again to 3% in the last period (p=0.07). The percentage of missing stage decreased significantly from 15% in 1989-1994 to 9% in 2001-2006 (p<0.001).

Although evaluation of the different treatment modalities was not the primary focus of this article, 91% of the patients (n = 1708) were treated with surgical resection including 7% (n = 124) with adjuvant treatment (i.e. chemotherapy, or radiotherapy, or a combination). Relatively more patients were treated with adjuvant treatment with increase of stage (data not shown) .

Patients with poorly differentiated tumors (G3) had worse 10-year survival compared with those with better differentiated tumors (66% (95% CI, 49% - 82%) for G3 vs. 73% (95% CI, 63% - 83%) for G2 and 77% (95% CI, 65% - 88%) for G1-tumours, respectively). As expected, patients with regional lymph node involvement (N+) had considerable worse survival compared with those without nodal involvement (No) (figure 3, 38% (95% CI: 26%-51%) vs. 90% (95% CI:82%-97%). Ten-year relative survival of patients with stage 0 (non-invasive) tumors at diagnosis was 93% (95% CI: 81%-103%), this was 89% for patients with stage I tumors (95% CI: 79% - 98%) and 81% for patients with stage II tumors (95% CI: 65% - 96%, figure 4). A nine-year relative survival of 50% (95% CI: 35% - 64%) was found for patients with stage III tumors and the two-year relative survival of patients with stage IV tumors was 21% (95% CI: 10% - 36%). No survival estimates were possible after 9 and 2 years for patients with stage III and IV tumors, respectively, because less than 10 patients were alive at that follow-up time.

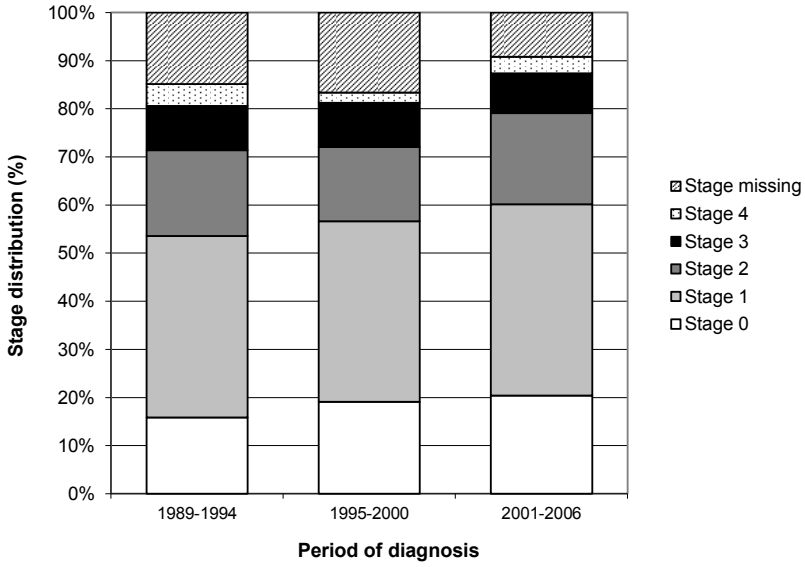

Figure 2. Disease stage by period of diagnosis of patients diagnosed with penile squamous cell carcinoma from 1989 to 2006

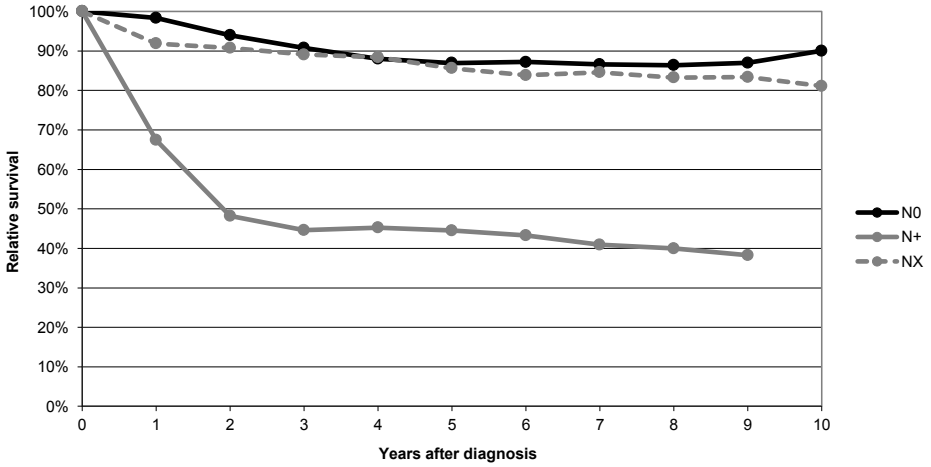

Figure 3. Ten-year annual relative survival of patients with penile squamous cell carcinoma according to regional lymph node involvement
(N0 = no regional lymph node involvement, N+ = presence of regional lymph node involvement, Nx = missing regional lymph node status. No survival estimate was possible after 9 for patients with N+ tumors, because less than 10 patients were alive at that follow-up time)

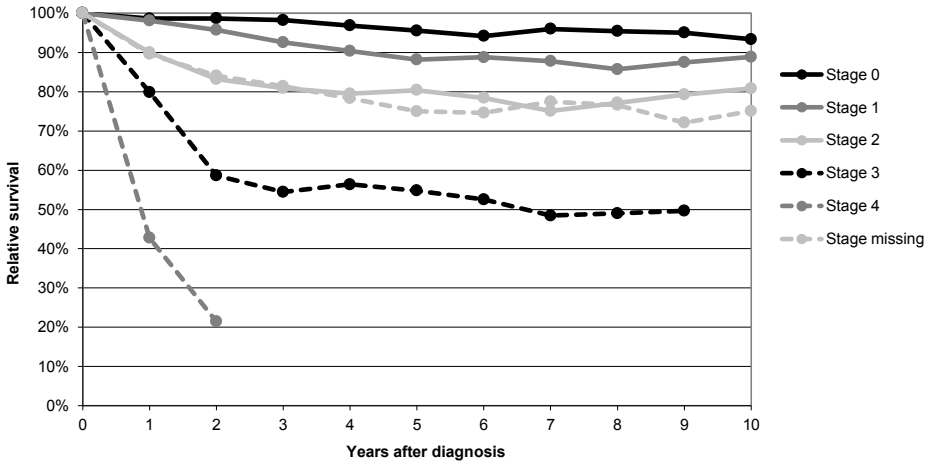

Figure 4. Ten-year annual relative survival of patients with penile squamous cell carcinoma according to disease stage at diagnosis
(No survival estimates were possible after 9 and 2 years for patients with stage III and IV tumors, respectively, because less than 10 patients were alive at that follow-up time)

The multivariate analysis showed that age, primary tumor stage, presence of regional lymph node involvement, and presence of distant metastasis were all prognostic factors for overall mortality (table 2).

Table 2. Cox multivariate regression analysis of variables associated with survival for patients diagnosed with invasive penile squamous cell carcinoma

Variables	Hazard ratio (95% CI)	*P*-value
Age, one year increment	1.06 (1.05 – 1.07)	< 0.001
T-stage		
T1	1.0	
T2	1.3 (1.0 – 1.6)	0.07
T3	2.4 (1.7 – 3.5)	< 0.001
T4	5.5 (2.7 – 11.3)	< 0.001
Missing Tx	1.3 (1.0 – 1.7)	0.04
Lymph node status		
N0	1.0	
N+	3.0 (2.3 – 3.8)	< 0.001
Missing, Nx	1.2 (1.0 – 1.6)	0.11
Presence of distant metastasis		
M0	1.0	
M1	2.6 (1.3 – 5.4)	0.01
Missing, Mx	1.2 (1.0 – 1.5)	0.09
Grade of differentiation		
Well	1.0	
Intermediate	1.0 (0.8 – 1.3)	1.00
Poor	1.1 (0.8 – 1.5)	0.5
Missing, Gx	0.9 (0.7 – 1.2)	0.4

95% CI: 95% Confidence Interval

Discussion

This study shows that the overall European age-standardized incidence rate of penile squamous cell carcinoma in the Netherlands has increased slightly from 1.4 to 1.5 per 100,000 person-years between 1989 and 2006 (with an EAPC of 1.3%). This finding is in contrast to recent studies from Finland and the United States, where the incidence rates decreased over time.[9, 12, 13] For example, Goodman *et al*. reported an EAPC of -1.2% between 1973 and 2003 in the United states, and showed that the incidence declined more markedly in Afro-American men compared with Whites.[13]

However, they only investigated invasive penile cancers possibly explaining parts of the differences in results. Our figures indicate that the significant increase in incidence of carcinoma *in situ* contributes to the overall increasing incidence rates of penile squamous cell carcinomas. Rippentrop *et al*. reported an increasing incidence trend of carcinomas *in situ* in the United Stated between 1973 and 1998.[14] A possible explanation for the higher rate of carcinomas *in situ* could be better awareness and less hesitation to seek treatment leading to earlier diagnosis and treatment.

In Denmark, a statistically significant decline in the overall rate of penile cancer was found between 1943 and 1990 despite a low and stable national circumcision rate of approximately 1.6%.[20] In that 50-year period the proportion of Danish dwellings having a bath and routine access to clean water gradually increased over the study period.[20] It is likely that such improvements in sanitary conditions have found place in the Netherlands far before the current study period (1989-2006) explaining why no decreased incidence was found in the current series. The incidence of penile carcinoma was already very low in 1989, the first year of the NCR. In an extra analysis using only the incidence data between 1970 and 1989 of the Comprehensive Cancer Centre South, located in the Southern region of the Netherlands and covering 1.0 million inhabitants in those years, the incidence rates did not change over time.

A likely explanation for the contrary results in invasive penile cancer incidence rates is not easily made. The incidence rates in the United States were evaluated using the Surveillance Epidemiology and End Results (SEER) data covering approximately 26% of the U.S. population. The incidence of penile carcinoma has shown disparities in the United States being higher in Hispanic and Afro-American men.[12-14] Although these data are considered representative of the greater U.S. populations, they might not be representative for certain cancer sites.[21] In the current study we used data of the NCR fully covering the Netherlands. Demographic differences between the populations might explain the different outcomes.

This study was consistent with previous studies that showed that approximately 95% of primary penile malignancies were squamous cell carcinomas, the majority of the tumors were well and intermediate graded (29% and 35%, respectively),[1, 12, 13] and survival is dependent on the stage at diagnosis with more deaths in higher staged tumours.[10, 11] Our multivariate analysis indicates that more advanced primary tumors (T3 and T4), presence of regional lymph node involvement and presence of distant metastasis are in particularly poor prognosticators for worse survival. Of interest, although the median age of patients was 68 years and the age-adjusted incidence of penile carcinoma peaks after 80 years, 1% of men with penile carcinoma were younger than 30 years at diagnosis and 5% younger than 40 years. While the exact pathogenesis of penile squamous cell carcinoma is largely unknown, the HPV virus is an established etiologic factor in at least 40% of penile tumours.[6] Unfortunately, HPV status was not known in the patients in the present study. Previous studies have shown that some subtypes are typically HPV related.[22] However, subgroup analysis of histological subtypes was also not possible because the histological subtype was often not classified by the pathology laboratories.

Most of the penile tumors (58%) were diagnosed at a localized stage, that is stage 0 (19%) and I (39%). Primary non-invasive carcinomas (stage 0) do not metastasize. Hence, invasive nodal staging is not needed in this subgroup. On the other hand, patients with clinical stage I tumors (cT1N0M0) could have occult metastases. These patients have potentially curable disease when treated adequately after diagnosis, emphasizing the need for optimal staging and treatment. The single most important prognostic factor for cancer-specific survival is presence of inguinal nodal involvement.[10, 11] Surgical removal of occult nodal metastases offers a survival benefit compared with lymphadenectomy when occult disease becomes clinically apparent during close surveillance.[23, 24] Unfortunately, elective lymphadenectomy is

associated with significant morbidity,[25] and is unnecessary in approximately 80% of clinically node-negative patients,[26] precluding its prophylactic use. Dynamic sentinel node biopsy is considered a more suitable staging method that only removes the lymph nodes on a direct lymphatic drainage pathway of the tumour.[27] Only groins with tumor-positive sentinel nodes undergo a completion ipsilateral inguinal lymphadenectomy avoiding unnecessary morbidity in tumor-negative groins.

During the years, fewer patients were registered with a missing stage, indicating that staging by the clinician in the medical reports and/or the quality of registration by our trained registrars has improved. The percentage of missing disease characteristics seems to increase with increasing age. This suggests that older patients are staged less accurately and are potentially undertreated. An explanation could be that this subgroup of patients has more co-morbidity interfering with (invasive) staging.

Our data show that relative survival rates in patients with stage 0 - II tumors is fairly good (81-93%) suggesting contemporary treatment is effective in the majority of these men. Patients with stage III and IV tumors have poor survival (figure 4). Relative survival rates of these patients appear to be at least similar as survival of patients in the United States as reported by SEER.[28] Several previous studies have shown that survival in node-positive patients is negatively influenced by the extent of nodal disease,[10, 11] especially pelvic metastases (stage IV) being a particularly poor prognosticator.[29, 30] Patients in previous series were treated by surgery with or without radiotherapy suggesting this management is suboptimal in those with prognostic unfavorable features. Recently, TPF chemotherapy treatment (Taxanes (T), cisplatin (P) and Fluorouracil (F)) has shown potential in down staging malignant disease in patients with unresectable or recurrent nodal penile carcinoma.[31] Induction treatment followed by surgical resection in responding patients may lead to improved outcome in those with prognostic unfavorable stage groups.[32]

Using data from population-based data registries is not without limitations. The primary focus of the NCR is collecting data on all incident cancer cases, including stage at diagnosis and patient survival data. Although the scope and magnitude of these data make it excellent for studying rare malignancies, several variables that could be of interest were missing, for example HPV status, tobacco use, circumcision status and socio-economic factors. Furthermore, race was not included in the present study, which has recently shown to be of importance in the incidence rates in the United States.[1, 12, 13] Finally, although the NCR also collects some information about treatment, full details were unavailable. Hence, we were not able to analyze the survival of patients with advanced penile tumors (stage III or IV) stratified by treatment modality.

In conclusion, our data indicate that the incidence of penile squamous cell carcinoma has increased slightly between 1989 and 2006 in the Netherlands caused largely by the increased incidence of carcinomas *in situ*. Survival is dependent on disease-stage at diagnosis. Especially, patients with stage III and IV tumors have poor survival.

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Chapter 3.2

Population-based survival of penile cancer patients in Europe and the USA: No improvement since at least 1990

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Abstract

Introduction

Penile cancer is a rare neoplasm in Western countries, and detailed studies on trends in population-based survival of penile cancer have never been published before. We examine population-based trends in survival in Europe and the USA.

Methods

Data from 3,297 European and 1,820 American penile cancer patients, contributed by 12 European cancer registries and the SEER Program of the USA were included in this study. Period analysis techniques were used to examine relative survival trends overall, as well as for four geographic regions in Europe, and for the age groups 15-54, 55-64, 65-74 and 75+ for both populations between 1990-1995 and 2002-2007. Survival trends were assessed in a multiple regression model of relative excess risk (RER) including period of diagnosis, age and continent.

Results

The 5-year relative survival of penile cancer patients increased statistically non-significantly from 65% to 70% in Europe and decreased (significantly) from 72% to 63% in the USA. Trends in age specific 5-year relative survival did not find any significant improvement in either Europe or the USA. The multiple regression analysis confirmed the lack of survival trend, and found significantly higher RER with age, and, apparently due to lower survival before 2002-2007, higher RER in Europe.

Conclusion

Our population-based survival trend analysis indicates that survival for penile cancer patients has not improved in either Europe or the USA since at least 1990. Stronger international cooperation in clinical research may be important to facilitate clinical progress in treatment and thereby improvement of survival of this rare malignancy.

Introduction

With an incidence of 0.5 to 1 per 100,000 person-years penile cancer is rare in Europe and the USA.[1] Infection with human papilloma virus and the medical condition phimosis have been found to be associated with an increased risk, while neonatal circumcision seems to have a protective effect.[2]
There is a lack of information on population-based survival of penile cancer patients, as published survival estimates are often based on small numbers and hospital-based registries [3-6] that may be affected by selection bias due to treatment and referral patterns. Available publications that provide information on population-based penile cancer survival offer little detail and relate to patients that were diagnosed at the end of the 20th century.[7] To the best of our knowledge, no study has examined time trends of population-based penile cancer survival before.

We describe and compare trends in 5-year relative survival of penile cancer patients in Europe and the USA since 1990 using data from population-based cancer registries participating in the European Network for Indicators on Cancer (EUNICE) Survival Cooperation and the American Surveillance, Epidemiology and End Results (SEER) program.

Methods

Data

For Europe, the database of the EUNICE Survival Cooperation was used, which includes cancer incidence and follow-up data from 12 European population based cancer registries from at least 1985 onwards. General inclusion criteria and data preparation procedures were described in detail in a previous publication.[8] In brief, we included all penile cancer cases aged 15 and above and diagnosed between 1985 and 2007, excluding those that were registered by death certificate or autopsy only. For the USA, the SEER 9 limited-use database was used, with the same selection and inclusion criteria.[9]

Due to the low case numbers in the majority of the individual European cancer registries in the study period, registry-specific survival estimates could be provided only for the entire study period. In order to analyze survival trends, European registries were grouped into four geographical regions: region 'North' includes Norway and Finland, region 'East' includes Cracow, Estonia, Lithuania, and Slovenia, region 'Central and south' includes the registries of Torino, Tuscany, Geneva, and Saarland and region 'West' includes Eindhoven and Scotland. Age-specific analyses were done for all European registries combined; the SEER 9 registries were also combined for all analyses.

Survival analyses

Relative survival estimates were calculated as the ratio of observed survival of the cancer patients and the expected survival of an age and sex matched group of the underlying general population.[10] Expected survival, using registry, age, sex, calendar period, and race (USA only) specific life tables, was calculated according to the Ederer II method.[11] All survival estimates were period survival estimates, which are exclusively based on the survival experience of patients during the specific calendar period for which they were derived.[12] Period analysis has been shown to provide more up-to-date survival estimates

than traditional cohort-based survival analysis. In particular, it has been shown that 5-year relative survival for a given period closely predicts 5-year relative survival later observed for patients diagnosed during that period.[13, 14]

Five-year relative survival estimates were calculated for the calendar periods 1990-1995, 1996-2001, and 2002-2007, using a period-specific saturated Poisson regression model for relative survival.[15] To derive a test for survival trends, the periods 1990-1995, 1996-2001, and 2002-2007 were additionally included as numerical terms (1990-1994=1, 1995-1999=2, 2000-2004=3). For registries with data available on incident cases until 2005 or 2006, but follow-up of vital status until 2007, hybrid analysis was used to enable the estimation of up-to-date survival estimates with follow-up data available for more recent years than incidence.[16, 17] Standard errors of the survival estimates were calculated with the delta method. Alpha = 0.05 was used as a level of significance for the different tests.

Multiple regression modeling

Survival trends between the European and the SEER 9 registries were compared using a multiple relative survival regression model, in which age group (numerical variable: 1=15-54, 2=55-64, 3=65-74, 4=75+ years), period of diagnosis (numerical variable: 1=1990-1995, 2=1996-2001, 3=2002-2007) and continent (EUNICE vs. SEER 9) were included to calculate variable-specific relative excess risk (RER) of death estimates.

Results

Table 1 provides an overview of the included registries, their underlying populations, and the number of included penile cancer cases. Overall, data from 3,297 and 1,820 penile cancer patients diagnosed in the period 1985-2007 could be included from the EUNICE and SEER 9 databases, respectively. In Europe the number of cases contributed by each cancer registry varied between 58 (Cracow) and 829 (Scotland), in the USA this varied between 58 (Hawaii) and 327 (Detroit).

Overall, the 5-year relative survival of the European penile cancer patients diagnosed in the period 1990-2007 from the EUNICE database was 67% (Table 2). The registry-specific estimates varied between 54% for Cracow and 81% for Tuscany, but standard errors were usually very large, with only four registries having overall estimates with a standard error below 4% units, effectively corresponding to a smaller than 16%-unit wide 95% confidence interval.

Table 3 shows the 5-year relative survival according to period of diagnosis and geographical region. Overall, changes in relative survival were small and non-significant for most European regions. The only significant improvement of survival was noted in Northern Europe, where 5-year relative survival increased from 63% in 1990-1995 to 77% in 2002-2007.

Figure 1 presents the period-specific overall 5-year relative survival estimates for all EUNICE and all SEER 9 registries combined. In the EUNICE registries, 5-year relative survival increased slightly from 65% in the first period to 70% in the last period, while the survival of the SEER 9 registries decreased significantly from 72% to 63%, respectively.

Table 1. Cancer registries, underlying populations, national coverage percentage, and number of penile cancer cases.

Registry	Country	Registry underlying population (millions)	National coverage (%)	Number of penile cancers (1985-2007)
Cracow	Poland	0.8	1.9	58
Estonia	Estonia	1.4	100	147*
Lithuania	Lithuania	3.4	100	317*
Slovenia	Slovenia	1.9	100	190
Turin	Italy	1.0	1.8	127*
Tuscany	Italy	1.2	2.1	166*
Eindhoven	The Netherlands	1.0	6.6	197
Scotland	U.K.	5.1	100	829
Finland	Finland	5.2	100	416
Norway	Norway	4.5	100	651
Geneva	Switzerland	0.4	5.3	67
Saarland	Germany	1.0	1.3	132
Total EUNICE		**26.9**	**4.5†**	**3,297**
Atlanta	USA	2.9	1.0	116
Connecticut	USA	3.4	1.2	325
Detroit	USA	4.0	1.4	327
Hawaii	USA	1.2	0.4	58
Iowa	USA	2.9	1.0	299
New Mexico	USA	1.8	0.6	141
San-Francisco-Oakland	USA	4.1	1.5	230
Seattle-Puget Sound	USA	4.0	1.4	236
Utah	USA	2.2	0.8	88
Total SEER 9	**USA**	**26.7**	**9.5**	**1,820**

** For Estonia and Tuscany, data were available up to 2005, for Turin up to 2006, while for Lithuania, data were available since 1990.*

† As percentage of Europe (not including Russia, Turkey, Kazakhstan, Azerbaijan, Armenia and Georgia)

Age-specific 5-year relative survival of all penile cancer patients registered in the EUNICE database and SEER 9 database was calculated according to period of diagnosis (table 4 & figure 2). In the EUNICE registries, between 1990-95 and 2002-07, survival increased in the age groups 15-54, 55-64 and 65-74 but decreased slightly in the oldest age group (75+ years). However, none of these trends were statistically significant. Among patients of the SEER 9 database, the age-specific survival was higher in the first and the second period in all age groups compared to the period of 2002-2007, which saw a large decline in survival. Most of the age specific changes were however not statistically significant. In both populations, 5-year relative survival seemed to decrease with increasing age.

Table 2. Five-year relative survival of patients with penile cancer by EUNICE registry in the period 1990-2007

Registry	*n*	PE	SE
Cracow	58	54.4	10.9
Estonia	147	69.4	6.2
Lithuania	317	59.7	3.9
Slovenia	190	57.7	5.8
Turin	127	74.8	7.0
Tuscany	166	80.7	5.0
Eindhoven	197	70.6	5.2
Scotland	829	61.3	2.6
Finland	416	67.0	3.5
Norway	651	75.3	3.0
Geneva	67	60.3	9.3
Saarland	132	79.2	6.5
Total	**2,397**	**67.4**	**1.3**

PE = point estimate; SE = standard error

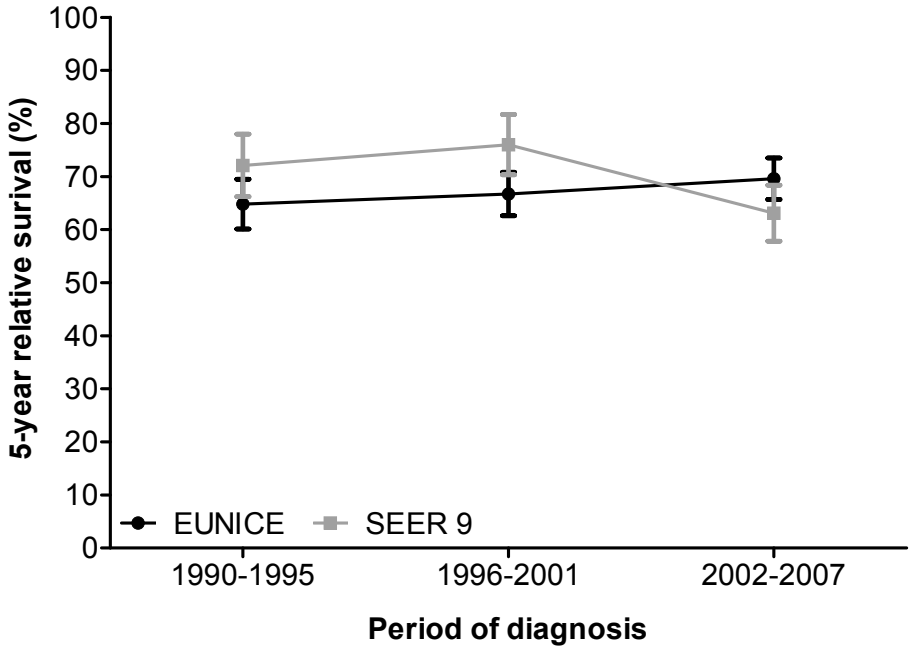

Figure 1. Period estimates of 5-year relative survival with 95% confidence limits of penile cancer patients by calendar period and grouped registries.

Table 3. Trends in model-based 5-year relative survival of European penile cancer patients according to geographical region

Geographical region	1990-1995			1996-2001			2002-2007			Change[a]	*P*-value
	n	PE	SE	*n*	PE	SE	*n*	PE	SE		for trend
Northern Europe	250	63.2	4.3	277	72.4	3.7	369	76.7	3.3	13.5	0.03
Eastern Europe	165	62.7	4.9	227	56.0	4.3	243	61.6	4.1	-1.1	0.72
Central and southern Europe	134	69.4	5.5	133	76.3	4.8	127	72.3	4.9	2.9	0.27
Western Europe	231	61.8	4.0	294	62.6	3.9	324	66.3	3.5	4.5	0.31
Total EUNICE	**780**	**64.8**	**2.4**	**931**	**66.7**	**2.1**	**1063**	**69.6**	**2.0**	**4.8**	**0.17**

PE = point estimate; SE = standard error

[a] Change in the 5-year relative survival between 1990-1995 and 2002-2007, in % units

Table 4. Trend in model-based 5-year age-specific relative survival of penile cancer patients from the EUNICE and SEER registries

Age group by registry group	1990-1995			1996-2001			2002-2007			Change[a]	*P*-value
	n	PE	SE	*n*	PE	SE	*n*	PE	SE		for trend
EUNICE											
15-54 years	171	70.8	3.7	229	72.0	3.2	250	74.2	3.0	3.4	0.52
55-64 years	173	66.3	4.4	198	67.4	3.9	242	72.3	3.5	6.0	0.40
65-74 years	210	58.7	4.5	266	68.7	3.9	272	69.4	3.5	10.7	0.23
75+ years	226	63.4	5.7	238	56.9	5.4	299	61.5	5.3	-1.9	0.63
Total	**780**	**64.8**	**2.4**	**931**	**66.7**	**2.1**	**1063**	**69.6**	**2.0**	**4.8**	**0.15**
SEER 9											
15-54 years	77	73.5	5.3	93	77.1	4.8	83	67.7	5.2	-5.8	0.37
55-64 years	95	74.4	5.5	89	77.8	5.0	89	65.3	5.5	-9.1	0.19
65-74 years	120	77.2	5.3	128	79.1	5.2	117	63.5	5.0	-13.7	0.04
75+ years	158	63.8	6.9	178	70.3	6.0	223	58.8	5.4	-5.0	0.55
Total	**450**	**72.1**	**3.0**	**488**	**76.0**	**2.9**	**512**	**63.1**	**2.7**	**-9.0**	**0.01**

PE = point estimate; SE = standard error

[a] Change in the 5-year relative survival between 1990-1995 and 2002-2007, in % units

Figure 2 shows the age-specific survival estimates of European and American penile cancer over time, for the age-group 65 to 74 years the survival of the two continents seemed to converge over time. The age-specific survival estimates of both continents were rather similar during the last period.

Results of the multiple relative survival regression analysis are presented in table 5. The calculated RERs indicated that there was no improvement of survival over time (i.e. RER for period of diagnosis = 1.00, p=0.96), but did confirm a significantly increasing relative excess risk of death with increasing age, and showed a higher RER in the EUNICE registries compared to the SEER 9 registries. The latter result appears likely due to the higher survival in the SEER 9 registries in the periods 1990-1995 and 1996-2001.

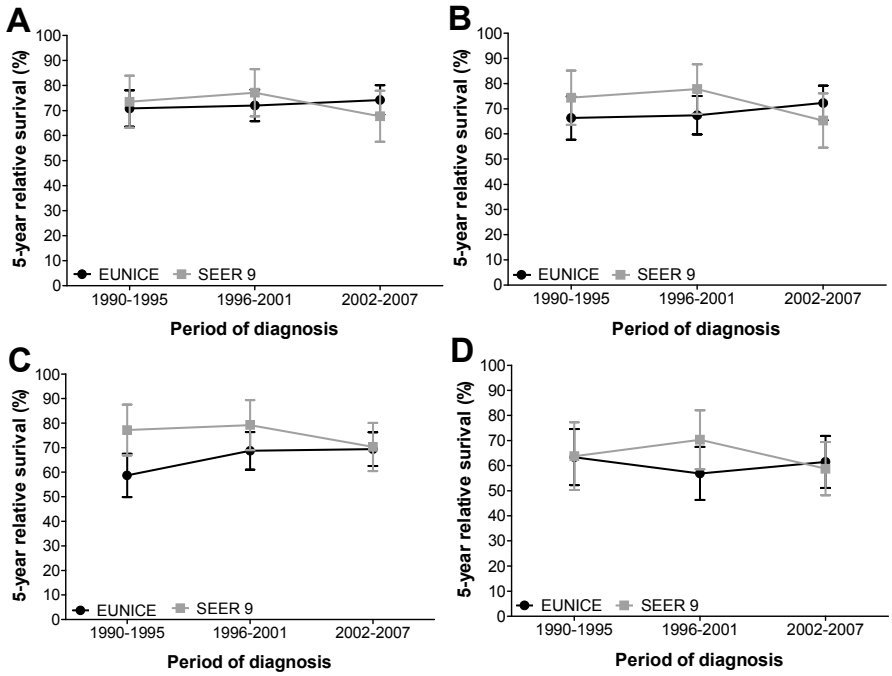

Figure 2. Age-specific period estimates of 5-year relative survival with 95% confidence limits of penile cancer patients by calendar period and grouped registries.
Age group (A) 15 to 54; (B) 55 to 64; (C) 65 to 74; (D) 75+

Table 5. Multiple relative survival regression analysis of penile cancer patients

	Relative excess risk of death	95% Wald Confidence limit	*P*-value
Period of diagnosis*	1.00	0.92-1.08	0.96
Age group**	1.15	1.08-1.22	<0.01
EUNICE vs SEER 9	1.22	1.06-1.42	0.01

** Period of diagnosis was included as a numerical variable (1=1990-1995, 2=1996-2001, 3=2002-2007)*
*** Age group was included as a numerical variable (1=15-54, 2=55-64, 3=65-74, 4=75+)*

Discussion

In this first comprehensive analysis of 5-year relative survival trends among patients with penile cancer, we found no improvement in the overall 5-year relative survival of the EUNICE and SEER 9 registries or in any of the age-specific survival estimates during the periods of 1990-1995, 1996-2001 and 2002-2007. Multiple regression analysis confirmed the lack of increasing survival in the examined periods and found statistically significantly decreasing relative survival with increasing age.

We showed that relative survival of penile cancer did not improve in three of the four defined European regions since 1990 and also did not improve in the complete group of EUNICE registries. Relative survival did however improve in the Northern European region, which was composed of data from Norway and Finland. A publication on the survival of patients with prostate cancer, testicular cancer and 'penis and other male genital cancers' in the Nordic countries showed that the 5-year age-standardized relative survival of 'penis and other male genital cancer' did not increase in Sweden and Finland in the period 1964-2003, with survival estimates consistently around 70% and 65%, respectively.[18] The 5-year relative survival did appear to have increased in Norway (from 61% to 80%) and Denmark (from 63% to 74%).[18] Because penile cancer comprises more than 91% of the group 'penis and other male genital cancer' in the period 1998-2002 in the Nordic countries, the survival trends of this group will thus largely reflect the survival trends of penile cancer.[1] The combination of the relatively stable survival in Finland and the increasing survival in Norway has probably resulted in the increase in survival of the Northern European region that we have found in this study. Hospital-based studies from France (*n*=102) and the UK (*n*=142) presented 5-year disease-specific survival rates of 72% and 66%, respectively, for patients diagnosed between 1960 and 1993.[5, 6] These disease specific survival estimates are quite similar to the relative survival estimates (which can be interpreted as a measurement of disease specific survival) found for the EUNICE and the SEER database in the study period of the current study (1990-2007). Therefore previously published results, partially relating to patients diagnosed and treated well before the periods of interest of the current study, might suggest that survival of penile cancer patients may not have improved in the decades before 1990, either.

The lack of a strong improvement in survival of penile cancer is probably due to a lack of major advances in curative treatment options for penile cancer. The most pronounced advances in the treatment of penile cancer that have been made in the past two decades have been in the area of less disfiguring treatment of the primary lesion and the recognition and management of occult regional lymph node metastases.[19, 20] While the primary goal of the development of less disfiguring treatment was to have a better functional and cosmetic result without compromising survival, the primary goal of the management of occult lymph node metastases was survival improvement. About 20% of the penile cancer patients have occult lymph node metastases at diagnosis and could thus benefit from the improvement in the management of occult lymph node metastases.[21] We did however not find any progress in survival of penile cancer patients in Europe or the USA. This might be caused by low referral rates to hospitals that are specialized in the treatment of penile cancer or the improvements in the treatments may have been too recent to have been fully implemented in the hospitals and to be noticeable in the survival estimates of the current study.

The multiple relative survival regression analysis showed that survival significantly decreased with increasing age. The EUROCARE 4 study showed a marked difference in the 5-year relative survival of penile cancer for patients aged over 75 years (5-year relative survival: 35%) compared to age groups younger than 75 years (5-year relative survival varied between 73% and 79%).[7] A hospital-based study from the UK found that penile cancer patients aged over 60 years had a worse survival in a multi-variable analysis on cause-specific survival than younger patients.[5] A possible explanation for the poorer survival for patients with a higher age at diagnosis could be that older patients have a more advanced stage at diagnosis than younger patients. Due to incomplete and non-comparable information on stage it was unfortunately not possible to analyze the stage distribution for the penile cancer patients included in this study or to include stage in the multiple regression model in this analysis.

According to the results of the multiple regression analysis, the relative survival of European patients was found to be poorer than that of the American patients. Based on the overall and age-specific survival estimates presented in table 4, it seems that the lower survival of European patients that was found in the multiple regression analysis is mainly due to poorer survival of European patients in the periods 1990-1995 and 1996-2001. In the last period (2002-2007) survival of the European patients seemed to be rather similar or even slightly higher than that of USA patients.

The overall survival estimate and all of the age-specific estimates of the American patients increased from the first to the second period and decreased from the second to third period by at least 9% units, yielding a lower relative survival in the last period in contrast to the first period. While such a decrease in survival is unusual and unexpected, these results might be due to random variation as survival estimates are based on rather small numbers of patients.

In the interpretation of our results, a number of limitations have to be kept in mind. Apart from the low case numbers leading to high standard errors of survival estimates, these include the lack of detailed information on diagnosis and therapy in particular. Although cancer registries from all regions of Europe were involved, our results are not necessarily representative for Europe as a whole. In particular, populations from Northern Europe, the only region for which significant improvement in survival over time was observed, were somewhat overrepresented.

In conclusion, the results of this study suggest that at a population level, the survival of penile cancer patients in the EUNICE and the SEER 9 registries has not improved since 1990. In order to promote the clinical understanding and treatment of this rare malignancy, increasing referral to larger volume centers, as well as intensifying international cooperation in clinical research may be helpful to facilitate progress in survival in the future.

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Chapter 4

Epidemiology of scrotal cancer

Chapter 4.1

Scrotal cancer: Incidence, survival and second primary tumors in the Netherlands since 1989

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Abstract

Background

Since the 1970s there have been few epidemiological studies of scrotal cancer. We report on the descriptive epidemiology of scrotal cancer in the Netherlands.

Methods

Data on all scrotal cancer patients was obtained from the Netherlands Cancer Registry in the period 1989-2006 and age-standardized incidence rates were calculated also according to histology and stage. Relative survival was calculated and multiple primary tumors were studied.

Results

The overall incidence rate varied around 1.5 per 1,000,000 person-years, most frequently being squamous cell carcinoma (27%), basal cell carcinoma (19%) and Bowen's disease (15%). Overall 5-year relative survival was 82%, being 77% and 95% for patients with squamous and basal cell carcinoma, respectively. In all, 18% of the patients were diagnosed with a second primary tumor.

Conclusion

The incidence rate of scrotal cancer did not decrease, although this was expected; affected patients might benefit from regular check-ups for possible new cancers.

Introduction

Pott (1775) described a relationship between soot exposure and a high incidence of scrotal cancer among chimney sweepers.[1] Scrotal cancer has also been linked to exposure to tar,[2-4] pitch,[2, 3] different types of lubricating and cutting oils,[2, 3, 5-11] creosotes,[4, 12] gas production,[4, 13] paraffin wax pressing,[14] and various treatments for skin diseases.[15-17]
With the knowledge on occupational risk factors and the accompanying improvements in working conditions, scrotal cancer has become rare. In the 1970s and early 1980s, its incidence rate in the United States was about one per million person-years, bus has been increasing again since the early 1980s.[10, 18-20]

Scrotal cancer should not be confused with the more common testicular cancer, which mainly affects young adults. The scrotum is the protuberance of muscles and skin containing the testicles. Therefore most scrotal tumors are sarcomas or skin tumors whereas testicular cancers are usually germ-cell tumors. Tumors of the skin of the scrotum might also be classified as skin cancer, but due to the historically strong etiological relationship between scrotal tumors and occupational exposures and the lack of this relationship between occupational exposures and other tumors of the skin, scrotal tumors are classified as a separate entity.

Little information on the incidence and survival of scrotal cancer has been published in the last 20 years, probably because it was expected that the incidence would become almost zero after removal of the known scrotal carcinogens from the working environment. Given the relative lack of recent work, we have used recent Dutch data to investigate the stage distribution, histological distribution, incidence, survival and occurrence of second primary tumors in patients with this rare cancer since 1989.

Materials and methods

Data were used from the nation-wide population-based Netherlands Cancer Registry (NCR), which combines the data from the eight Dutch regional cancer registries since 1989. These registries receive lists of newly diagnosed cancer patients on a regular basis from hospital pathology departments, all participating in a nation-wide network (PALGA). In addition, hospital medical records departments provide lists of diagnoses of outpatients and hospitalized cancer patients. Following these notifications, trained registrars extract patient and tumor characteristics (among other things, topography, histology, stage and date of diagnosis) data from the medical records. According to the registration rules of the NCR scrotal skin tumors are categorized in the topographic group of scrotal cancer and not in the group of skin cancers.

Topography and histology were coded according to the International Classification of Diseases for Oncology (ICD-O).[21] All tumors with an ICD-O topography code scrotum (C63.2) were selected for this study. We grouped the histological codes according to the classification in Table 1. For all other analyses lymphomas and mesotheliomas of the scrotum were excluded.
The stage of the squamous cell carcinomas, basal cell carcinomas, Paget's diseases and the tumors that were grouped in the histological 'other' group was categorized according to

the IUCC carcinoma of the skin TNM classification:[22] stage 0 (TisNoMo), stage 1 (T1NoMo), stage 2 (T2-3NoMo), stage 3 (T4NoMo, any T N1Mo), and stage 4 (any T, any N, M1). The stage of the melanomas diagnosed before 2003 were categorized according to the fifth TNM classification of malignant melanomas of the skin and since 2003 and later according to the sixth TNM classification.[22, 23] Because Bowen's disease tumors are by definition *in situ* tumors and because sarcomas have no current TNM classification these groups were excluded from the analyses according to stage.

Age- and stage-distributions were calculated according to histology. Five-year moving average age-standardized incidence rates were calculated per 1,000,000 person-years for the entire group of scrotal cancers. Age-standardized incidence rates in 6-year diagnostic periods per 1,000,000 person-years were calculated according to histology. Standardization of age was performed according to the European standard population. The Joinpoint regression program (v3.0) was used to test whether there were increases or decreases in the overall incidence rate of scrotal cancer.[24]

The frequency of patients with invasive primary tumors before and/or after the scrotal cancer diagnosis was calculated. The strict rules of the NCR on registering second primary tumors ensured that only primary tumors were included in this analysis, as tumors with the same ICD-O topography group had to be diagnosed with a time difference of at least 6 months or had to belong to different morphologic groups. For squamous cell carcinomas of the skin only the first tumor could be included in the analyses due to differences of registration methods over time and between regions.

Vital status data (available until January 1, 2008) were obtained from the hospital records and the mortality register of the Central Bureau for Genealogy (an institution that registers all deaths in the Netherlands via the municipal population registries). For patients with 2 scrotal tumors, only the data on the first tumor was used for survival analyses. Relative survival was calculated for the total group of scrotal cancer patients and according to histology. Relative survival is an estimation of the disease-specific survival, being the absolute survival among the scrotal cancer patients divided by the expected survival for the general population with the same sex and age structure.[25] Relative survival was computed by means of traditional cohort-analysis.

Results

In all, 200 scrotal tumors in 194 patients were diagnosed in 1989-2006 in the Netherlands; their histology is shown in table 1. The largest histological groups were squamous cell carcinomas (27%), basal cell carcinomas (19%), Bowen's disease (15%), sarcomas (13%) and extramammary Paget's disease (12%). Mesotheliomas and the lymphomas were excluded from further analyses.

Patients with basal cell carcinomas were oldest at diagnosis with a median age of 72 years, while patients with scrotal sarcoma had a median age of 56.5 years (Figure 1).

Table 1. Histological classification and distribution of scrotal cancer patients in the Netherlands

Histological group	Morphology code according to ICD-O[21]	*n*	%
Squamous cell carcinoma and variants	8033, 8070, 8071, 8072, 8076, 8083, 8094	53	27%
Basal cell carcinoma	8090, 8091, 8096	38	19%
Bowen's disease	8081	29	15%
Sarcoma	8804, 8810, 8850, 8851, 8852, 8853, 8857, 8890, 8900	26	13%
Extramammary Paget's disease	8542	24	12%
Malignant melanoma	8720, 8721, 8743	16	8%
Lymphoma	9675, 9680, 9699	4	2%
Mesothelioma	9050	1	1%
Other	8000, 8010, 8051, 8140, 8247, 8400, 8402, 8410, 8830	9	5%
Total		**200**	**100%**

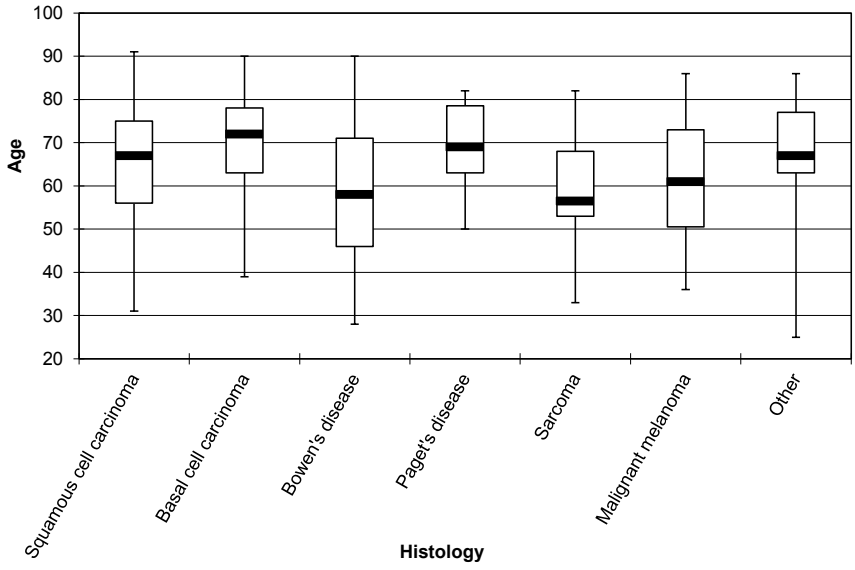

Figure 1. Age distribution of patients diagnosed with scrotal cancer in the Netherlands according to histology (Median, Q1, Q3, lowest and highest age).

In the study period, the age-standardized 5-year moving average incidence rate varied between 0.9 and 1.8 per 1,000,000 male person-years (Figure 2), with no statistically significant increase or decrease over time.

Figure 3 presents age-standardized scrotal cancer incidence rates in 6-year periods according to histology. The highest incidence rates were found for squamous cell and basal cell carcinoma and the lowest incidence rates for the malignant melanomas and "other" group. During 1995-2000 the incidence rates of scrotal squamous cell carcinoma, basal cell carcinoma, Paget's disease, sarcoma and the "other" group seem to have increased temporarily.

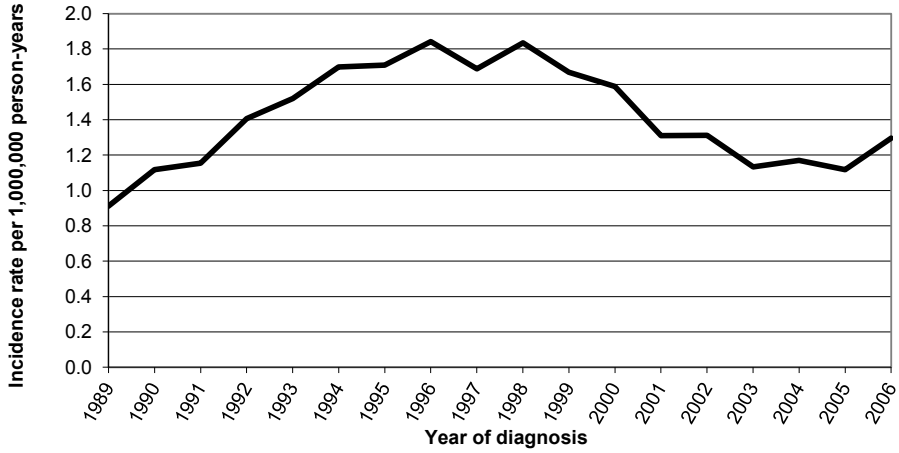

Figure 2. Five-year moving average European standardized scrotal cancer incidence rates per 1,000,000 person-years (mesotheliomas and lymphomas excluded).

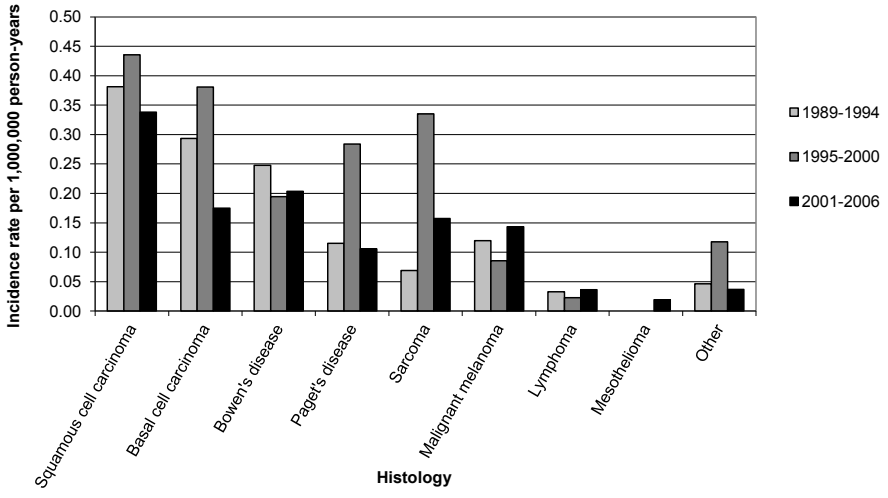

Figure 3. European standardized scrotal cancer incidence rates per 1,000,000 person-years according to histology.

The stage distribution of the different histological groups is presented in Table 2. In all histological groups there are large percentages of tumors with an unknown stage, ranging from 13% to 47%. The majority of the patients with squamous cell carcinoma, basal cell carcinoma and Paget's disease had stage 1 or 2 tumors, whereas the majority of the malignant melanomas were stage 2 or 3.

Table 2. Number of scrotal tumors according to stage and histology

	Squamous cell carcinoma	**Basal cell carcinoma**	**Paget's disease**	**Malignant melanoma**	**Other**
Stage	***n***	***n***	***n***	***n***	***n***
0	1	0	2	0	1
1	22	12	2	1	2
2	18	8	9	6	1
3	2	0	2	6	1
4	0	0	0	1	1
Unknown	10	18	9	2	3
Total	**53**	**38**	**24**	**16**	**9**

The histological groups 'Sarcomas', 'Lymphomas' and 'Mesotheliomas' do not have a TNM stage distribution and the 'Bowen's Disease' are by definition in-situ tumors, therefore these histology's are not included in this table.

Data on vital status was missing for 34 (18%) of the 189 patients, most of them were diagnosed before 1995 (*n*=25). For this period follow-up of vital status is still incomplete in most of the regional cancer registries. Relative survival 1 year after diagnosis was 97% (95% Confidence Interval (95%CI): 91%-100%), which decreased gradually to 82% (95%CI: 71%-90%) 5-year relative survival and overall crude survival being 66% (95% CI: 58%-74%). From 6 to 10 years after diagnosis the relative survival remained about 80%, resulting in a 10-year relative survival of 77% (95% CI: 62%-91%). Five-year survival estimates of patients with scrotal basal cell carcinomas, Bowen's diseases and sarcomas were 95% or higher, yet with wide CIs. The 5-year relative survival of patients with extramammary Paget's disease was 68% (95% CI: 36%-94%), but 1- and 3-year relative survival were both 100%. The 1-, 3- and 5-year relative survival of patients with squamous cell carcinomas was relatively low, being respectively, 93% (95% CI: 79%-100%), 80% (95% CI: 61%-94%) and 77% (95% CI: 56%-94%)

The distributions of the tumors diagnosed before or after the first diagnosis of scrotal cancer are presented in table 3. A high percentage of skin tumors and tumors located near the scrotum (penis, prostate, anal canal, urinary bladder, colorectal, etc.) was found in both before and after the diagnosis of scrotal cancer. Six men with a scrotal cancer (3 Bowen's disease, 1 squamous cell carcinoma, 1 basal cell carcinoma and 1 "other" tumor) were diagnosed with a second scrotal tumor, three of these second scrotal tumors were squamous cell carcinomas, two belonged to the other category and one was a Bowen's disease. Four of these six patients also had other tumors (i.e. two cutaneous, one tumor of soft tissue, lung, larynx tumor or bladder and one plasma cell tumor) .

The 24 tumors found before the diagnosis of scrotal cancer were found in 22 patients (12%) and 34 patients (18%) had at least one cancer diagnosis after the first scrotal cancer diagnosis during 1989-2006.

Table 3. Tumors of scrotal cancer patients diagnosed before and after the first diagnosis of scrotal cancer

Site	Number of tumors before scrotal cancer	Number of tumors after scrotal cancer
Skin, squamous cell carcinoma	9	7
Lung	1	8
Colorectal	5	4
Scrotum	N.A.	6
Prostate	2	4
Non-Hodgkin lymphoma	2	1
Urinary bladder	2	1
Anal canal	1	1
Skin, melanoma	1	1
Chronic myeloproliferative disorder	1	0
Eye	0	1
Larynx	0	1
Pancreas	0	1
Penis	0	1
Plasma cell tumor	0	1
Primary site unknown	0	1
Skin, other	0	1
Soft tissue	0	1
Total	**24**	**41**

N.A. = Not applicable

Discussion

During 1989-2006 scrotal cancer occurred predominantly in men older than 50 years. The age-standardized incidence rate was around 1.5 per 1,000,000 person-years and did not seem to change over time. Squamous cell carcinomas were the most frequent histological type, followed by basal cell carcinomas. The stage of most tumors was unknown or low. The relative survival of scrotal patients was good. Multiple primary tumors were quite common among patients with scrotal cancer.

The incidence of scrotal cancer in the United Kingdom decreased during the 1970s and the beginning of the 1980s, probably because of previous improvement in occupational hygiene and the removal of carcinogens; a further decrease in the incidence was expected.[2] However, although we found a relatively steady incidence, a recent American study found an increase since the early 1980s.[20] This may indicate that not only occupational exposures influence the risk of scrotal cancer, which is also indicated by their histological distribution. In this study 27% of the scrotal tumors were squamous cell carcinomas and 15% Bowen's disease

(*in situ* squamous cell carcinomas), whereas previous studies report that the great majority of the scrotal tumors were squamous cell carcinomas (up to 93%).[6, 9, 26, 27] The recent US study reported a similar percentage of squamous cell carcinomas (32%) as our study.[20] Because almost all occupationally caused scrotal tumors were squamous cell carcinomas,[6] the current low percentage of such tumors may indicate that certain non-occupational are relevant. Possible non-occupational risk factors are sun exposure, several types of treatments for skin diseases and the human papilloma virus, might influence the risk of scrotal cancer.[15-17, 28, 29]

The relatively high percentage of tumors with unknown stage in this study probably reflects the very good prognosis of most of the tumors. In general, these superficial tumors are surgically removed without further staging or treatment. If most tumors with unknown stage tumors are indeed of lower stage, the percentage of low stage (stage 0, 1 or 2) would be around 90%, being somewhat higher than that in other studies.[20, 26, 30]

Both our study and the recently published study in the United States found that survival of patients with squamous cell carcinomas of the scrotum seems to be lower than that of patients with a scrotal basal cell carcinoma or sarcoma.[20] Some extra therapeutic caution may thus be needed for scrotal squamous cell carcinomas. The 5-year relative survival of scrotal squamous cell carcinoma patients (77%) was also lower, although not significantly, than the 5-year relative survival of male skin squamous cell carcinoma patients in the Netherlands (91%).[31] Previous studies have not calculated relative survival based on reasonable numbers of scrotal cancer patients. A study in a region of the United Kingdom which included 324 patients diagnosed from 1936 to 1976 reported crude 5-year survival estimates of 51%, with no change over time,[3] which albeit being significantly lower than our crude 5-year survival of 66%, it is not that largely different.

Of scrotal cancer patients, 18% developed one or more tumors after the scrotal tumor and six (3%) patients developed a second scrotal cancer. All of these tumors were diagnosed in the period 1989-2006, so patients who were diagnosed recently only had a short time to manifest a second (scrotal) tumor, and a longer follow-up would probably reveal a higher percentage of second (scrotal) cancers. This also applies to tumors that were diagnosed before the scrotal cancer diagnosis. However, the number of scrotal tumors and the number of tumors diagnosed after a first scrotal tumor could also have been increased by increased surveillance on new tumors by medical specialists in the patients who were already diagnosed with a previous tumor. Regular follow-up of scrotum cancer patients might thus be useful to detect new tumors at an early stage, but might also result in overdiagnosis.
In another study, 8 of the 19 patients with a squamous cell carcinoma of the scrotum had a cancer in their medical history, 5 of these 8 prior cancers were skin cancers.[18] A patient series from the UK reported 69 (20%) of the 344 scrotal cancer patients to have second primary tumors, similar to our study.[3] It is generally known that people with skin tumors have a high chance of developing more skin cancers; scrotal skin cancer does not seem to be an exception.[32]
We found the incidence rate of scrotal cancer to be relatively stable, varying between 0.9 and 1.8 per million person-years, although we had expected a decreasing trend. The largest histological groups were the squamous cell carcinomas, basal cell carcinomas and Bowen's

disease. The 5-year relative survival for the whole group of scrotal cancer patients was high (81%). The high percentage of second primary tumors after scrotal cancers suggest that scrotal cancer patients might benefit from regular check-ups for possible new cancers.

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Chapter 4.2

New insights into the etiology of scrotal cancer, a nationwide case-control study in the Netherlands

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Abstract

Background

Although scrotal cancer is traditionally regarded as an occupational disease, there is increasing evidence that factors which are involved in cutaneous and genital carcinogenesis might play a role in the carcinogenesis of scrotal cancer. However, due to a lack of recent etiological studies, it remains unknown which additional exposures have actually contributed to the occurrence of scrotal cancer in the last decades. This exploratory study aimed to detect exposures that might have an etiological relation with scrotal cancer.

Methods

A nationwide population-based case-control study was conducted in the Netherlands. The patients were identified through the Netherlands cancer registry. Controls were recruited among acquaintances of the cancer registry registrars. The participants completed a questionnaire that included questions on occupational exposures, naked sun bathing, use of sun beds, skin diseases and treatments for skin diseases, treatments for cancer and sexually transmitted diseases. Age-adjusted odds ratios (ORs) were calculated.

Results

Forty-seven scrotal cancer patients and 125 controls completed the questionnaire. The patients were categorized according to histology of the scrotal tumors. Having had a skin disease (OR=6.3, 95%CI=1.8-22), especially psoriasis (OR=8.7), increased the risk of squamous cell carcinomas of the scrotum. A previous cancer diagnosis may affect the risk of scrotal basal cell carcinomas (OR=4.9 95%CI=0.9-27.3). Furthermore, an association between the number of sexual partners and the occurrence of scrotal sarcoma was found.

Conclusions

Scrotal squamous cell carcinomas may be related with skin diseases or skin disease treatments. Having had cancer may be a risk factor for a basal cell carcinoma of the scrotum. Scrotal sarcomas seem to be correlated with the number of lifetime sexual partners. This study suggests that scrotal cancer has characteristics of both cutaneous and genital carcinogenesis.

Introduction

Scrotal cancer is a very rare malignancy that has been associated with occupational exposures, the first being reported by Percival Pott in 1775. He described a high incidence of scrotal cancer among chimney sweepers.[1] Since then many other occupational causes of scrotal cancer have been suggested, including exposure to soot,[2] pitch,[3, 4] tar,[3, 4] different types of lubricating and cutting oils,[3-11] creosotes[12, 13] and paraffin wax pressing.[14] Most of these carcinogens are related to unhygienic working environments. In the 1960s the hygiene of the industrial working places improved and exposure to carcinogens decreased. During the 1970s and the beginning of the 1980s the number of patients with scrotal cancer in the United Kingdom decreased.[3] Although it was expected that this decrease of incidence would continue, a recent American study describes an increasing incidence of scrotal cancer from 1985 until the end of the study period (2002).[15] In the Netherlands, data of the Netherlands cancer registry (NCR) on the incidence of scrotal cancer since 1989 describes a steady incidence rate.[16] Thus, based on these recent studies, it seems that the decrease of the incidence of scrotal cancer stopped somewhere in the 1980s.

These changes in the incidence may be explained by particular subtypes of scrotal cancer. The scrotal tumors that are caused by occupational exposure are usually squamous cell carcinomas (SCCs).[9, 17,18] For example, a hospital based study that was published in 1967 reporting on 28 men with scrotal cancer, described that 26 (93%) of the tumors of these men were SCCs and that 22 (79%) of these men were occupationally exposed to a known carcinogen for scrotal cancer.[6] Data of the NCR shows that only 27% of the 200 men with a scrotal tumor in the period 1989-2006 had a SCC.[16] The other histological subtypes included basal cell carcinoma (BCC) (19%), Bowen's disease (15%), Paget's disease (12%), sarcoma (13%), malignant melanoma (8%) and a group of other rare and undefined histological subtypes (8%). The relatively small percentage of SCCs among the scrotal cancer patients may indicate that non-occupational exposures nowadays play an important role in the etiology of scrotal cancer. The results of a study that was performed with data of the Nordic Occupational Cancer (NOCCA) project also suggested that scrotal cancer is no longer related to occupational risk factors.[19]

Several non-occupational factors have been suggested to influence the risk of scrotal cancer. As the majority of scrotal cancers are cutaneous malignancies, it is obvious that skin carcinogens might be involved. Earlier studies showed that several treatments for skin diseases (e.g. psoriasis and eczema) such as arsenic treatment and different kinds of light therapies (Psoralen + ultraviolet A (PUVA), and ultraviolet B (UVB)) have been related to an increased risk of (scrotal) skin cancer.[20-22] The role of sun exposure, which is obvious in non-genital skin carcinogenesis, is under discussion for scrotal cancer.[23-25]

Another possible risk factor for scrotal cancer is genital infection with the human papilloma virus (HPV). This virus plays an important role in SCC of both the penis and vulva; 20%-40% of all penile cancers and about one third of SCCs of the vulva are HPV-positive.[26, 27] Data with respect to the role of HPV in skin carcinogenesis are not conclusive; viral loads in tumors are usually lower than that in precursor lesions and HPV-negative and -positive tumors may coexist in the same patient.[28, 29] Recently, transcriptome sequencing failed to

identify papillomavirus expression in cutaneous SCC.[30] These data demonstrate that HPV mRNA expression is not a factor in the maintenance of SCCs, but might have an essential role in cutaneous oncogenesis through a hit-and-run mechanism and is contributing to the development of malignancies in co-operation with the mutagenic effects of UV radiation.[31] Earlier studies showed that more than 50% of cutaneous SCCs in immunocompetent individuals were HPV-positive. These tumors contained not only cutaneous (β) HPV-types but also mucosal (α), high risk, genotypes types (6, 16, 31, 32, 34, 42, 51).[32, 33]
Several case reports and small studies have reported on the presence of HPV in scrotal tumor tissue of immune suppressed men.[34-37] Oncogenic HPV has also been detected on the scrotum of asymptomatic men.[38, 39]

In conclusion, the fact that the incidence of scrotal cancer no longer seems to decrease and the more heterogeneous distribution of histological subtypes indicates that non-occupational exposures, which might be analogous to that in cutaneous and genital carcinogenesis, may be related to the development of scrotal cancer. Therefore, the aim of this explorative study was to identify possible risk factors of scrotal cancer.

Methods

In the period 1989-2005 186 men were registered in the NCR with a scrotal tumor (International Classification of Disease for Oncology topography code: C63.2) (figure 1).[40] The NCR is a population-based cancer registry and all cancers diagnosed in the Netherlands since 1989 are registered. The registration is carried out by trained registrars of the comprehensive cancer centers, who collect data on diagnosis, staging, and treatment from hospital records, including pathology and surgery reports.
The (former) treating physicians of the patients who were alive (*n*=91) were asked for their approval to invite the patient for participation in the study. After approval of the physician an invitation letter with an information leaflet and an informed consent form was sent to the patient. In case a patient agreed to participate, a postal questionnaire was sent. Patients who did not return the informed consent form within three weeks received a reminder. From all patients, the tumor characteristics (e.g. histology, stage at diagnosis) were retrieved from the NCR.

In order to ascertain a nation-wide control group, we asked for cooperation of all registrars from the comprehensive cancer centers to recruit up to four men among their acquaintances to participate as a control in this study. Seven of the eight comprehensive cancer centers agreed to collaborate in this recruitment procedure. The registrars received oral and written explanation of the goals and design of the study. Each participating registrar received four information packages, which they could hand out to eligible men. The registrars were instructed to recruit one man in each of four age-groups (23 to 56, 57 to 65, 66 to 74 and 75 to 89 years old) in order to arrive at an age distribution similar to that of the patients. The information packages contained an invitation letter, an information leaflet and an informed consent form. If men decided to participate in the study they had to fill out the informed consent form and return it to the coordinating comprehensive cancer centre east. Subsequently, the same questionnaire as the one which was sent to the patients, was sent to these controls.

The questionnaire was designed to determine exposure to possible risk factors for scrotal cancer and included questions on demographic characteristics, occupational exposures, naked sun bathing, use of sun beds, diagnosis of skin diseases and treatments for skin diseases, treatments for cancer, family history of cancer, sexual behavior and sexually transmitted diseases (STDs) and a group of diverse exposures that might physically or medically be related to the development of scrotal cancer. Participants who did not return the questionnaire within two weeks received a reminder. A telephone call was made in case the questionnaire had not been sent in within the next two weeks.

Due to great diversity of histological subtypes of scrotal cancer and the possible different underlying etiology, all analyses were stratified according to histological type. The tumors were classified as follows: SCC (including SCC and Bowen's disease), sarcoma, BCC, extra mammary Paget's disease (EMPD), malignant melanoma, lymphoma and other.
We used descriptive statistics to display the demographic characteristics and the exposure to the different possible risk factors of the patients and controls. Because of the small number of patients in each histological subgroup it was decided that odds-ratios (ORs) should only be calculated for the three largest histological groups: SCC (n=15), sarcoma (n=15) and BCC (n=8). Due to small numbers and, consequently, the higher chance of false-positive findings, it was decided that ORs were only calculated for exposures that showed a relatively large frequency difference between cases and controls.

The mean age of the controls was significantly lower than that of the patients, therefore in all logistic regression analyses an adjustment was made for age. All statistical analyses were carried out using the SAS package (V9.1.3).[41]

The study protocol was approved by the Institutional Review Board of Radboud University and the Review Committee of the Association of Comprehensive Cancer Centers.

Results

In total 186 patients were diagnosed with scrotal cancer in the Netherlands between 1989 and 2005 and 91 (49%) were still alive at the start of this study (figure.1). For 80 (88%) patients, we obtained permission from their treating physicians to invite them for the study. The questionnaire was completed by 48 of the 80 (60%) invited patients.
Four hundred and four information packages were handed out to the registrars for the recruitment of controls and 126 (31%) controls completed and returned the questionnaire. One patient and one control were excluded from the analyses because of incomplete questionnaires.
The frequencies of exposure of all the different exposures according to histological subgroup are presented in the supplementary table. Table 1 shows the response rate and mean age of the total group of scrotal cancer patients and according to histological group. The mean age of the total group of scrotal cancer patients and the mean age of the three largest histological groups were all significantly higher compared to the mean age of the controls.

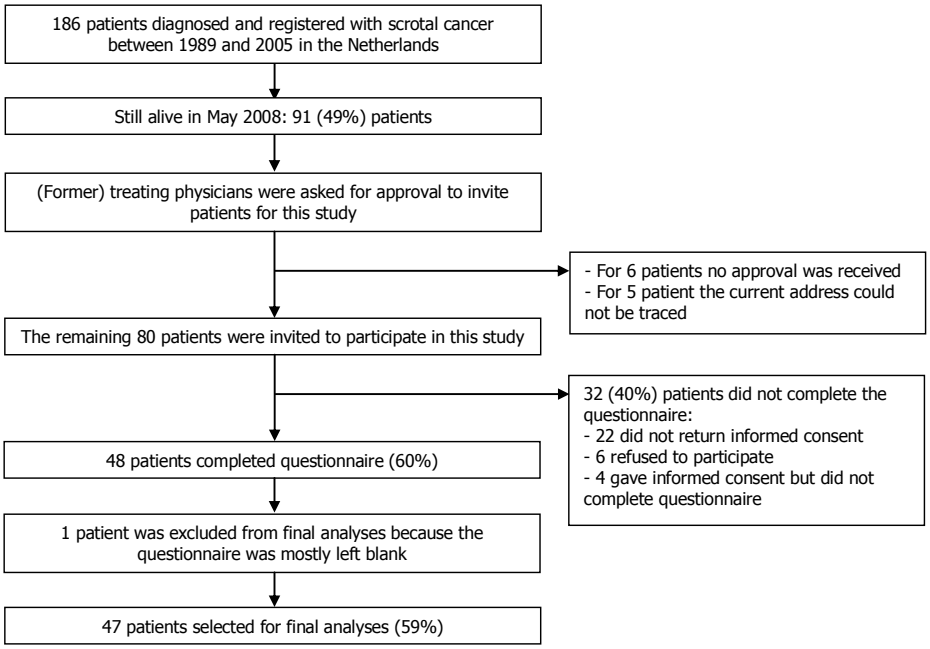

Figure 1. Flow-chart of the data collection process of the patients.

Table 1. Response characteristics of the patients and controls

	Invited to study ***n*** **(%)**	**Completed questionnaire** ***n*** **(%)**	**Age of included men** **Mean (sd)**
All scrotal cancer patients	80	48 (60%) [a]	66.5 (12.4) [‡]
Squamous cell carcinoma	32 (40%)	16 (50%) [a]	68.1 (12.5) [†]
Sarcoma	19 (24%)	15 (79%)	64.1 (11.5)*
Basal cell Carcinoma	12 (15%)	8 (67%)	70.3 (13.1) [†]
Extra mammary Paget's disease	8 (10%)	4 (50%)	68.5 (7.0)
Malignant melanoma	3 (4%)	2 (67%)	63.5 (16.3)
Lymphoma	1 (1%)	1 (100%)	64
Other	5 (6%)	2 (40%)	57 (31.1)
Controls	404 [b]	125 (31%)	56.7 (13.8)

**, †, ‡ Age is significantly higher than age of controls (* p<0.05, † p<0.01), ‡ p<0.0001)*

[a] 1 patient of this group was not included in the final analyses due to missing values on most of the variables.

[b] Number of information packages handed out to registrars, it's unknown how much men are actually invited by the registrars to participate in this study

Squamous cell carcinomas

The exposures that were found to be increased in the descriptive analyses of scrotal SCC were related to ultraviolet radiation and skin diseases. Age-adjusted ORs are calculated for these exposures and presented in table 2. With respect to nude sunbathing, only a medium lifetime duration of nude sunbathing (26 to 150 hours) showed a near significantly increased risk (OR=6.7, 95% confidence interval (CI)=1.0-45.6). The use of sun beds appears to increase the risk of SCC scrotal cancer (OR=3.2, 95%CI=1.0-10.4), but no clear dose-response relationship was detected in the subcategories of duration of lifetime exposure to sun beds.
Having (had) skin diseases (OR=6.3), especially psoriasis (OR=8.7), increased the risk of scrotal SCC. The risks were even higher when the skin diseases involved the genital area (21.9 for skin diseases in general). The increased risks were the most prominent in patients who had skin diseases for over ten years (OR=12.1 95%CI=3.1-47.0) and in patients who where treated for their skin diseases (OR=16.4).The ORs of skin disease treatments were not adjusted for the prevalence of skin diseases. Occupational exposures did not seem to increase the risk of scrotal SCCs (data not shown).

Sarcomas

The fifteen patients diagnosed with a sarcoma of the scrotum included nine patients with a liposarcoma and six patients with a leiomyosarcoma. Compared to the controls, men with four to ten sexual partners during their life experience an increased age-adjusted risk for sarcomas of the scrotum with an OR of 5.3 (95%CI=1.2-24.4), while sexual intercourse with more than ten partners during life did not increase the OR significantly (OR=3.1, 95%=0.5-18.9) (Table 3). None of the scrotal sarcoma patients reported to have (had) any STD, a HPV infection, a wart or skin rash on penis or scrotum or any immunosuppression. Regular long cycling trips seem to decrease the risk of sarcomas of the scrotum (OR=0.2, 95%CI=0.0-0.7), but no effect was found with respect to the number of years that these cycling trips took place.

Basal cell carcinomas

BCCs of the scrotum may be related with previous cancer diagnoses (OR=4.9, 95%CI=0.9-27.3) (Table 4). Two of the three patients with previous cancer diagnoses had previous skin tumors, while the third patient had received radiotherapy for a tumor in his lower back.

Extra mammary Paget's Disease

Two of the four patients with EMPD of the scrotum reported no remarkable exposures. One patient with EMPD reported to having had a bacterial skin disease at the genital area for over 32 years preceding the EMPD, for which over 20 x-rays of the genital area had been taken. In addition, the patient reported to have had an ureter transplantation 24 years preceding the EMPD and to have polymyalgia rheumatica. One other patient reported to have sunbathed nude during his twenties and to have used a sun beds for an average of 80 times a year in the ten years preceding the diagnosis of EMPD.

Table 2. Exposures associated with scrotal squamous cell carcinomas

Exposure	Controls (*n*=125) *n* (%)	Scrotal SCC patients (*n*=15) *n* (%)	Age-adjusted OR (95% CI)
Nude sunbathing	19 (15%)	4 (27%)	2.2 (0.6-8.0)
Duration of nude sunbathing (lifetime)			
Low (1 to 25 hours)	9 (7%)	0	N.A.
Medium (26 to 150 hours)	4 (3%)	2 (13%)	6.7 (1.0-45.6)
High (more than 150 hours)	6 (5%)	1 (7%)	3.0 (0.3-29.1)
Use of sun beds	33 (26%)	7 (47%)	3.2 (1.0-10.4)
Number of times sun beds use (lifetime)			
Low (1 to 15 times)	11 (9%)	2 (13%)	4.7 (0.7-31.3)
Medium (16 to 100 times)	9 (7%)	0	N.A.
High (more than 100 times)	13 (10%)	5 (33%)	5.7 (1.4-23.3)
Skin disease	37 (30%)	11 (73%)	6.3 (1.8-21.8)
Skin disease at genital area	6 (5%)	7 (47%)	21.9 (4.9-97.3)
Psoriasis	9 (7%)	7 (47%)	8.7 (2.5-31.0)
Psoriasis at genital area	3 (2%)	5 (33%)	23.2 (4.2-130.0)
Duration of skin disease			
Less than 10 years	18 (15%)	1 (7%)	1.2 (0.1-11.3)
More than 10 years	14 (11%)	8 (62%)	12.1 (3.1-47.0)
Skin disease treatments (treated vs. not treated)	8 (6%)	8 (53%)	16.4 (4.4-62.0)
(Coal) tar	4 (3%)	4 (27%)	10.8 (2.1-56.1)
Arsenic	1 (1%)	2 (13%)	9.7 (0.8-122.1)
Light therapy	2 (2%)	5 (33%)	28.2 (4.5-178.5)
PUVA	2 (2%)	3 (20%)	12.6 (1.8-88.1)
Methotrexate	2 (2%)	3 (20%)	14.1 (1.8-107.7)
Skin disease treatment in genital area	1 (1%)	2 (13%)	29.1 (2.2-383.0)

SCC=squamous cell carcinoma, OR=Odds-ratio

N.A. = Not Applicable, it is impossible to calculate an odds ratio due to 0 exposed patients.

Table 3. Exposures associated with scrotal sarcomas

Exposure	Controls (*n*=125) *n* (%)	Scrotal sarcoma patients (*n*=15) *n* (%)	Age-adjusted OR (95% CI)
Number of sexual partners			
0 sexual partners	1 (1%)	1 (7%)	0.02 (0.0-1.0)
1-3 sexual partners	88 (70%)	8 (53%)	Ref.
4-10 sexual partners	19 (15%)	4 (27%)	5.3 (1.2-24.4)
More than 10 sexual partners	11 (9%)	2 (13%)	3.1 (0.5-18.9)
Regularly long cycling trips	65 (52%)	2 (13%)	0.1 (0.0-0.7)
Less than 5 years	28 (22%)	1 (7%)	0.2 (0.0-1.4)
6-10 years	12 (10%)	1 (7%)	0.3 (0.0-3.0)
More than 10 years	24 (19%)	0	N.A.

OR = Odds-ratio
N.A. = Not Applicable, it is impossible to calculate an odds ratio due to 0 exposed patients
Ref = Reference category

Table 4. Exposures associated with scrotal basal cell carcinomas

Exposure	Controls (*n*=125) *n* (%)	Scrotal BCC patients (*n*=8) *n* (%)	Age-adjusted OR (95% CI)
Previous cancer diagnosis	8 (6%)	3 (38%)	4.9 (0.9-27.3)
Previous benign skin tumor	9 (7%)	1 (13%)	1.1 (0.1-11.1)
Radiotherapy treatment near scrotum	2 (2%)	1 (13%)	5.9 (0.4-90.7)

BCC = Basal cell carcinoma, OR = Odds-ratio

Malignant melanomas

One patient with a scrotal melanoma had worked with oil and paraffin wax for a period of nine years and reported to have had a wart or skin rash on his penis or scrotum. The other patient with a malignant melanoma on the scrotum had sunbathed nude with an average of ten days a year during ten years.

Lymphoma of scrotum

The single patient with a lymphoma was diagnosed with a large B-cell lymphoma at the age of 59 years after having had two benign skin tumors on his back.

Other tumors of the scrotum

One patient was diagnosed with a scrotal tumor at the age of 25 years, but the morphology of the tumor was not specified. The patient reported to have sunbathed nude during holidays in his childhood and had occasionally used sun beds during puberty. In the three years preceding the diagnosis of the scrotal tumor, he worked intensively with oil and varnish. The second patient in this group was first diagnosed with a sweat gland adenocarcinoma of the scrotum and five years later with a Bowen's disease on the scrotum. After his first

scrotal tumor the patient also suffered several other skin malignancies, a lung tumor and a tumor on his vocal cords. The patient reported to have severe psoriasis since his puberty and occasionally eczema. The treatment of his psoriasis included administration of arsenic, (coal)tar and radiotherapy.

Discussion

Our data suggest that occupational risk factors may no longer be the most important cause of scrotal cancer. Skin diseases and skin disease treatments seem to increase the risk of developing scrotal SCC. In addition, a previous cancer diagnosis might be related to an increased risk of scrotal BCC. Furthermore, an association between the number of sexual partners and the occurrence of scrotal sarcoma was found.

Squamous cell carcinomas

Having had skin diseases and/or treatment for skin diseases appeared to increase the risk of scrotal SCC. Several studies have suggested a relation between skin diseases, especially psoriasis, and scrotal and skin cancer.[10, 20, 42-47] Several other studies have shown that PUVA, methotrexate and UVB are carcinogenic for the human skin and that PUVA and UVB are especially carcinogenic for the genital skin.[21, 22, 48] The carcinogenicity of tar has been demonstrated in animal studies and in occupational settings, but not due to the dermatologic use.[49]

Unfortunately, it was not possible to differentiate whether the increased risk of scrotal SCC found in this study is due to the skin disease itself or the treatments directed against the skin disease. Both options have been suggested in the literature.[47]

Several patients were treated with (coal)tar, light therapy or PUVA in the genital area while no controls were treated in a similar manner, which made comparison impossible.

Sunbathing and the use of sun beds are well-known risk factors for skin cancers,[23, 24, 50, 51] but have not been evaluated earlier as risk factors for scrotal cancer. We did find indications that these factors may increase the risk of scrotal SCC, but a dose-response relationship could not reliably be evaluated due to the low number of exposed patients.

Sarcomas

The increased risk of sarcomas in men with more than 3 sexual partners might indicate a viral etiology in scrotal cancer. A previous study showed significant, independent associations between multiple HPV infection and increasing life time numbers of female sexual partners.[38] Furthermore, it has been shown that acquisition of oncogenic HPV infection was significantly higher in man who had more than one lifetime sexual partner.[52] The association between scrotal sarcomas and more than 10 life time sexual partners could not be established in our study; this might be due the small number of patients and sarcomas in this group.

Cycling together with horse riding was assumed to be a possible risk factor for scrotal cancer because of the irritation and prolonged increased pressure of the scrotum and the testis.[53, 54] We however found a protective effect. This could possibly be related to a general healthier lifestyle of those who undertake cycling trips, although this is only speculation.

Basal cell carcinomas

BCC of the scrotum was associated with a previous cancer diagnosis. All three patients with a previous cancer diagnosis either had a previous skin tumor or had received radiotherapy near the scrotum. It is known that both previous skin tumors and radiation increase the risk of BCCs.[55-57]

General considerations

Several interesting results were found in this exploratory study although it suffered from some weak points. This retrospective population-based nationwide study, based on all patients diagnosed from 1989 until 2005 who were still alive at the start of this study, only included 47 patients distributed over different histological subgroups. Therefore, the results should be interpreted with caution, but may be applied for generating new hypotheses.

Selection bias may have been introduced in this study because the controls were not a random sample of the Dutch male population. But being recruited among acquaintances of registrars of the comprehensive cancer centers. The controls were younger and were somewhat higher educated. We did not correct the ORs for level of education, because of the low number of patients in each histological subgroup. The difference in level of education may have resulted in an overestimation of the odds-ratios that are related to low socio-economic status. However, we did not find any significant occupational risk factor, while almost all occupational risk factors are related to low income occupations. Thus, the difference in socio-economic status does not seem to influence our results and occupational risk factors do not seem to influence the risk of scrotal cancer in the current Dutch population. Selection bias could also have been introduced by the fact that 51% of the men diagnosed with a scrotal tumor between 1989 and 2005 were deceased at the start of this study (May 2008). The deceased patients could have been more exposed to certain exposures due to an older age or a higher stage of the cancer.
As in every case-control study, recall bias may also have affected the results. Patients may have a better recall of their past exposures than the controls and therefore the ORs could be overestimated.

Based on the results of the current study and the results of a study on scrotal cancer and occupation in the Nordic countries, it seems that scrotal cancer is no longer related to occupational exposures.[19] We hypothesize that scrotal carcinogenesis nowadays has characteristics of that of skin cancer as there might be an association with UV-radiation, skin disease and skin disease treatments. Besides, the possible relationship with HPV might indicate a common etiology for scrotal cancer and other genital malignancies.
Scrotal cancer has been considered to be a separate entity because of its distinct etiological relationship with occupational exposures. If scrotal cancer is no longer related to occupational exposures, it is attractive to speculate that scrotal carcinogenesis is intermediate between cutaneous and genital carcinogenesis. The possible etiological factors found in this explorative study should be confirmed in larger studies.

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Supplementary table, frequency of exposed persons according histology

Exposures	**Controls** *n* (%)	**SCC** *n* (%)	**Sarcoma** *n* (%)	**BCC** *n* (%)	**EMPD** *n* (%)	**MM** *n* (%)	**Other** *n* (%)	**Lymphoma** *n* (%)
n	**125**	**15**	**15**	**8**	**4**	**2**	**2**	**1**
Residential environment								
Rural	96 (77%)	13 (87%)	11 (73%)	7 (88%)	3 (75%)	1 (50%)	1 (50%)	1 (100%)
Urban	29 (23%)	2 (13%)	4 (27%)	1 (13%)	1 (25%)	1 (50%)	1 (50%)	0
Education[a]								
Low	25 (20%)	6 (40%)	7 (47%)	3 (38%)	1 (25%)	0	0	0
Middle	30 (24%)	4 (27%)	2 (13%)	3 (38%)	2 (50%)	1 (50%)	2 (100%)	0
High	70 (56%)	5 (33%)	6 (40%)	1 (13%)	1 (25%)	1 (50%)	0	1 (100%)
Smoker (current or former smoker)	77 (62%)	15 (100%)	12 (80%)	5 (63%)	2 (50%)	1 (50%)	1 (50%)	1 (100%)
Alcohol consumption								
Low (0 to 3 glasses a month)	23 (18%)	1 (7%)	5 (33%)	4 (50%)	1 (25%)	1 (50%)	0	0
Medium (1 to 6 glasses a week)	68 (54%)	5 (33%)	4 (27%)	3 (38%)	3 (75%)	1 (50%)	0	1 (100%)
High (more than 6 glasses a week)	32 (26%)	9 (60%)	6 (40%)	1 (13%)	0	0	2 (100%)	0
Occupational exposures								
Oil	23 (18%)	3 (20%)	4 (27%)	3 (38%)	0	1 (50%)	1 (50%)	0
Soot	3 (2%)	1 (7%)	1 (7%)	0	0	0	0	0
Tar and pitch	2 (2%)	0	2 (13%)	0	0	0	0	0
Creosotes	2 (2%)	1 (7%)	0	0	0	0	0	0
Polycyclic aromatic hydrocarbons	1 (1%)	0	0	0	0	0	0	0
Paraffin waxes	4 (3%)	0	0	0	0	1 (50%)	0	0
Metal splinters	17 (14%)	3 (20%)	4 (27%)	2 (25%)	0	0	2 (100%)	0
Gasses and vapors	25 (20%)	4 (27%)	6 (40%)	2 (25%)	0	0	2 (100%)	0
X-rays	5 (4%)	0	0	0	0	0	0	0
Paint	18 (15%)	4 (27%)	5 (33%)	2 (25%)	1 (25%)	0	1 (50%)	0
Chemical pesticides	11 (9%)	1 (7%)	0	0	0	0	0	0

Exposure to occupational exposure in unoccupied time	35 (28%)	5 (33%)	6 (40%)	2 (25%)	1 (25%)	1 (50%)	1 (50%)	0
Exposure to occupational exposure in genital area	6 (5%)	0	1 (7%)	0	0	0	1 (50%)	0
Nude sunbathing	19 (15%)	4 (27%)	2 (13%)	0	1 (25%)	1 (50%)	1 (50%)	0
Duration of nude sunbathing								
Low (1 to 25 hours)	9 (7%)	0	0	0	0	0	0	0
Medium (26 to 150 hours)	4 (3%)	2 (13%)	0	0	0	0	0	0
High (more than 150 hours)	6 (5%)	1 (7%)	2 (13%)	0	1 (25%)	1 (50%)	1 (50%)	0
Nude sunbathing, genital sunburns	3 (2%)	0	0	0	0	1 (50%)	0	0
Use sun beds	33 (26%)	7 (47%)	3 (20%)	1 (13%)	1 (25%)	0	1 (50%)	0
Number of times sun beds use								
Low (1 to 15 times)	11 (9%)	2 (13%)	1 (7%)	1 (13%)	0	0	0	0
Medium (16 to 100 times)	9 (7%)	0	2 (13%)	0	0	0	1 (50%)	0
High (more than 100 times)	13 (10%)	5 (33%)	0	0	1 (25%)	0	0	0
No coverage of genital area during use of sun beds	25 (20%)	5 (33%)	2 (13%)	1 (13%)	1 (25%)	0	1 (50%)	0
Sun beds, sunburn on part of body	5 (4%)	2 (13%)	0	0	0	0	0	0
Sun beds, sunburn on genital area	1 (1%)	0	0	0	0	0	0	0
Any skin disease	37 (30%)	11 (73%)	1 (7%)	0	1 (25%)	1 (50%)	1 (50%)	0
Any skin disease at genital area	6 (5%)	7 (47%)	0	0	1 (25%)	0	1 (50%)	0
Psoriasis	9 (7%)	7 (47%)	1 (7%)	0	0	0	1 (50%)	0
Psoriasis at genital area	3 (2%)	5 (33%)	0	0	0	0	1 (50%)	0
Eczema	19 (15%)	1 (7%)	1 (7%)	0	0	1 (50%)	1 (50%)	0
Eczema at genital area	4 (3%)	0	0	0	0	0	1 (50%)	0
Dermatitis	1 (1%)	0	0	0	0	0	0	0
Vitiligo	1 (1%)	0	0	0	0	0	0	0
Other skin disease	12 (10%)	3 (20%)	0	0	1 (25%)	0	0	0
Other skin disease genital area	2 (2%)	2 (13%)	0	0	1 (25%)	0	0	0

Supplementary table continues on next page

Continuation of supplementary table

Exposures	Controls *n* (%)	SCC *n* (%)	Sarcoma *n* (%)	BCC *n* (%)	EMPD *n* (%)	MM *n* (%)	Other *n* (%)	Lymphoma *n* (%)
Duration of skin disease								
0 Years / None skin disease	7 (6%)	1 (7%)	0	0	0	0	0	0
Less than 1 year	9 (7%)	0	0	0	0	0	0	0
1 until 5 years	2 (2%)	0	1 (7%)	0	0	0	0	0
5 until 10 years	14 (11%)	8 (62%)	0	0	1 (25%)	0	0	0
Treated for skin disease	8 (6%)	8 (53%)	0	0	0	0	1 (50%)	0
Treated for skin disease at genital area	1 (1%)	2 (13%)	0	0	0	0	1 (50%)	0
(Coal) tar treatment	4 (3%)	4 (27%)	0	0	0	0	1 (50%)	0
(Coal) tar treatment at genital area	0	2 (13%)	0	0	0	0	1 (50%)	0
Arsenic treatment	1 (1%)	2 (13%)	0	0	0	0	1 (50%)	0
Arsenic treatment at genital area	0	0	0	0	0	0	1 (50%)	0
Light therapy	2 (2%)	5 (33%)	0	0	0	0	0	0
Light therapy at genital area	0	2 (13%)	0	0	0	0	0	0
PUVA	2 (2%)	3 (20%)	0	0	0	0	0	0
PUVA at genital area	1 (1%)	1 (7%)	0	0	0	0	0	0
Methotrexate tablets	2 (2%)	3 (20%)	0	0	0	0	0	0
Methotrexate intravenously	0	0	0	0	0	0	0	0
Previous cancer diagnosis	8 (6%)	2 (13%)	2 (13%)	3 (38%)	0	0	1 (50%)	0
Benign skin tumor (yes vs. no)	9 (7%)	3 (20%)	1 (7%)	1 (13%)	0	0	0	1 (100%)
Treated with chemotherapy	2 (2%)	0	0	0	0	0	0	0
Treated with radiotherapy	2 (2%)	0	1 (7%)	1 (13%)	0	0	1 (50%)	0
Treated with radiotherapy in genital area	2 (2%)	0	1 (7%)	1 (13%)	0	0	1 (50%)	0
Chronic infection	14 (11%)	4 (27%)	0	1 (13%)	1 (25%)	0	0	0
Immunosuppressive medicines	2 (2%)	1 (7%)	0	0	0	0	0	0
Organ transplant	0	0	0	0	1 (25%)	0	0	0

Decreased immune system	4 (3%)	1 (7%)	0	0	0	0	0	0
Hereditary disease in family	21 (17%)	4 (27%)	2 (13%)	3 (38%)	1 (25%)	1 (50%)	1 (50%)	0
X-ray / CT-scan	14 (11%)	1 (7%)	2 (13%)	2 (25%)	0	0	0	0
Infertile (not sterilized)	0	0	0	1 (13%)	0	1 (50%)	0	0
Infertile (sterilized)	35 (28%)	4 (27%)	4 (27%)	1 (13%)	1 (25%)	0	0	0
Incontinent	2 (2%)	2 (13%)	0	0	0	0	0	0
Cycling yes/no	65 (52%)	5 (33%)	2 (13%)	2 (25%)	1 (25%)	1 (50%)	1 (50%)	0
Duration of Cycling								
Less then 5 year	28 (22%)	1 (7%)	1 (7%)	1 (13%)	0	0	0	0
6 to 10 years	12 (10%)	1 (7%)	1 (7%)	1 (13%)	1 (25%)	0	0	0
More than10 years	24 (19%)	3 (20%)	0	0	0	1 (50%)	1 (50%)	0
Horse Riding	8 (6%)	0	0	0	0	1 (50%)	0	0
Washing lower body								
Twice or less times a week	7 (6%)	2 (13%)	1 (7%)	1 (13%)	1 (25%)	0	0	0
2 to 4 times a week	28 (22%)	1 (7%)	3 (20%)	3 (38%)	0	1 (50%)	1 (50%)	0
4 to 7 times a week	81 (65%)	8 (54%)	8 (54%)	3 (38%)	2 (50%)	1 (50%)	1 (50%)	1 (100%)
More than 7 times a week	9 (7%)	3 (20%)	3 (20%)	0	1 (25%)	0	0	0
Congenital disease of genitals	8 (6%)	0	0	1 (13%)	0	0	0	0
Lotions and creams on scrotum								
Done several times	6 (5%)	3 (20%)	0	1 (13%)	1 (25%)	1 (50%)	0	0
Done regularly	3 (2%)	2 (13%)	0	0	0	0	1 (50%)	0
Injury on scrotum	5 (4%)	1 (7%)	0	1 (13%)	0	0	1 (50%)	0
Scar on scrotum (surgery)	11 (9%)	1 (7%)	1 (7%)	2 (25%)	0	0	0	0
Scar on scrotum (other cause)	1 (1%)	0	0	0	0	0	1 (50%)	0
Shaved scrotum regularly	13 (10%)	2 (13%)	1 (7%)	0	0	0	0	0
Freckles and moles on scrotum	13 (10%)	2 (13%)	2 (13%)	1 (13%)	0	0	0	0
Wart or rash on penis or scrotum	14 (11%)	1 (7%)	0	1 (13%)	0	1 (50%)	1 (50%)	0
HPV infection	1 (1%)	0	0	0	0	0	0	0
HPV infection sexual partner	1 (1%)	0	0	0	0	0	0	0

Supplementary table continues on next page

Continuation of supplementary table

Exposures	Controls *n* (%)	SCC *n* (%)	Sarcoma *n* (%)	BCC *n* (%)	EMPD *n* (%)	MM *n* (%)	Other *n* (%)	Lymphoma *n* (%)
Sexually transmittable disease	4 (3%)	1 (7%)	0	0	0	0	0	0
No. of sexual partners								
0 sexual partners	1 (1%)	0	1 (7%)	1 (13%)	0	0	0	0
1 to 3 sexual partners	88 (70%)	9 (60%)	8 (53%)	7 (88%)	3 (75%)	1 (50%)	1 (50%)	1 (100%)
4 to 10 sexual partners	19 (15%)	3 (20%)	4 (27%)	0	0	0	1 (50%)	0
More than 10 sexual partners	11 (9%)	2 (13%)	2 (13%)	0	1 (25%)	0	0	0
Sexual contact with a man	4 (3%)	0	0	0	10	0	0	0

SCC= squamous cell carcinoma
BCC=basal cell carcinoma
EMPD=extramammary Paget's disease
MM=malignant melanoma

[a] *Categories of educations:*
Low = Elementary school and junior secondary vocational education
Middle = Lower general secondary education and senior secondary vocational education
High = Higher general secondary education, higher vocational education and university

Chapter 4.3

Letter to the editor: Occupation and scrotal cancer: Results of the NOCCA study

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To the Editor,

Since the discovery of Percival Pott in 1775 that chimney sweeps had an increased risk of scrotal cancer, many occupations have been linked to an increased risk of cancer at this site.[1,2] With the hygienic improvement of the industrial working place in the 1960s and 1970s exposure to substances such as tar and mineral oils, that may have caused these increased risks, have decreased substantially. It was expected that this would lead to a decrease of the incidence of scrotal cancer, but this does not seem to be the case in the USA and the Netherlands.[3,4]

Because the current risk factors for scrotal cancer are largely unknown, a nationwide population-based case-control study on the risks of scrotal cancer was conducted in the Netherlands. This study indicated that skin diseases or certain treatments for skin diseases might increase the risk of squamous cell carcinoma of the scrotum (chapter 4.2). However, there were found no associations between exposure to any of the occupational substances and the risk of scrotal cancer, but the small size of the study (47 scrotal cancer cases) precluded firm conclusions.

To further study the association between occupations and scrotal cancer risk, we used the Nordic Occupational Cancer (NOCCA) cohort database, which holds accurate information on occupation and long-term follow-up for cancer for the populations of five Nordic countries (Denmark, Norway, Sweden, Finland and Iceland). The methods of the NOCCA project have been described in detail elsewhere.[5] Based on the observed and expected number of incident scrotal cancer cases, standardized incidence ratios (SIRs) were calculated for 53 occupational groups. We present here the SIRs for the occupational categories that have been previously reported in the literature as possibly associated with scrotal cancer (technical workers, textile workers, smelting workers, mechanics, chemical process workers, engine operators and chimney sweeps), as well as the occupational categories that we found to have significant or borderline significant (increased or decreased) SIRs.

Altogether 328 scrotal cancers were diagnosed among the 7.4 million men (185 million person-years) who were followed up during the period 1961-2005 in the NOCCA cohort. Of all occupations with previous reports of elevated risks of scrotal cancer, only mechanics showed an overall increased risk (SIR=1.4, 95% Confidence Interval (95% CI): 1.0 – 2.0) (Table 1a); this risk was only increased in the period 1961-1985 (SIR=1.9, 95% CI: 1.1 – 3.0), and not in the period 1986-2005 (SIR=1.1, 95% CI: 0.6 – 1.9). None of the chemical process workers or the chimney sweeps was diagnosed with scrotal cancer.

Significant or borderline significant SIRs were further found among sales agents (SIR=1.6, 95% CI: 1.0 – 2.5) and wood workers (SIR=0.6, 95% CI: 0.3 – 1.1) during the entire study period (Table 1b) and for launderers for the period 1986-2005 (SIR=7.9, 95% CI: 1.0 – 28.5). There were no launderers diagnosed with scrotal cancer in the first period, resulting in a SIR for the entire study period of 4.2 (95% CI: 0.5 – 15.3).

Thus, from the occupational categories that have been previously reported as associated with scrotal cancer, only mechanics (including metal workers) were found to have an increased risk in this study, and only in the first period (1961-1985). Taking into account the latency period between exposures to carcinogenic substances and the development of

scrotal cancer, as well as the substantial improvements in the working environment hygiene conditions during the first part of the observation period of this study, an increased risk for a traditional risk occupation for scrotal cancer, if any, would likely be detected in the first time period of our study (1961-1985).
We did not find any other increased risk of scrotal cancer among men in occupations previously reported to be associated with an increased risk of scrotal cancer. This may indicate that there no longer is an association with occupations or that the exposure to scrotal cancer carcinogens has decreased to such a low level that there no longer is an increased risk. However, since most previous most observations on the possible risk factors of scrotal cancer have been made in the UK and the USA, it is also possible that there never has been an increased risk for these occupations in the Nordic countries.

The increased risk among launderers in the last study period and the increased risk among sales agents over the whole study period can not be explained easily. Consistence of results between countries and the existence of biological plausibility might indicate that increases in SIRs are causally related to occupational exposures. Because there were only 2 launderers diagnosed with scrotal cancer (both Swedish), it is impossible to look at consistency among the countries for this occupational group, which in turn makes it impossible to make any strong conclusions on the causal association between launderers and scrotal cancer. The increase in SIR among sales agents was consistent in each of the Nordic countries for the entire study period. However, sales agents are not expected to have any occupational exposure to carcinogenic substances such as soot, tar and oil, and therefore there is little biological plausibility for an occupationally increased risk of scrotal cancer. A previous report from the NOCCA-cohort showed that male sales agents have increased SIRs for melanoma and non-melanoma skin cancer.[5] As almost all of the scrotal cancers are skin cancers, the same risk factors as for melanoma and non-melanoma skin cancers (sun exposure and sun burns) could in theory explain the association. However, the scrotal region is usually protected from the sunshine by clothing and an increased risk of scrotal cancer by UV-radiation therefore seems unlikely. The SIRs for wood workers were consistently below unity in all Nordic countries, but we are unaware of any plausible biological mechanism that may explain this finding. Finally, we cannot rule out the possibility that these are change findings. For this study SIRs have been presented for 53 occupational categories and two different time periods. Inevitably, a number of these combinations may by chance have had significantly decreased or increased SIRs.
In conclusion, this study suggests that scrotal cancer is not related to occupational risk factors in the Nordic countries during at least the last two decades.

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Table 1. Observed numbers of scrotum cancer among men in the Nordic countries and standardized incidence ratios, by occupational category and period

Table 1A. Occupations that have been linked to scrotal cancer based on previous findings

	Total period			Period 1961-1985			Period 1986-2005		
Occupational category	**Obs**	**SIR**	**95% CI**	**Obs**	**SIR**	**95% CI**	**Obs**	**SIR**	**95% CI**
Technical workers, etc	23	1.1	0.7 – 1.6	6	0.9	0.3 – 1.9	17	1.2	0.7 – 2.0
Textile workers	2	0.6	0.1 – 2.3	[1.5]	0.0	0.0 - 2.4	2	1.3	0.2 – 4.5
Smelting workers	5	1.0	0.3 – 2.3	4	1.7	0.5 – 4.3	1	0.4	0.0 – 2.6
Mechanics	31	1.4	1.0 – 2.0	16	1.9	1.1 – 3.0	15	1.1	0.6 – 1.9
Chemical process workers	[4.2]	0.0	0.0 – 0.9	[2.1]	0.0	0.0 – 1.8	[2.1]	0.0	0.0 – 1.8
Engine operators	7	1.2	0.5 – 2.4	2	0.9	0.1 – 3.1	5	1.3	0.4 – 3.1
Chimney sweeps	[0.2]	0.0	0.0 – 18.2	[0.1]	0.0	0.0 – 43.6	[0.1]	0.0	0.0 – 31.1

Table 1B, Occupations with significant or near-significant SIRs for scrotal cancer in the NOCCA-project

	Total period			Period 1961-1985			Period 1986-2005		
Occupational category	**Obs**	**SIR**	**95% CI**	**Obs**	**SIR**	**95% CI**	**Obs**	**SIR**	**95% CI**
Sales agents	22	1.6	1.0 – 2.5	8	1.4	0.6 – 2.8	14	1.8	1.0 – 3.0
Wood workers	11	0.6	0.3 – 1.1	3	0.4	0.1 – 1.0	8	0.8	0.4 – 1.6
Launderers	2	4.2	0.5-15.3	[0.2]	0.0	0.0 – 16.8	2	7.9	1.0 – 28.5

Obs = observed number of cases; SIR = standardized incidence ratio; 95% CI = 95% confidence interval
In cells where the observed number of cases is zero, the expected number cancer cases are presented in square brackets.

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Chapter 5

Discussion

Testicular cancer

Incidence

Based on our studies it seems that the incidence of testicular cancer has been increasing in the Netherlands since the late 1980s (chapter 2.1 and 2.2). This increase took place for both histologies (seminomas and non-seminomas), all stages (although somewhat more pronounced in the localized stage) and most age-groups. In chapter 2.2 we also showed that the increased incidence in the Southern Netherlands was related to birth cohorts, already for men born since 1945.

Similar trends in the incidence of testicular cancer have also been noted in other Western countries.[1-4] However, earlier i.e. during the 1960s and 1970s, while in the Netherlands the increase did not increase until the late 1980s.[1-4] This later start of the increase does not seem to be explained by a registration artifact due to the later onset of a nationwide cancer registration in the Netherlands. After all, data of the Eindhoven cancer registry show a stable incidence rate of testicular cancer in the 1970s and the beginning of he 1980s and a similar increase of incidence as in the whole Netherlands since the start of the Netherlands cancer registry in 1989.

The incidence of a tumor can be increased by improved diagnostics or improved awareness, i.e., tumors that otherwise would not have been detected would now be detected and diagnosed. In this case, there should previously have been a large number of subclinical testicular tumors that were never going to be diagnosed or would spontaneously regress. It is unlikely that an increase in the annual number of cases in the Netherlands from 336 in 1989 to 667 in 2009 can solely be explained by tumors that remained undiagnosed previously.

The most logical explanation for the increase in incidence seems to be an increased or changed exposure to risk factors for testicular cancer. Unfortunately, the etiology of testicular cancer is not well understood and we can therefore not say which risk factor is most likely responsible for the observed trend. The etiology of testicular cancer is discussed in detail in the next section. For now it remains unknown what is causing the increasing trend in the Netherlands and most other Western countries.

Etiology

The etiology of testicular cancer is not well understood. An important established risk factor is cryptorchidism, although it is unclear whether this predisposes to testicular cancer or whether it shares common risk factors with testicular cancer.[5, 6] A prevailing hypothesis on the etiology of testicular cancer is the testicular dysgenesis syndrome hypothesis. This hypothesis proposes that four conditions (cryptorchidism, hypospadias, impaired spermatogenesis and testicular cancer) might be associated with each other, as different manifestations of disturbed prenatal testicular development.[7] Development of this syndrome is supposed to be multifactorial, in which both genetic and exogenous exposures play a role. *In utero* or perinatal exposure to endocrine disruptors (exogenous estrogens and anti-androgens) is the presumed exogenous exposure for the development of the testicular dysgenesis syndrome.[7, 8] However, if this hypothesis is true, the different conditions that are associated with the syndrome should have somewhat similar trends in incidence. While it is clear that the incidence of testicular cancer has been increasing in most Western countries, it is not clear whether the incidence of cryptorchidism and hypospadias has increased simarly.[9] Because

of the complexity of the pathogenic and epidemiologic features of each component of the syndrome it will probably take a while before we know whether this hypothesis is correct.

A lot of research has been performed on the etiology of testicular cancer and many possible risk factors have been investigated. Based on several meta-analyses and reviews on the etiology of testicular cancer, I made an overview of the established and possible risk factors of testicular cancer (table 1). Cryptorchidism, a contralateral testicular tumor and familial occurrence of testicular cancer are the best established risk factors for testicular cancer.[5, 10-13] But it also seems clear that various types of gonadal dysgenesis, including intersex malformations, increase the risk of testicular and other germ cell tumors.[10, 14, 15]

The testicular dysgenesis syndrome hypothesis suggests that exposure to estrogens plays an important role in the development of the syndrome.[16] Next to the exogenous administration of hormones, a prenatal excess of estrogen might also be caused by increased maternal endogenous estrogen levels. Several factors that are investigated as possible testicular cancer risk factors are also associated with increased maternal estrogen levels.[10, 17] These factors are in fact thus indicators of exposure to a mutual risk factor (increased maternal estrogen levels) for testicular cancer and not risk factors on their own. Maternal estrogen levels are for example higher during the first pregnancy, in pregnant women aged ≥30 years and in women who are pregnant of (dizygotic) twins.[10, 18] All of these surrogate parameters are only weak indicators of maternal estrogen levels and therefore tend to show conflicting results in respect to the risk of testicular cancer.

Another hypothesis, the childhood nutrition hypothesis, suggests that the increasing incidence of testicular cancer is caused by increased amounts of calorie intake during early childhood.[10, 19, 20] Since the beginning of the 20th century the availability and quality of nutrition has constantly been improving. The incidence of testicular cancer has also been increasing in many European countries in men from birth cohorts from the beginning of the 20th century.[1] As childhood nutrition is hard to assess accurately, surrogate parameters such as adult height are used. Although height is partly determined by genetic factors, but high calorie intake also strongly influences body length. The increasing food availability and food quality have probably caused the constant increasing adult height that has been noticed over the past several generations. The underlying biological mechanisms are not very clear yet, but it is suggested that high-calorie intake during childhood would have promoting or at least conserving effects on germ cell tumor precursor cells that are known to evolve *in utero*.[20] An important observation to support this hypothesis is the temporary decrease of incidence of testicular cancer in men born during and short after World War II (chapter 2.2).[1] In that period food was short in supply and malnutrition was common in Europe. When food supply improved in the years after the war, the testicular cancer incidence rates of men born in those birth cohorts also started to increase again.

It is also suggested that increased temperature of the testes during early childhood due to the use of modern disposable plastic lined diapers could increase the risk of testicular cancer.[21] Although, the scrotal skin temperature does indeed seem to be higher in children wearing disposable diapers in contrast to children wearing cotton daipers.[21] A case-control

Table 1. Established and possible risk factors for testicular cancer

Risk factor	Strength of association	95% CI	Type of risk estimate	Strength of evidence	Type of study	Ref
Perinatal factors						
Cryptorchidism	4.3	(3.6-5.1)	OR	+++	Meta-analysis	5
Gonadal dysgenesis	Up to 25%		Cum. risk	++	Review	10
Low birth weight	1.3	(1.1-1.7)	OR	0/+	Meta-analysis	5
Low gestational age	1.3	(1.1-1.6)	OR	0/+	Meta-analysis	5
Twinning	1.2	(1.0-1.4)	OR	+	Meta-analysis	5
Birth order						
2nd vs. 1st	0.9	(0.9-1.0)	OR	+	Meta-analysis	17
3rd vs. 1st	0.9	(0.8-1.0)	OR	+	Meta-analysis	17
4th vs. 1st	0.8	(0.7-0.9)	OR	+	Meta-analysis	17
Sibship size						
2 vs. 1	0.9	(0.8-1.2)	OR	+	Meta-analysis	17
3 vs. 1	0.9	(0.7-1.1)	OR	+	Meta-analysis	17
4+ vs. 1	0.8	(0.6-0.9)	OR	+	Meta-analysis	17
Disposable nappy use	0.8	(0.3-2.0)	OR	0	Case-control	22
Maternal perinatal factors						
Maternal bleeding	1.3	(1.0-1.7)	OR	0	Meta-analysis	17
Maternal age						
Low	1.0	(0.9-1.1)	OR	+	Meta-analysis	17
High	1.0	(1.0-1.1)	OR	+	Meta-analysis	17
Maternal smoking	1.0	(0.9-1.1)	OR	+	Meta-analysis	24
Hormone use during pregnancy	0.8-8.0		OR	0	Review	10
Medical conditions						
Contralateral TC	12.4-27.6		RR	+++	Review	10, 13
Subfertility	1.7	(1.2-2.3)	RR	+	Meta-analysis	25
Testicular atrophy	2.7-12.7		RR	+	Review	10
Inguinal hernia	1.6	(1.4-1.9)	OR	0	Meta-analysis	5
Other factors						
Familial occurrence of TC						
Father	4.3	(2.1-8.0)	SIR	+++	CR based study	12
Brother	8.5	(6.0-11.7)	SIR	+++	CR based study	12
Adult height (per 5 cm incr.)	1.1	(1.1-1.2)	OR	+	Meta-analysis	19
Early begin of puberty	0.7-2.0		RR	0	Review	10
Higher social class	1.0-2.0		RR	0	Review	10

Ref=Reference; TC=Testicular Cancer; OR=Odds Ratio; Cum. risk=Cumulative life time risk; RR=Relative Risk; SIR=Standardized incidence ratio; CR=Cancer Registry
0 = Inconsistent/inconclusive; + = Probable; ++ = Likely; +++ = Definite

study among Danish men showed no increased risk of testicular cancer due to the use of disposable diapers.[22] The start of the widespread use of disposable diapers does also not correspond with the birth cohorts of men that experienced an increased risk of testicular cancer.[22] It thus seems unlikely that the increase of incidence that has taken place in many industrialized countries can be attributed to the introduction of disposable diapers.

Although a lot of studies have investigated the etiology of testicular cancer, it remains poorly understood. The reasons for the marked increase of incidence of testicular cancer are therefore also unknown. Most studies on the risk factors of testicular cancer have problems with recall bias, because they generally have to ask the mothers of testicular cancer cases and mothers of healthy controls questions on the period around the birth of their son, which was typically 20 to 40 years earlier. Studies on the etiology of testicular cancer are often also limited to investigating proxies of the suspected exposures, such as maternal age as a proxy for maternal estrogen levels and adult height as a proxy for calorie intake during childhood. To overcome these problems, a prospective cohort should be created, in which boys would have to be followed from one of the first prenatal appointments of their mother had with a physician to the age of 40 years. In addition to questionnaires that would have to be filled in by the parents and later the boy/men himself, biological samples would have to be collected to get information on for instances maternal estrogen levels during pregnancy. Because the risk of getting testicular cancer before the age of 40 is 0.41% (1 in 244 men), you would however need to recruit 122.000 men and follow them for 40 years to come up with only 500 testicular cancer patients.[23] Due to high costs and long duration of such a study and the low mortality of testicular cancer, such a cohort will not be started if the sole cause of the cohort is to improve knowledge on the etiology of testicular cancer.
Previous set up cohorts may however be useful in the investigation of the etiology of testicular cancer. Another possibility is the linkage of several sources of data. A study in the Nordic countries for instance linked data of cancer registries with measurements in blood that was collected among pregnant women.[24] They found that maternal blood cotinine levels, which are an indication of smoking, during the first trimester of the pregnancy were not related to testicular cancer in the sons.
Although there are several possibilities to further investigate the etiology of testicular cancer, it will probably still take a while before we fully understand the etiology of testicular cancer.

Survival

As seen in chapter 2.3 the survival for patients with testicular has improved markedly since the 1970s. This improvement has been observed in most Western countries and is mainly due to the introduction of cisplatin based chemotherapy.[26-28] Before that time patients with metastasized tumors, especially the patients with non-seminomas, could not be treated effectively. The introduction of cisplatin and the continuing improvement of the care for testicular cancer resulted in an overall 5-year relative survival of 97% for seminoma and 94% for non-seminoma patients in the period 2000-2002 (chapter 2.3). In chapter 2.1 we showed that the 5-year relative survival of both seminoma and non-seminoma patients with localized diseases or regional lymph nodes was very close to 100%. Survival of patients with distant metastases continued to improve over the past two decades and 5-year relative survival of

seminoma and non-seminoma patients diagnosed in the period 2004-2009 was 88% and 85%, respectively.

Survival for patients with testicular cancer is high in most European countries, but seems to be lower in some central European countries.[29, 30] However, survival in these countries seems to be catching up with the survival in other parts of Europe.[29, 31] In Estonia a detailed population-based study was performed on survival and patterns of disease management of testicular cancer.[31] Relative survival improved significantly from 1985 to 2004, but remained considerably lower than elsewhere in Europe. The study pointed to several deficiencies in disease management, including not referring patients to an oncologist after orchidectomy, less careful diagnostic workup for older patients and low use of radiotherapy, which suggest poor access to contemporary equipment. Furthermore, cisplatin based chemotherapy was not introduced in Estonia until the 1990s.

In 1997 the International Germ Cell Consensus Classification was introduced, which classifies metastatic germ cell cancers, also including extragonadal germ cell cancers, into good, intermediate and poor prognosis groups.[32] For non-seminomas the 5-year survival for the good, intermediate and poor prognosis groups was 92%, 80% and 48%, respectively. For seminomas, who can only be classified in good and intermediate prognosis, the 5-year survival was 86% and 72%, respectively. Unfortunately, patients within the poor prognosis groups (16% of all non-seminoma patients with metastases) still have a high chance of dying from germ cell cancer, while the overall survival of testicular cancer is extremely high. This lower survival can partially be attributed to respiratory failure in patients with extensive lung metastases who have received bleomycin as part of the standard BEP (bleomycin, etoposide and cisplatin) chemotherapy.[33] Bleomycin is known for its severe lung toxicity.[34, 35] It is therefore suggested to start poor prognosis patients with extensive lung metastases on an adapted dose of the BEP regime during the first cycle of chemotherapy.[33, 36] Besides the poor prognosis patients with extensive lung metastases, bleomycin also causes (fatal) lung toxicity in other patients, especially in patients aged 40 years or older or patients with poor renal function.[34, 35]

Previous studies showed that survival for testicular cancer patients aged 55 years and older was lower than that of younger patients.[30, 37] We have found clinically meaningful differences in the survival for both European and American patients aged over 50, even up to 20% lower 5-year relative survival in patients aged 65 years or older (chapter 2.1 & 2.4). A lower survival for older patients could have been caused by several reasons, such as a less favorable stage distribution, delayed diagnosis, different biologic behavior of the tumor, less tolerability to specific therapy modalities such as chemotherapy, and/or suboptimal treatment.[38] Less tolerability to chemotherapy seems to be the most important factor.
All three main chemotherapeutic agents for testicular cancer have been associated with increased toxicity in the elderly and especially bleomycin is known for its lung toxicity in patients aged over 40.[34, 35, 39] Older patients might therefore have received dose reductions due to (expected) toxicities, which could have affected their long-term survival or they could have died due to the toxicities. Next to that, there is also a general tendency to assume that tolerance to chemotherapy is lower in aged people, which results in undertreatment of

elderly cancer patients.[39] Although a reduction of the doses of chemotherapy is generally not recommended for elderly cancer patients, it could be a viable option for managing the toxicity and giving an effective treatment.[38-40]

Future perspectives

Closely monitoring the incidence pattern of testicular cancer during the following decades is important to determine whether the increasing trend continues or whether it flattens or even starts decreasing. Possible future changes in the pattern of incidence could hold important clues for determining the etiology of testicular cancer. Unraveling the pathogenesis and etiology of testicular cancer could result in knowledge about important exposures for the risk of testicular cancer. These exposures could then possibly be targeted as primary prevention for testicular cancer. However, with the numerous studies that have been performed on the etiology of testicular cancer in the past decades, it seems unlikely that a single exposure with a high risk of testicular cancer will be found easily in the forthcoming years.

Research into the lower survival of older testicular cancer patients should focus on the causes of the lower survival. If suboptimal treatment is the main cause, it would be interesting to study which factors influence the choice between optimal and suboptimal treatment for the older patients.

Due to the very low incidence and lower survival of testicular cancer in the age-groups above 50 it might be good to centralize the treatment of older patients with metastasized diseases in expert centers.

Penile cancer

Incidence

In chapter 4.1 we showed that the age-standardized incidence rate of penile cancer in the Netherlands increased slightly, but significantly, from 1.4 per 100,000 person-years in 1989 to 1.5 in 2006 (Estimated Annual Percentage of Change (EAPC)=1.3%). This increase was mainly due to an increase of non-invasive tumors (EAPC=4.5%), while the incidence of invasive tumors remained relatively stable (non significant EAPC of 0.9%). These Dutch trends in incidence are in contrast with the USA where the incidence of invasive penile tumors seems to be decreasing.[41, 42] The difference between these trends of invasive penile tumors is not easily explained. The American studies were based on data of the Surveillance Epidemiology and End Results (SEER) program, which covers about 10% of the US population. Although the SEER data are generally considered to be representative for the whole US population, they might not be representative for certain cancer sites.[43] SEER also has problems with full coverage of patients without health insurance and this group has increased in the last 25 years. A study based on SEER data showed that the age-standardized incidence of invasive penile tumors varied from 2.2 to 5.6 per 1,000,000 person-years between different geographical regions in the USA.[42] Next to that it also showed that the incidence of penile cancer varied markedly among the different ethnic groups in the USA, being higher in Hispanics and Afro-Americans. Differences in coverage of the cancer registries in the Netherlands and the USA and demographic differences between the populations of these countries might explain the different trends of invasive penile cancer.

Survival

In chapter 4.2 we showed that 5-year relative survival in the period 2002-2007 was rather similar in Europe and the USA (70% and 63%, respectively). Survival decreased with increasing age, but more importantly, in the period 1990-2007 the survival did not improve in either Europe or the USA. The lack of an improvement is most probably due to a lack of major advances in curative treatment options for penile cancer.

Less disfiguring treatment of the primary lesion and the recognition and management of occult regional lymph node metastases are the most important advances that have been made in the treatment of penile tumors in the past decades.[44, 45] While the development of less disfiguring treatment focused on better functional and cosmetic results without compromising survival, improvement of survival was the primary goal of the changes in the management of occult lymph node metastases. About 20% of the penile cancer patients have occult lymph node metastases at diagnosis and could thus benefit from the improvement in its management.[46] Surgical removal of occult nodal metastases offers a survival benefit compared to removal of the nodes when they become clinically apparent during surveillance.[47, 48] Because lymphadenectomy for penile cancer is associated with serious morbidity, prophylactic lymphadenectomy for every clinical node negative patient would expose 80% of the patients (the patients without occult lymph node metastases) to a chance of serious morbidity without improvement of survival.[49] Dynamic sentinel node biopsy, wherein only the lymph nodes on the direct lymphatic drainage pathway of the tumor are removed, therefore seems to be a more suitable staging method.[50] Thereafter only the patients with tumor-positive sentinel nodes undergo a complete inguinal lymphadenectomy on the affected groin.

Although this treatment should improve survival of penile cancer patients, we did not find any progress in survival of penile cancer patients in Europe or the USA. This might be caused by a low referral to specialized hospitals or the improvements in the treatments may have been too recent to be noticeable in the survival estimates in chapter 4.2.

Future perspectives

Because of the lack of improvement of survival of penile cancer in the last decades and the rarity of penile cancer stronger international cooperation in clinical research may be important to facilitate clinical progress in treatment of this rare malignancy.

Survival could possibly be improved by an increased awareness of the general public on penile cancer and cancer in general. This could lead to less hesitation to seek treatment which would result in the earlier diagnosis and treatment of the penile cancer and improved chances of survival.

Scrotal cancer

Incidence

Due to the rarity of scrotal cancer and the lack of a nationwide cancer registry before 1989, it is unknown what the incidence of scrotal cancer was in the Netherlands before 1989. However, studies from the UK might give us a rough picture of the trends of incidence of scrotal cancer.

The incidence of scrotal cancer seems to have increased in the 1950s in a part of the UK, probably due to exposure to mineral oils.[51] It decreased again in entire England and Wales

during the 1970s and early 1980s. This was probably related to improvements in occupational hygiene in the decades before.[52] It was therefore expected that a decline in incidence would also be noted in the Netherlands since 1989. Although we showed that the incidence of scrotal cancer was low in the Netherlands in the period 1989-2006, there was certainly no decreasing trend of incidence (chapter 3.1). A study with SEER-data showed that the incidence in the USA remained relatively stable from 1973 to the beginning of the 1980s, whereafter the incidence increased until the end of the study period (2002), no differences were found between the incidence trends of scrotal squamous cell carcinomas, basal cell carcinomas and melanomas.[53] An increasing incidence in the USA and a relatively stable incidence in the Netherlands suggest that the incidence of scrotal cancer is no longer decreasing.

Etiology

In 1775 Percival Pott was the first to describe an etiologic relationship between cancer and occupation. He had observed that chimney sweepers had a remarkably high incidence of scrotal cancer.[54] Later it was discovered that the soot from the chimneys caused the scrotal cancer.[55] Since the discovery of Pott scrotal cancer has also been linked to exposure to tar, pitch, different types of lubrication and cutting oils, creosotes, gas production, and paraffin wax pressing.[51, 52, 55-66] Most of these carcinogens are related to unhygienic working environments. In the 1960s the hygiene of the industrial working places improved and exposure to these carcinogens decreased.

In our nationwide case-control study on the etiology of scrotal cancer (chapter 3.2) we found no evidence for an increased risk of scrotal cancer by any of the investigated occupational exposures. This study had some limitations due to the small population-size and the fact that our control-population was not a complete random sample of the Dutch male population. Nevertheless, we believe that if occupational exposures would still influence the risk of scrotal cancer, this would have led to at least some increased risks by occupational exposures in our study.

We also studied the relationship between occupations and the risk of scrotal cancer in the Nordic countries (chapter 3.3), in which we used data of five longstanding nationwide cancer registries. This study confirmed our previous finding that the occupations that are traditionally linked to scrotal cancer no longer seem to be related to scrotal cancer. We therefore believe that due to the improvements in occupational hygiene occupational exposure no longer has an important role in the development of scrotal cancer. Because most tumors of the scrotum are tumors of the scrotal skin, we hypothesize that those tumors nowadays might have the same etiology as other tumors of the skin. The possible relationship between HPV and scrotal cancer might however also indicate a common etiology for scrotal cancer and other genital malignancies such as penile and cervical cancer.

Future perspectives

As long as we do not know if scrotal skin cancers are truly different from other skin cancers, we suggest that cancer registries continue to register scrotal cancers as a separate entity. However, to investigate whether scrotal skin cancers share etiology with skin cancers at other body parts, we suggest to include scrotal skin cancers into future etiological research on skin cancers. With the data of these studies, subanalyses can be performed on the differences

between the etiology of scrotal skin cancers and other skin cancers. This is probably more cost- and time effective than to set up specific studies on scrotal cancer.

Current en future perspectives of rare cancers in general

To improve research on rare cancers the RARECARE project has started in 2003 within the EUROCARE group. After quite a bit of work already done on this topic by the Eindhoven cancer registry in it reports marking its 40th and 45th birth years in 1995 and 2001.67, 68 The RARECAREproject has among others resulted in a definition of rare cancers (incidence of less than 6 per 100,000 person-years) and a list of cancers that meet this definition.69 Of course it depends a lot on how subclassifications of histology and subsites develop and there is marked variation of incidence across the EU, e.g. for testicular cancer. According to this definition about 22% of all diagnosed cancers are rare cancers.69, 70 Through pooling of data of many European cancer registries they have also managed to calculate incidence, prevalence, mortality, and survival estimates of a large number of rare cancers. They published these results on their website (www.rarecare.eu) and are using these data for a series of scientific articles.

Provided the quality is sufficient, combination of population-based cancer registry data on rare cancers can be very useful for cancer epidemiological studies on rare cancers and possibly is the only option for good research on very rare cancers. Registries could be used as sampling frames to collect more data i.e. construct special biobanks. Results of such studies can be used to improve treatment and survival. Initiatives like RARECARE should be encouraged and supported by national and international governments. Ideally, data of such initiatives should be easily made available for researchers who are interested in doing analyses with this data to ensure optimal use of the data.

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Summary

Male genital cancers compromised about 23% of all cancers diagnosed in males in the Netherlands in 2009. Of those male genital cancers, 92% were prostate cancers, 6% were testicular cancers, 1.3% were penile cancers and only 0.2% were scrotal cancers.

Testicular cancer

Although testicular cancer only accounts for 1.4% of all cancers diagnosed in males, it is the most common cancer among men aged 20 to 39 years. With nationwide data from the Netherlands Cancer Registry and Statistics Netherlands we conducted a study on trends in testicular cancer incidence, treatment, survival, and mortality in the Netherlands (**chapter 2.1**). The annual number of testicular cancer cases doubled from 336 in 1989 to 667 in 2009, while the age-standardized incidence rate increased in that same period from 4.1 to 8.5 per 100,000 person-years. The incidence increased for all stages of both seminoma and non-seminoma testicular cancer. The stage distribution of the non-seminomas shifted towards more localized tumors. Most patients received primary treatment according to the guidelines and 5-year relative survival improved for most groups of stage and histology. A clinically significant improvement of 15% (from 73% to 88% 5-year survival) was found for seminoma patients with distant metastases. Five-year survival of non-seminoma patients with distant metastases improved from 78% to 85%.

In **chapter 2.2** we studied the incidence trends of testicular cancer in the Southern Netherlands since 1970. We used data of the longstanding population-based Eindhoven cancer registry. The age-standardized incidence rate remained relatively stable around 3 per 100,000 person-years until 1987 and started to increase thereafter. At the end of the study period (2004) the incidence rate was 6.1 per 100,000 person-years and it had increased with an annual average of 4.4% since 1988. Age-period-cohort analysis showed that the increase of incidence was mainly caused by men of birth cohorts since 1945. Studies in other Western countries also showed increased incidence rates, which were also mainly caused by birth-cohort effects. In contrast to the Netherlands the increases in the other countries already started during the 1960s and 1970s. Because the etiology of testicular cancer is poorly understood, the causes for the increase in incidence remain elusive.

Treatment, survival and mortality of testicular cancer in the Southern Netherlands were evaluated in **chapter 2.3**. Most of the patients received the treatment according to the guidelines. Ten-year relative survival of seminoma patients increased from 81% in the period 1970-1979 to 95% in the period 2000-2002, for non-seminoma patients survival improved from 54% to 92%. These improvements have been observed in most Western countries and are mainly due to the introduction of cisplatin based chemotherapy in the late 1970s. In the period 1979-1986 the mortality decreased from 1.0 to 0.4 per 100,000 person-years in the Southern Netherlands, also mainly due to the cisplatin chemotherapy.

Data from several European and American cancer registries were used to calculate histology- and age-specific relative survival for testicular cancer patients in **chapter 2.4**. In the period 2003-2007 5-year relative survival of both European and American seminoma patients younger than 50 years was at least 98%. For non-seminoma patients in the same age category the survival varied between the 93% and 96%. The relative survival of seminoma

patients aged 50 years and older in the period 2003-2007 was 2% to 5% units lower than that of younger seminoma patients. For non-seminoma patients of ≥50 years the relative survival during this period was 5% to 9% units lower than that of younger non-seminoma patients. A multiple regression analyses also showed that relative survival decreased with increasing age at diagnosis, the worst survival was found for patients aged 55 years and older. This analyses further showed that relative survival improved over time and was higher in America than Europe and higher for seminomas than for non-seminomas. The lower survival of patients aged 55 years and older could have been caused by several reasons, such as a less favorable stage distribution, delayed diagnosis, different biologic behavior of the tumor, less tolerability to specific therapy modalities such as chemotherapy, and/or suboptimal treatment. Future research into the poorer survival of older testicular cancer patients should focus on the causes of this worse survival.

Penile cancer

Penile cancer is a rare neoplasm in the Western world with an age-standardized incidence rate of 0.5 to 1.0 per 100,000 men. There is a worldwide geographic variation in its incidence that is caused by differences in socio-economic status, hygiene/infections, religious and cultural conditions (circumcision). Although the exact pathogenesis is still largely unknown, inflammation may represent an important component in penile tumor development and progression, as many penile cancers arise at sites of infection, chronic irritation or injury. We examined trends in the incidence and mortality, and described the survival of patients with penile cancer in the Netherlands (**chapter 3.1**). From 1989 until 2006, 2000 primary penile cancers were diagnosed in the Netherlands of which 1883 (94%) were squamous cell carcinomas. The majority of patients (57%) were diagnosed with localized tumors (stage 0 or stage I). The incidence rate of patients with penile squamous cell carcinoma increased slightly, but significantly, from 1.4 per 100,000 person-years in 1989 to 1.5 in 2006, mainly due to an increase of *in situ* tumors. The stage-specific 10-year relative survival of patients with stage 0 was 93%, 89% for stage I, and 81% for stage II. Due to low number of patients, no survival estimates were possible after 9 and 2 years for patients with stage III and IV tumors. For patients with stage III disease the nine-year survival was 50% and a two-year survival of 21% was found for patients with stage IV disease.

Survival of penile cancer patients was further investigated in **chapter 3.2**, in which we analyzed data of several European and American population-based cancer registries. Overall, 5-year relative survival in the period 2002-2007 was 70% and 63% among European and US patients, respectively. Survival estimates from 1990-1995, 1996-2001 and 2002-2007 were compared, but no improvement in survival over time was detected in either Europe or the US. Stronger international cooperation in clinical research may be important to facilitate clinical progress in treatment of this rare malignancy.

Scrotal cancer

Since the 1970s there have been few epidemiological studies of scrotal cancer. We used the nation-wide population-based data of the Netherlands cancer registry to report on the descriptive epidemiology of scrotal cancer in **chapter 4.1**. In all, 200 scrotal tumors in 194 patients were diagnosed in 1989-2006 in the Netherlands, most frequently being squamous cell carcinoma (27%), basal cell carcinoma (19%) and Bowen's disease (15%). The age-standardized incidence rate varied between 0.9 and 1.8 per 1,000,000 male person-years, with no significant increase or decrease over time. The overall 5-year relative survival was 82%, being 77% and 95% for patients with squamous and basal cell carcinoma, respectively. In total, 18% of the patients were diagnosed with a second primary tumor, which suggests that scrotal cancer patients might benefit from regular check-ups for possible new cancers.

In 1775 Sir Percival Pott described a high incidence of scrotal cancer among chimney sweepers. Later, scrotal cancer has also been linked to other occupations, e.g. men who worked with the distillates of coal or mineral oils. Due to improvements in working conditions during the 1960s and 1970s scrotal cancer has become a very rare tumor. Due to a lack of etiologic studies on scrotal cancer since the 1980s, it is uncertain whether occupational exposures are still the most important risk factors for the currently diagnosed scrotal cancers. We have therefore performed two studies on the etiology of scrotal cancer.

In the first study (**chapter 4.2**), we conducted a nationwide population-based case-control study in the Netherlands. In which the patients were identified through the Netherlands cancer registry and the controls were recruited among acquaintances of the cancer registry registrars. The participants completed a questionnaire that included questions on a variety of exposures that might be related to scrotal cancer. Age-adjusted Odds Ratios (ORs) were calculated according to histology of the scrotal tumors. Forty-seven scrotal cancer patients and 125 controls completed the questionnaire. No increased risk was found for any of the questioned occupational exposures. Having had a skin disease (OR=6.3), especially psoriasis (OR=8.7), increased the risk of squamous cell carcinomas of the scrotum. A previous cancer diagnosis may affect the risk of scrotal basal cell carcinomas (OR=4.9).

For the second etiologic study on scrotal cancer (**chapter 4.3**), we used the Nordic Occupational Cancer (NOCCA) cohort database, which holds accurate information on occupation and long-term follow-up for cancer for the populations of five Nordic countries (Denmark, Norway, Sweden, Finland and Iceland). Based on the observed and expected number of incident scrotal cancer cases, standardized incidence ratios (SIR) were calculated for 53 occupational groups. Altogether 328 scrotal cancers were diagnosed among the 7.4 million men who were followed up during the period 1961-2005. Of all occupations with previous reports of elevated risks of scrotal cancer, only mechanics showed an increased risk (SIR=1.4); this risk was however only increased in the period 1961-1985 (SIR=1.9) and not in the period 1986-2005 (SIR=1.1).

Based on the results of chapter 4.2 and 4.3 we believe that occupational exposure no longer has an important role in the development of scrotal cancer.

Samenvatting

Van alle nieuwe gevallen van kanker die in 2009 gediagnosticeerd werden bij mannen, betrof 23% een tumor van de mannelijke genitaliën. Van deze 10.992 tumoren waren 10.166 (92%) prostaattumoren, 667 (6%) zaadbaltumoren, 143 (1,3%) penistumoren en slechts 17 (0,2%) waren scrotumtumoren of tumoren van andere delen van de mannelijke genitaliën.

Zaadbalkanker

Ondanks dat maar 1,4% van alle nieuwe kankergevallen in mannen zaadbalkanker betreft, is zaadbalkanker wel de meest voorkomende tumor in mannen tussen de 20 en 39 jaar. Met landelijke gegevens van de Nederlandse kankerregistratie en het Centraal Bureau voor de Statistiek hebben wij een studie uitgevoerd naar de incidentie, behandeling, overleving en mortaliteit van zaadbalkanker in Nederland (**hoofdstuk 2.1**). Het jaarlijks aantal nieuw gediagnosticeerde zaadbaltumoren verdubbelde van 336 in 1989 tot 667 in 2009. De leeftijdsgestandaardiseerde incidentie in dezelfde periode steeg van 4,1 naar 8,5 per 100.000 persoonsjaren. De incidentie steeg voor alle stadia van zowel seminoom als non-seminoom zaadbaltumoren. De stadiumverdeling van de non-seminomen verschoof richting meer gelokaliseerde tumoren. Vrijwel alle patiënten kregen een primaire behandeling die overeenkwam met de richtlijn. De 5-jaars relatieve overleving steeg voor de meeste stadia van zowel de seminomen als de non-seminomen. Een klinisch significante verbetering van de 5-jaars relatieve overleving van 15% (van 73% naar 88%) werd gevonden voor patiënten met een seminoom met afstandsmetastasen. De 5-jaars overleving van patiënten met een non-seminoom met afstandsmetastasen verbeterde van 78% tot 85%.

In **hoofdstuk 2.2** hebben we de trends in de incidentie van zaadbalkanker in het zuiden van Nederland voor de periode 1970-2004 bestudeerd. We hebben daarvoor data gebruikt van de kankerregistratie van het Integraal Kankercentrum Zuid (IKZ). De leeftijdsgestandaardiseerde incidentie van zaadbalkanker bleef tot 1987 relatief stabiel rond de 3 per 100.000 persoonsjaren en nam daarna toe. In 2004 was de incidentie 6,1 per 100.000 persoonsjaren na een toename van gemiddeld 4,4% per jaar sinds 1988. Age-Period-Cohort analyses lieten zien dat de toename van de incidentie vooral 'veroorzaakt' werd door mannen die geboren waren in de geboortecohorten vanaf 1945. Studies in andere Westerse landen laten ook stijgende incidentiecijfers van zaadbalkanker zien, die ook daar met name te wijten zijn aan geboortecohorteffecten. In tegenstelling tot Nederland begon de toename van de incidentie in andere landen vaak al in de jaren zestig en zeventig van de vorige eeuw. Omdat de oorzaken van zaadbalkanker niet goed bekend zijn, blijft het onduidelijk wat de oorzaak is van de toename van de incidentie.

De behandeling, overleving en mortaliteit van zaadbalkanker in het zuiden van Nederland is bestudeerd in **hoofdstuk 2.3**. De meeste patiënten kregen de behandeling die was voorgeschreven in de richtlijn. De 10-jaars relatieve overleving van patiënten met een seminoom verbeterde van 81% in de periode 1970-1979 naar 95% in de periode 2000-2002. Voor patiënten met een non-seminoom nam de overleving toe van 54% tot 92%. Deze verbeteringen zijn vooral te wijten aan de introductie van cisplatinum chemotherapie aan het einde van de jaren zeventig. In de periode 1979-1986 daalde de mortaliteit van zaadbalkanker van 1,0 naar 0,4 per 100.000 persoonsjaren, ook met name door de cisplatinum chemotherapie.

Data van verschillende Europese en Amerikaanse kankerregistraties zijn gebruikt om leeftijdsspecifieke relatieve overleving te berekenen voor patiënten met zaadbalkanker (**hoofdstuk 2.4**). In de periode 2003-2007 was in zowel Europa als Amerika de 5-jaars relatieve overleving van de patiënten met een seminoom en jonger dan 50 jaar ten minste 98%. Voor patiënten met een non-seminoom in deze zelfde leeftijdsgroep varieerde de overleving tussen 93% en 96%.
Voor de seminoom patiënten van 50 jaar en ouder was de relatieve overleving in de periode 2003-2007 2% tot 5% lager dan de overleving van de jongere seminoom patiënten. Voor non-seminoom patiënten van 50 jaar en ouder was de overleving in deze periode 5% tot 9% lager dan de overleving van jongere patiënten. Een multivariabele overlevingsanalyse liet zien dat de relatieve overleving afnam bij toenemende leeftijd, de slechtste overleving werd dan ook gevonden voor patiënten van 55 jaar en ouder. Verder liet deze analyse zien dat de relatieve overleving verbeterde gedurende de studieperiode en hoger was in Amerika dan in Europa en hoger was voor seminomen dan voor non-seminomen. De slechtere overleving van patiënten van 55 jaar en ouder kan veroorzaakt zijn door verschillende factoren zoals een minder gunstige stadiumverdeling, vertraagde diagnose, veranderd biologisch gedrag van de tumoren, verminderde verdraagzaamheid van specifieke therapieën zoals chemotherapie en/of suboptimale behandeling. Toekomstig onderzoek naar de slechtere overleving van oudere zaadbalkankerpatiënten zou zich moeten richten op de oorzaken van deze slechtere overleving.

Peniskanker

Peniskanker is relatief zeldzaam in de Westerse wereld met een leeftijdsgestandaardiseerde incidentie van 0,5 tot 1,0 per 100.000 persoonsjaren. Er is een wereldwijde geografische variatie in de incidentie van peniskanker die veroorzaakt wordt door verschillen in sociaal-economische status, hygiëne/infecties, religie en cultuur (besnijdenis). Ondanks het feit dat de exacte pathogenese nog grotendeels onbekend is lijkt een ontstekingsproces een belangrijke invloed te hebben op de ontwikkeling en progressie van penistumoren. Veel penistumoren ontstaan op plekken waar eerder een ontsteking, chronische irritatie of wond is geweest. In **hoofdstuk 3.1** hebben wij gekeken naar de trends van de incidentie en mortaliteit van peniskanker. Daarnaast hebben we de overleving van patiënten met peniskanker bestudeerd. In de periode 1989-2006, zijn er 2000 primaire penistumoren gediagnosticeerd in Nederland waarvan 1883 (94%) plaveiselcelcarcinomen waren. De meerderheid van de patiënten (57%) werd gediagnosticeerd met een gelokaliseerde tumor (stadium 0 of I). De incidentie van plaveiselcelcarcinomen van de penis steeg licht van 1,4 per 100.000 persoonsjaren in 1989 tot 1,5 in 2006. Dit was met name te wijten aan een toename van *in situ* tumoren. De stadium-specifieke 10-jaars relatieve overleving van patiënten met een stadium 0 tumor was 93%, voor stadium I tumoren 89% en voor patiënten met stadium II tumoren 81%. Door het kleine aantal patiënten konden voor stadium III en IV, alleen de 9- respectievelijk 2-jaars relatieve overleving berekend worden De 9-jaars overleving voor stadium III patiënten was 50% en de 2-jaars overleving voor stadium IV patiënten was 21%.

De overleving van peniskankerpatiënten is verder onderzocht in **hoofdstuk 3.2**, waarin we data hebben gebruikt van verschillende Europese en Amerikaanse kankerregistraties. De 5-jaars relatieve overleving in de periode 2002-2007 was 70% en 63% voor respectievelijk de

Europese en Amerikaanse peniskankerpatiënten. In de periode 1990-2007 is de overleving van peniskanker in zowel Europa als Amerika niet verbeterd. Sterkere internationale samenwerking in het klinisch onderzoek naar peniskanker zou mogelijk kunnen leiden tot vooruitgang in de behandeling van deze zeldzame tumor.

Scrotumkanker

Sinds de jaren zeventig van de vorige eeuw zijn er weinig epidemiologische studies gepubliceerd over scrotumkanker. In **hoofdstuk 4.1** hebben wij met behulp van landelijke population-based data van de Nederlandse kankerregistratie een beschrijvende epidemiologische studie uitgevoerd naar scrotumkanker. In totaal zijn in Nederland de periode 1989-2006 200 scrotumtumoren gediagnosticeerd in 194 patiënten. Bij zes patiënten zijn in deze periode twee tumoren op het scrotum gediagnosticeerd. De meest voorkomende histologische types scrotumtumoren waren plaveiselcelcarcinomen (27%), basaalcelcarcinomen (19%) en de ziekte van Bowen (15%). De leeftijdsgestandaardiseerde incidentie van scrotumkanker varieerde tussen de 0,9 en 1,8 per 1.000.000 persoonsjaren, met geen significante toename of afname over de tijd. De 5-jaars relatieve overleving van patiënten met scrotumkanker was 82%. Uitgesplitst voor patiënten met een plaveiselcelcarcinoom of een basaalcelcarcinoom was dit respectievelijk 77% en 95%. In totaal werd bij 18% van de patiënten met een scrotumtumor nog een tweede primaire tumor ontdekt na de scrotumkankerdiagnose. Dit suggereert dat patiënten met scrotumkanker mogelijk baat hebben bij reguliere controles op nieuwe tumoren.

In 1775 werd door Sir Percival Pott ontdekt dat scrotumkanker veel vaker voorkwam bij schoorsteenvegers dan bij mannen met andere beroepen. Later is scrotumkanker ook nog gerelateerd aan andere beroepen, zoals werk met bepaalde kolen of oliën werkten. Door verbeteringen in de hygiëne van de werkomgeving in de jaren zestig en zeventig van de vorige eeuw komt scrotumkanker tegenwoordig waarschijnlijk minder vaak voor. Door een gebrek aan studies naar de oorzaken van scrotumkanker sinds de jaren tachtig, was het onbekend of beroepsmatige blootstellingen tegenwoordig nog steeds de belangrijkste risicofactor zijn voor ontwikkeling van scrotumkanker. Wij hebben daarom twee studies uitgevoerd naar de etiologie van scrotumkanker.
In de eerste studie (**hoofdstuk 4.2**) hebben we een landelijk population-based patiënt-controle onderzoek uitgevoerd. In deze studie werden patiënten geïdentificeerd met behulp van de Nederlandse kankerregistratie en werden de controlepersonen geworven onder familieleden en bekenden van de medewerkers van de kankerregistratie. De deelnemers vulden een vragenlijst in, waarin vragen waren opgenomen over allerlei blootstellingen die mogelijk gerelateerd zijn met het risico van scrotumkanker. Voor leeftijd gecorrigeerde odds-ratio's (ORs) werden berekend voor de verschillende histologische types scrotumtumoren. Zevenenveertig scrotumkankerpatiënten en 125 controlepersonen vulden de vragenlijst in. Er werden geen verhoogde risico's van scrotumkanker gevonden voor beroepsmatige blootstellingen. Het hebben of hebben gehad van een huidziekte (OR=6,3), met name psoriasis (OR=8,7), verhoogde het risico van plaveiselcelcarcinomen. Een eerder kankerdiagnose verhoogde mogelijk het risico op scrotale basaalcelcarcinomen (OR=4,9).

Voor de tweede etiologische studie over scrotumkanker (**hoofdstuk 4.3**) hebben we gebruikt gemaakt van de database van het Nordic Occupational Cancer (NOCCA) cohort. Deze database bevat accurate informatie over beroepen en kanker voor de bevolking van 5 Noord-Europese landen (Denemarken, Noorwegen, Zweden, Finland en IJsland). Gebaseerd op het waargenomen en verwachte aantal scrotumkankergevallen werden gestandaardiseerde incidentieratio's (SIRs) berekend voor 53 beroepsgroepen. In totaal werden 328 scrotumtumoren gediagnosticeerd in de 7,4 miljoen mannen die gedurende de periode 1961-2005 gevolgd werden. Van alle beroepen waarvoor eerder in de literatuur verhoogde risico's op scrotumkanker werden gerapporteerd, vertoonde alleen de groep van monteurs en metaalbewerkers een verhoogd risico (SIR=1,4). Het risico was echter alleen verhoogd in de periode 1961-1985 (SIR=1,9) en niet in de periode 1986-2005 (SIR=1,1).
Op basis van de resultaten in hoofdstuk 4.2 en 4.3 denken wij dat beroepsmatige blootstelling niet langer een belangrijke rol speelt in de ontwikkeling van scrotumkanker.

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Zoals de ondertitel van dit proefschrift al weergeeft, zijn de studies in dit proefschrift gebaseerd op gegevens uit kankerregistraties. Ik wil alle medewerkers van de kankerregistratie dan ook hartelijk bedanken voor hun werk. Jullie werk is van onschatbare waarde geweest voor dit en vele andere proefschriften en voor de vooruitgang van de kankerzorg in Nederland.

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Curriculum vitae

Rob Verhoeven werd geboren op 26 februari 1985 te Veghel. In 2003 behaalde hij het VWO diploma aan het Udens College te Uden, waarna hij startte met de studie Biomedische wetenschappen aan de Radboud Universiteit Nijmegen. Tijdens zijn bachelorstage epidemiologie in 2006 deed hij onderzoek naar trends in de incidentie, behandeling, overleving en sterfte van zaadbalkanker bij het Integraal Kankercentrum Zuid (IKZ) te Eindhoven. Dit onderzoek resulteerde in twee hoofdstukken van dit proefschrift. Na afloop van deze stage heeft hij in de zomers van 2006 en 2007 bij de afdeling onderzoek van het IKZ meegewerkt aan verschillende studies.
In de masterfase van zijn studie heeft hij de hoofdvakken Bewegingswetenschappen en Epidemiologie gevolgd. Voor zijn hoofdvakstage Beweginswetenschappen heeft hij onderzoek gedaan naar de relatie tussen motorische vaardigheden, depressie en apathie bij patiënten met de ziekte van Huntington en patiënten met cerebellaire ataxie (Universitair Medisch Centrum St Radboud, Nijmegen, afdeling neurologie, prof. dr. Kremer). Zijn hoofdvakstage epidemiologie voerde hij uit bij het Integraal Kankercentrum Oost te Nijmegen onder begeleiding van prof. dr. Kiemeney, waar hij keek naar risicofactoren voor het ontwikkelen van scrotumkanker. Ook deze studie resulteerde in een hoofdstuk van dit proefschrift. In augustus 2008 studeerde hij af en sindsdien is hij werkzaam bij het IKZ als epidemiologisch onderzoeker. Daar houdt hij zich naast de studies voor dit proefschrift ook bezig met studies naar trends en kwaliteit van zorg bij urologische en gynaecologische tumoren en mogelijke kankerclusters.

List of publications

In this thesis

1. Verhoeven RHA, Karim-Kos HE, Coebergh JWW, Brink M, Horenblas S, de Wit R, Kiemeney LALM. Markedly increased incidence and improved survival of testicular cancer in the Netherlands. Submitted.
2. Verhoeven RHA, Houterman S, Kiemeney LALM, Koldewijn EL, Coebergh JWW. Testicular cancer: Marked birth cohort effects on incidence and a decline in mortality in southern Netherlands since 1970. Int J Cancer 2008;122:639-642.
3. Verhoeven RHA, Coebergh JWW, Kiemeney LALM, Koldewijn EL, Houterman S. Testicular cancer: Trends in mortality are well explained by changes in treatment and survival in the southern Netherlands since 1970. Eur J Cancer 2007;43:2553-2558.
4. Verhoeven RHA, Gondos A, Janssen-Heijnen MLG, Saum KU, Brewster DH, Holleczek B, Crocetti E, Rosso S, Hakulinen T, Aareleid T, Brenner H & the EUNICE Survival Working Group. Testicular cancer in Europe and the US: Survival still rising among older patients. Submitted.
5. Graafland NM, Verhoeven RHA, Coebergh JWW, Horenblas S. Incidence trends and survival of penile squamous cell carcinoma in the Netherlands. Int J Cancer 2011;128:426-432.
6. Verhoeven RHA, Janssen-Heijnen MLG, Saum KU, Zanetti R, Caldarella A, Holleczek B, Brewster DH, Hakulinen T, Brenner H, Gondos A & the EUNICE Survival Working Group. Population-based survival of penile cancer patients in Europe and the USA: No improvement since at least 1990. Submitted.
7. Verhoeven RHA, Louwman WJ, Koldewijn EL, Demeyere TBJ, Coebergh JWW. Scrotal cancer: Incidence, survival and second primary tumours in the Netherlands since 1989. Br J Cancer 2010;103:1462-1466.
8. Verhoeven RHA, Aben KKH, van Rossum MM, Reedijk AM, Botterweck AM, Veerbeek L, Visser O, Van der Aa MA, Ho VKY, Coebergh JWW, Kiemeney LALM. New insights into the etiology of scrotal cancer, a nationwide case-control study in the Netherlands. Submitted.
9. Verhoeven RHA, Kiemeney LALM, Coebergh JWW, Weiderpass E, Kjaerheim K, Martinsen JI, Lynge E, Pukkala E. Occupation and scrotal cancer: Results of the NOCCA study. Acta Oncol 2011;50:1244-1246.

Other publications

10. Louwman WJ, Vulto JCM, Verhoeven RHA, Nieuwenhuijzen GAP, Coebergh JWW, Voogd AC. Clinical epidemiology of breast cancer in the elderly. Eur J Cancer 2007;43:2242-2252.
11. Kiemeney LALM, Lemmers FAMO, Verhoeven RHA, Aben KKH, Honing C, de Nooijer J, Peeters PHM, Visser O, Vlems FA. De kans op kanker voor Nederlanders. Ned Tijdschr Geneeskd 2008;152:2233-2241.
12. Cremers RGHM, Karim-Kos HE, Houterman S, Verhoeven RHA, Schroder FH, van der Kwast TH, Kil PJM, Coebergh JWW, Kiemeney LALM. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. Eur J Cancer 2010;46:2077-2087.
13. Boll D, Verhoeven RHA, van der Aa MA, Lybeert MLM, Coebergh JWW, Janssen-Heijnen MLG. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008. Eur J Cancer 2011;47:1504-1510.
14. Verhoeven RHA, Louwman WJ, Buntinx F, Botterweck AM, Lousbergh D, Faes C, Coebergh JWW. Variation in cancer incidence in northeastern Belgium and southeastern Netherlands seems unrelated to cadmium emission of zinc smelters. Eur J Cancer Prev 2011;20:549-555.
15. Boll D, Verhoeven RHA, Van der Aa MA, Pauwels P, Karim-Kos HE, Coebergh JWW, van Doorn HC. Incidence and survival trends of uncommon corpus uteri malignancies in the Netherlands, 1989-2008. In print, Int J Gynecol Cancer.
16. van de Schans SAM, Aben KKH, Mulders PFA, Haanen JBAG, van Herpen C, Verhoeven RHA, Karim-Kos HE, Oosterwijk E, Kiemeney LALM. Modest improvement in 20 years of kidney cancer care in the Netherlands. Submitted.

PhD portfolio summary

Summary of PhD training and teaching

Name PhD student:	Rob Verhoeven
Erasmus MC Department:	Public Health / Comprehense Cancer Centre South (Eindhoven)
PhD period:	August 2008 - January 2012
Promoters:	Prof.dr. J.W.W. Coebergh
	Prof.dr. L.A.L.M. Kiemeney

	Year	Workload Hours (ECTS)
Courses		
'Essentials of descriptive cancer epidemiology', Karolinska Institutet, Stockholm, Zweden	2010	40 hrs (1.4 ECTS)
'Basiscusus oncologie', Nederlandse Vereniging voor Oncologie	2010	40 hrs (1.4 ECTS)
'Cancer epidemiology', Netherlands Institute for Health Sciences	2010	40 hrs (1.4 ECTS)
Seminars and workshops		
'PhD Day' ErasmusMC	2009	4 hrs (0.1 ECTS)
'Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen'	2009	8 hrs (0.3 ECTS)
'Write it right' and 'Subsidieaanvragen', Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NOW)	2009	8 hrs (0.3 ECTS)
Farewell symposium prof. Oosterhuis 'Testicular germ cell tumors and beyond'	2011	3 (0.1 ECTS)
'Hands on Grants' KWF	2011	8 hrs (0.3 ECTS)
NCR seminar series	2008-2010	12 hrs (0.4 ECTS)
Theme specific IKZ seminar series	2008-2011	18 hrs (0.6 ECTS)
Statistical IKZ seminars	2008-2010	4 hrs (0.1 ECTS)
IKZ Urologic seminars	2008-2011	12 hrs (0.4 ECTS)
IKZ Dermatologic seminar	2009	2 hrs (0.1 ECTS)
IKZ Gynaecologic seminar	2009	2 hrs (0.1 ECTS)
IKL Sarcoma seminar	2010	3 hrs (0.1 ECTS)
Presentations		
Oral presentation WEON	2009	32 hrs (1.1 ECTS)
Poster presentation WEON	2009	32 hrs (1.1 ECTS)
Poster presentations EMUC	2011	96 hrs (3.4 ECTS)
4 presentations IKZ urology seminars	2008-2011	128 hrs (4.6 ECTS)
1 presentation IKZ dermatology seminar	2010	64 hrs (2.3 ECTS)
2 presentations IKZ theme specific seminars	2009, 2011	64 hrs (2.3 ECTS)
3 presentations for registry clerks (IKA, IKO, IKZ)	2008-2009	96 hrs (3.4 ECTS)
2 presentations Eurocourse meetings	2010, 2011	64 hrs (2.3 ECTS)

	Year	Workload Hours (ECTS)
International conferences		
European Multidisciplinary Meeting on Urological Cancers (EMUC), Barcelona, Spanje	2011	20 hrs (0.7 ECTS)
Dutch conferences		
Werkgroep Epidemiologisch Onderzoek Nederland (WEON)	2008, 2009 2010, 2011	64 hrs (2.3 ECTS)
'Cancer screening: trials and modelling to guide public health policies', ErasmusMC	2009	8 hrs (0.3 ECTS)
'Leven met kanker' CORPS	2009	8 hrs (0.3 ECTS)
'Oncologiedag' Nederlandse Vereniging voor Oncologie	2010	6 hrs (0.2 ECTS)
Other		
Internship at German Cancer Research Centre, Heidelberg, Duitsland	2010	200 hrs (7.1 ECTS)
Conducting analyses and answering questions for medical specialists	2008-2012	100 hrs (3.6 ECTS)
Eurocourse meetings	2010-2011	60 hrs (2.1 ECTS)
Contributed to the development of GGD guideline on cancer clusters	2010-2011	24 hrs (0.9 ECTS)
Total		**1270 hrs (45.4 ECTS)**