Progress against Cancer in the Netherlands since the late 1980s

Population-based Studies of Incidence, Prognosis and Mortality

Vooruitgang in de strijd tegen kanker in Nederland vanaf eind jaren tachtig

Populatie studies naar incidentie, prognose en sterfte

Henrike Elisabeth Karim-Kos

COLOPHON

Financial support for printing this thesis was provided by:
- Comprehensive Cancer Centre South (Integraal Kankercentrum Zuid)
- Comprehensive Cancer Centre Netherlands (Integraal Kankercentrum Nederland)
- Dutch Cancer Society
- Erasmus University Rotterdam
- Department of Public Health, Erasmus MC Rotterdam
- Bayer
- Pfizer Oncology
- Prostaatkankerstichting.nl

Cover design: Corina van den Berg-van Sabben
Layout: Legatron Electronic Publishing, Rotterdam
Printed by: Ipskamp Drukkers B.V., Enschede

ISBN/EAN: 978-94-6191-457-6

Progress against Cancer in the Netherlands since the late 1980s

Population-based Studies of Incidence, Prognosis and Mortality

Vooruitgang in de strijd tegen kanker in Nederland vanaf eind jaren tachtig

Populatie studies naar incidentie, prognose en sterfte

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
21 november 2012 om 11.30 uur

door

Henrike Elisabeth Karim-Kos

geboren te Zeist

PROMOTIECOMMISSIE

Promotoren:	Prof. dr. J.W.W. Coebergh
	Prof. dr. L.A.L.M. Kiemeney
Overige leden:	Prof. dr. ir. F.E. van Leeuwen
	Prof. dr. J. Verweij
	Prof. dr. C.W. Burger
Co-promotor:	Dr. E. de Vries

'Voor mijn ouders'

CONTENTS

CHAPTER 1

Introduction

In the second part of the 20th century, cancer became an important health problem worldwide. Life expectancy increased for many western populations from about 70 years in the 1950s to more than 80 years in 2010. Thereby the life span to develop cancer increased, as age is the most important risk indicator of cancer. The Danish Cancer Registry, the oldest nationwide cancer registry, showed that cancer incidence almost doubled in the last 70 years. In the Netherlands, cancer incidence increased with 50% since the 1970s. Fortunately, mortality from cancer started to decrease from the 1980s (**Figure 1.1**).

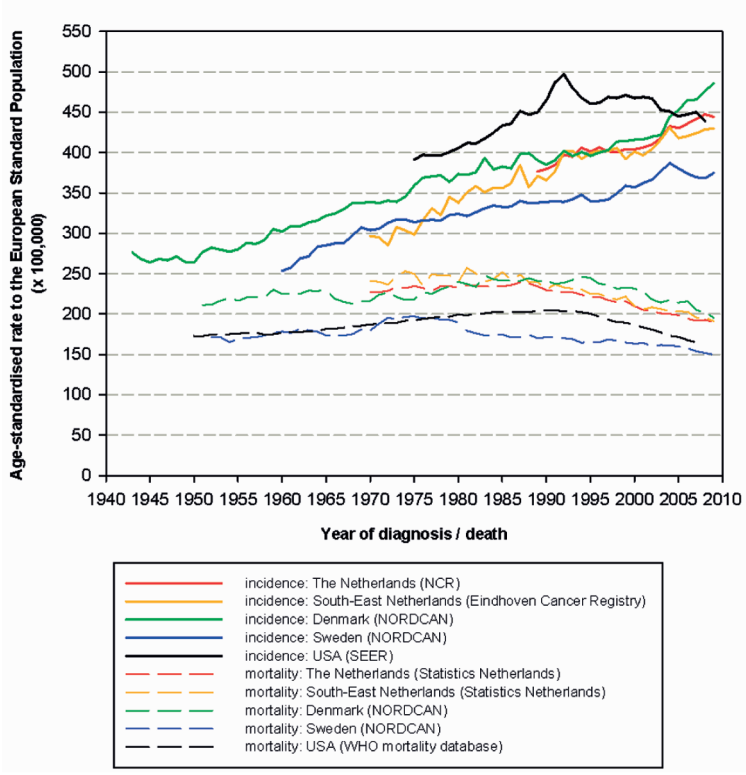


Figure 1.1 | Long-term incidence trends of total cancer (except non-melanoma skin cancers).

As a reaction to the enormous increase in cancer incidence, governments in the US and Europe started to make cancer plans. President Nixon even declared a 'war on cancer' in 1971 by signing the 'National Cancer Act'. This National Cancer Program planned to create new cancer centres, stimulate cancer research and develop cancer

control activities, such as prevention programs.[1] Since that first National Cancer Program, the United States has invested over $200 billion on cancer research.[2] Europe followed with the 'Europe against cancer program' in 1986, developed together with the 'European Code Against Cancer'. The main goal of the cancer program was to lower cancer mortality in 2000 by 15%, by focusing on three major themes: prevention (particularly tobacco control), screening (particularly for breast, cervical and colon cancer) and education and training (e.g., stimulation of collaborative cancer research and development of cancer registries).[3]

To evaluate outcomes of cancer programs, cancer incidence, prognosis and mortality are useful outcome measures. In the Netherlands, a national cancer registry was started in 12 regions in 1953 under auspices of and financed by the Dutch Cancer Society. These regional cancer registries developed each in their own way. Possibly because of that, from 1968 only the regional registries of The Hague, Rotterdam, Friesland and Southeast-North Brabant survived. The financing was stopped in 1974, because of lack of perspective for and incompleteness of the registries. However, the registry of Southeast-North Brabant persisted and expanded its catchment area to North and Middle Limburg.[4] In the mid 1970s the Comprehensive Cancer Centres developed to improve cancer care at the regional level. The Netherlands Cancer Registry was born in 1984 and reached a national coverage in 1989. Data on prognosis have become available more recently (since 2007) by an annual link of the cancer registry with the nationwide database of all municipal population registries. These registries have information on all deceased Dutch citizens. Data on cancer mortality were already available since the beginning of the 20th century through the Causes of Death Registry of Statistics Netherlands.

DUTCH CANCER TRENDS IN THE PAST

Incidence trends

In the 1970s, Harmse and De Waard[5] described Dutch trends in cancer incidence for the first time. These trends covered the time period 1960-1969 and were based on incidence data from Friesland, The Hague and Rotterdam. They observed an increasing incidence of cancer of the colon, kidney and malignant lymphoma in both sexes, an increasing incidence of cancer of the larynx, lung, prostate and bladder

cancer among males, a decreasing incidence of oral cancer among males and an increasing incidence of cancers of the breast, ovary and cervix among females.

Later on, Coebergh et al.[4] published incidence data over 1975-1986 based on data from the Eindhoven cancer registry, which covered Southeast-North Brabant and North Limburg. The total cancer incidence among males increased to 424 per 100,000 person-years (European Standardised Rate(ESR)) until 1983 and thereafter decreased to 407 in 1984-1986. Among females the total cancer incidence steadily increased over time to 292 per 100,000 person-years in 1984-1986.

Since the national coverage of the Netherlands Cancer Registry in 1989 many trend publications were published, like the annual reports published initially by the Dutch Cancer Society and later on by the Comprehensive Cancer Centres. The first long-term incidence trends were published for the period 1989-1998. During this period incidence increased for cancer of the pharynx, oesophagus and skin melanoma while cancers of the stomach and gallbladder decreased among both sexes. For males, colorectal, prostate and testicular cancer increased and cancer of the lip, larynx, lung, pancreas, bladder, renal pelvis and ureter showed decreasing trends. For females, cancer of the head and neck, larynx, lung and breast increased and ovarian and cervical cancer showed decreasing trends.[6, 7] Most of these national trends had previously been observed in the southeastern part of the Netherlands.[4,8] In a later publication with trends updated until 2003, it was shown that these increasing and decreasing incidence trends continued. New observations were the increase in liver cancer among males and increase in colon cancer among females. Overall, the total cancer incidence among males remained stable at about 445 per 100,000 person-years (ESR) and slightly increased for females from 313 per 100,000 person-years in 1989 to 358 in 1998.[9]

All these changes in cancer incidence resulted in changes in the five most common cancer types among males and females, excluding non-melanoma skin cancers (**Figure 1.2**). Most remarkable are the increase of testicular cancer from the third place in 1989-1991 to the first place in 2007-2009 among young men (30-44 yr) and the replacement of lung cancer as the most common cancer by prostate cancer among males aged 45 and older. For females, breast cancer remained the most common cancer except for females aged 75 and older where breast cancer was replaced by colorectal cancer. Lung cancer became more common among females and skin melanoma among both sexes.

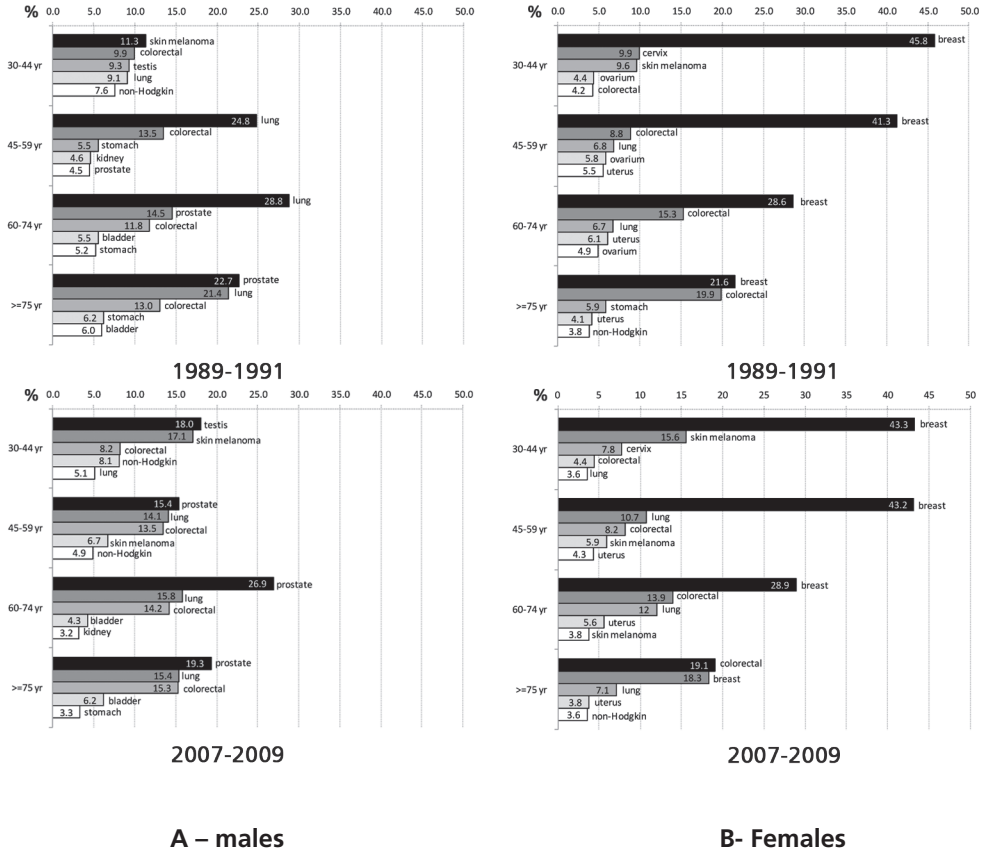


Figure 1.2 | Five most common cancer types (exclusive non-melanoma skin cancer) by gender and age group in 1989-1991 and 2007-2009, the Netherlands

Survival trends

Survival trends based on population-based cancer registry data were first published by Coebergh et al.[10] During 1975-1985, the overall 5 and 10-year relative cancer survival proportions were 33% and 27% for males and 51% and 44% for females. Improvements in survival were seen for females and patients younger than 45 years. However, the cancer registry of the southeastern part of the Netherlands has survival data from 1955, which were published later on and showed that between 1955 and 2002 cancer survival improved with about 20%. Five and 10-year relative survival improved from 38% and 30% in 1955-1969 to 60% and 50% in 2000-2002.[11]

The impressive survival improvement was only seen since the 1970s, first for the younger patients and later on also for the elderly. For patients aged 15-44 the 5 and 10-year relative survival improved from 55% and 44% in 1970-1979 to 75% and 70% in 2000-2002; for patients aged 45-69 from 40% and 33% in 1970-1979 to almost 60% and 50% in 2000-2002; for patients aged 70 and over from 34% and 28% in 1970-1979 to 50% and 40% in 2000-2002. These improvements were mainly due to survival improvements for patients with cancer of the rectum, female breast, cervix, ovary, prostate, testis, skin melanoma and Hodgkin lymphoma.[8,11-18] In the past, no survival improvements were found for patients with cancer of the stomach, kidney and liver and survival even worsened for patients with non-cardia carcinomas of the stomach.[19-22]

Mortality trends

The first Dutch cancer mortality data were described by Korteweg[23] for the time period 1918-1922. He found that before the age of 60 more women died of cancer than men, while after the age of 60 the gap between both sexes increased in disadvantage for men (**Figure 1.3**).

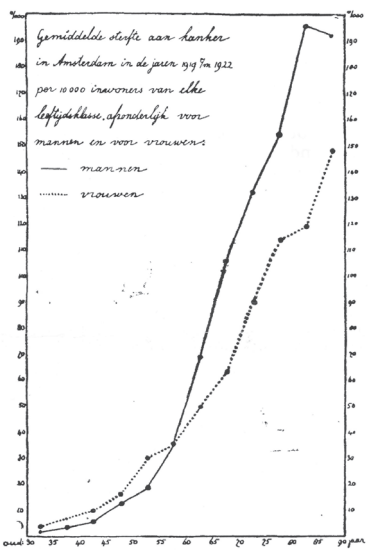


Figure 1.3 | Cancer mortality in Amsterdam per 10,000 inhabitants by gender, 1919-1922[23]

In the mid-1950s, Hoogendoorn[24] described the cancer mortality trends over the first part of the 20th century and showed that cancer mortality had slightly increased until the mid-1940s. In the 1980s, he published an update of cancer mortality trends up to 1980.[25] He observed that since the 1970s cancer mortality decreased for all female age groups and for males aged 60 and below. Above this age cancer mortality increased.

Since the 1970s, cancer mortality among males increased with 12% until the end of the 1980s (from 278 per 100,000 person-years in 1970 to 312 in 1987 (ESRs)). Thereafter mortality decreased with 27% to 228 per 100,000 person-years in 2009. Among females, cancer mortality decreased during the 1970s with 10% (from 177 per 100,000 person-years in 1970 to 160 in 1980), was stable during the 1980s and was followed by a decrease of 13% to 152 per 100,000 person-years in 2009.[26]

Compared to other causes of death, the decrease in cancer mortality was not that strong as for mortality from cardiovascular diseases (CVD), which was therefore even surpassed by cancer mortality (**Figure 1.4**). In 2005, for the first time the cancer mortality rate per 100,000 person-years became higher than the CVD mortality rate and in 2008 the absolute numbers of cancer deaths became higher. Among the population aged 60 and below, the cancer mortality rate already surpassed the CVD mortality rate since the 1970s and over time the gap has been growing. In 1970, 27% of total mortality among the young population (≤60 years) was attributed to cancer and 24% to CVD, while in 2009 these percentages were 42% and 17%, respectively. Since the mid-1990s, the mortality rate from cancer was higher than from CVD among the population aged 60-74. While in 1970, cancer mortality among this age group was 29% of total mortality and CVD mortality was 47%, in 2009 these percentages were 49% and 23%, respectively. For the elderly, the CVD mortality rate remained higher than the cancer mortality rate, although the gap became smaller over time. Seventeen percent of total mortality was due to cancer mortality and 54% due to CVD mortality in 1970 and these percentages were 22% and 33% in 2009, respectively.[26]

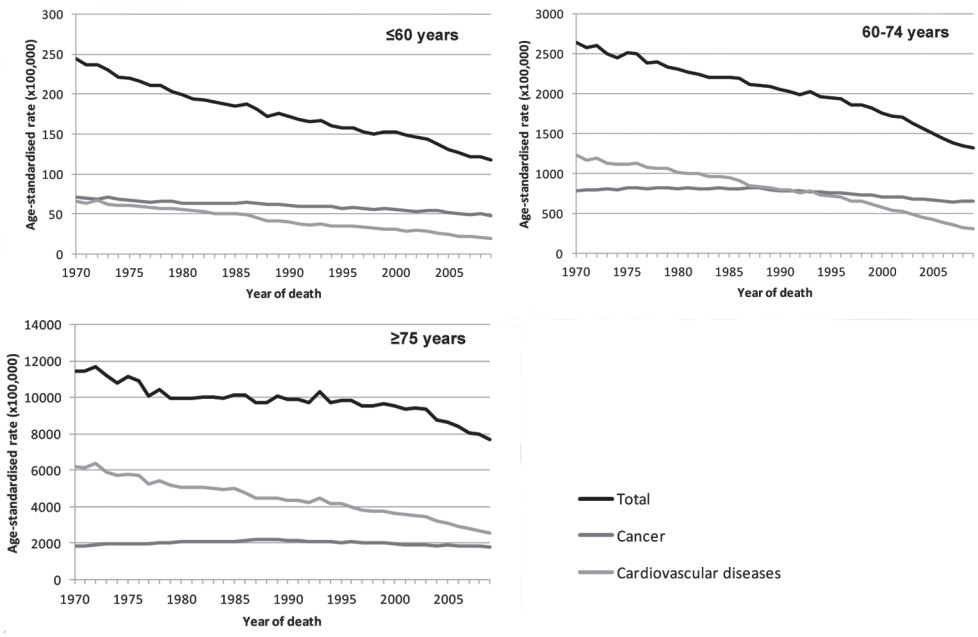


Figure 1.4 | Trends in total mortality and mortality from cardiovascular diseases and cancer (European standardised rate) by age, the Netherlands 1970-2009.

EFFORTS IN THE 'WAR AGAINST CANCER' IN THE NETHERLANDS

Cancer incidence and survival trends can be influenced by external factors, such as changes in risk factor prevalence, primary and secondary prevention and changes in diagnostics and treatment (**Figure 1.5**). Below the main initiatives and developments in prevention and cancer management in the Netherlands are described.

Main initiatives focusing on primary prevention

Smoking

Besides ageing, smoking is the most important risk factor for cancer, particularly for cancer of the lung, head and neck, oesophagus and bladder cancer. In the past, initiatives on primary prevention against smoking were taken mainly by the Dutch government and carried out through regional public health organizations. Anti-smoking policies, like increasing tobacco taxes and installing smoking-free public areas, are examples. Particularly, the foundation of STIVORO, the Dutch expert

centre for tobacco control, in 1974 by the Dutch Cancer Society, the Netherlands Heart Foundation and the Netherlands Asthma Foundation played an important role in these initiatives. As a result of these initiatives the smoking prevalence decreased from 75% among males and 40% among females in the 1970s to 28% and 26% in 2010, respectively.[27] However, the prevalence did not decrease as fast as in other Western countries and remained more or less stable since 2000. Countries like Canada and Australia are much more aggressive in their anti-smoking policy and consequently, the smoking prevalence was 17% in 2010 and 19% in 2007, respectively.[28,29] In the Netherlands, the lobby of the tobacco industry was and is still strong, because of having a large tobacco industry. This strong lobby resulted in late action of the Dutch government against smoking. Recently, the government even reversed the smoking ban in small pubs. In the 1990s, it became clear that this industry, present in the south-east Netherlands, had also a big influence on the local community. The percentage of male smokers in the south-east Netherlands was approximately the same between 1958 and 1981, while this percentage decreased with 50% on the national level. The lung cancer incidence for men was also clearly higher in this region.[30]

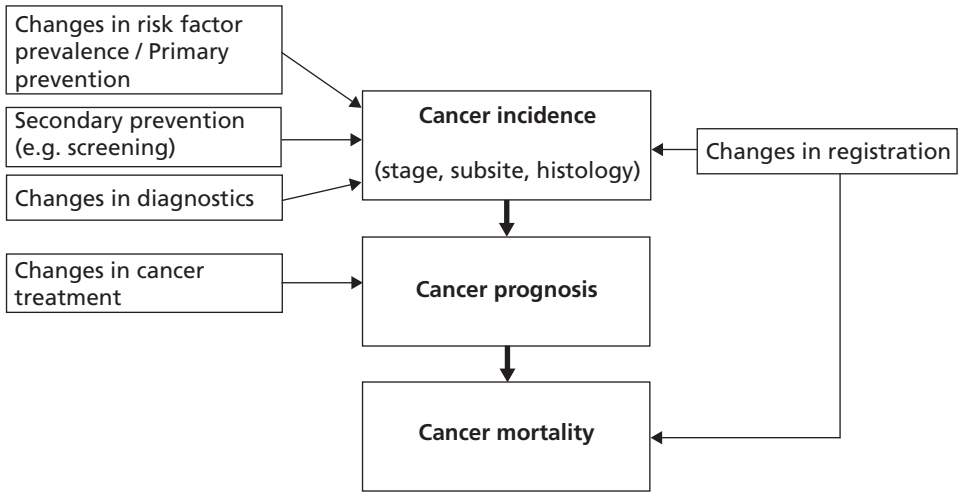


Figure 1.5 | Relationship between incidence and prognosis of and mortality from cancer

Alcohol

Alcohol is a risk factor for cancer of the oral cavity, pharynx, larynx, oesophagus, liver, colorectal and breast. The risk of getting cancer increases as consumption and frequency of consumption increases.[31-34]

In the Netherlands, alcohol consumption per capita increased with the increase of prosperity since the 1950s and was highest during the 1970s and early 1980s.[35,36] The prevalence of alcohol drinkers among the Dutch population aged 16 and over increased from 80% in 1989 to 86% in 1999 and thereafter slightly decreased to 83% in 2009. Alcohol use among males is higher than among females.[37] Compared to other European countries the per capita consumption of alcohol in the Netherlands is moderate.[36]

The strong increases in alcohol use during the 1970s did not provoke any strong negative reaction, either from the public at large or from the government. Moreover, the Dutch government had no tradition in developing and implementing a restrictive alcohol policy.[38] Since 1977, there is an advertising code for alcoholic beverages and this changed in 2000 to a voluntary advertising ban for all media when 25% of the public is below 18 years of age. Since 2009, alcohol advertising at radio and television is prohibited during day time. Furthermore, there are the alcohol taxes and a national campaign 'Drank maakt meer kapot dan je lief is' initiated by the government, started in 1986 aiming to reduce health risks and social problems by alcohol abuse.[39] Recently, the Minister of Health decided to stop such behavior changing campaigns from 2012 on.

Excessive sun exposure

Since the mid 20th century the popularity of sunbathing increased a lot among the Dutch population and excessive sun exposure is an important risk factor for skin melanoma. At the end of the 1990s, Van der Rhee and Coebergh[40] advocated primary prevention by focusing on avoiding sunburns in young people under the age of 20 and providing extra information by medical doctors to high-risk patients. The Dutch Cancer Society organized many information campaigns on the risk of excessive sunbathing and sunburns (the so-called 'verstandig zonnen' campaigns) including course materials for primary schools. At the moment, there is even a 'Sun app',[41] which can measure the UV-index, has a skin type test and gives a personal advice for sun protection. and a 'Skin monitor app',[42] which can compare suspected lesions with examples of melanomas.

Overweight and physical activity

Overweight has been endemic in the Netherlands since the early 1990s and is strongly associated with cancer of the oesophagus (only adenocarcinoma), colon, gallbladder, thyroid, kidney and endometrium. Weaker positive associations are found for cancers of the postmenopausal breast, pancreas, rectum, skin melanoma, leukemia, multiple myeloma and non-Hodgkin lymphoma.[43] In the Netherlands, the prevalence of overweight (25<BMI>30 kg/m^2) increased from 33% in 1981 to 41% in 2009 among males, and among females from 23% to 30%. The prevalence of obesity (BMI>=30 kg/m^2) increased more dramatically from 4% in 1981 to 11% in 2009 among males and among females from 6 to 12%.[26]

In the past, many campaigns and actions were organized to inform the Dutch population about the importance of healthy food and sufficient physical activity to reduce the risk of overweight. These campaigns were (partly) financed by the government. Examples of healthy food campaigns are the so-called 'Balance day' ('Balansdag') and healthy school cantines ('De gezonde schoolkantine') organized by The Netherlands Nutrition Centre Foundation. Pregnant women are informed about the influence of nutrition during pregnancy and breastfeeding on the risk of overweight of their child. To stimulate physical activity, the so-called 30 minutes movement campaign is going on since 2007 ('30 minuten bewegen') and organized by The Netherlands Institute for Sport and Movement.

Occupational exposure: Asbestos

Exposure to asbestos has created an important health problem, particularly among men. In 1929, a British pathologist concluded that inhalation of asbestos could cause pulmonary asbestosis. In the Netherlands the same conclusion was drawn 13 years later, in 1942. Asbestos as risk factor for mesothelioma was internationally acknowledged in the mid-1960s and the Netherlands followed at the end of the 1960s after the publication of the thesis of Stumphius.[44] However, it took until 1993 before all uses of asbestos were forbidden.[45]

For the period 1995-2030 it has been estimated that about 20,000 cases of mortality from pleural mesothelioma among men will have been caused by occupational exposure to asbestos in the past. The peak will be reached in 2018 with 700 deaths.[46] However, it is also found that environmental exposure to asbestos increases the risk of pleural mesothelioma among women who lived nearby an asbestos cement facility.[47,48]

Main initiatives focusing on secondary prevention

Breast cancer screening

In the mid-1970s, two projects on breast cancer screening started in Utrecht (the DOM project) and Nijmegen inviting women aged 50-64 years and aged 35-65 years, respectively. The Nijmegen project with biannual mammography showed a mortality reduction of 50% after six years and the DOM project with palpation and xeromammography showed even a 70% reduction in breast cancer mortality. Results of both studies were published in the Lancet in 1984.[49,50] Based on these two landmark papers on breast cancer screening and later on the results of a Swedish trial[51] and a cost-effectiveness study by Van der Maas and his colleagues (Rotterdam; not published) caused the government to decide to introduce a population-based nationwide breast cancer screening program with biannual mammography in women aged 50-70 years. The screening programme reached nationwide coverage in 1996 and in 1998 the programme was expanded up to the age of 75. Nowadays, annually, one million women are screened for breast cancer in the Netherlands preventing approximately 1000 women from dying of breast cancer each year.[52]

Cervical cancer screening

The first initiatives for cervical cancer prevention in the Netherlands were taken in the 1970s. Three pilot screening programs were started in the regions of Nijmegen, Rotterdam and Utrecht, which were soon adopted in other regions. These centrally organized programs were stopped by the mid-1980s when decentralized programs were introduced in the whole country. Cervical cancer screening using the Pap smear test was then offered every three years to all women aged between 35 and 54. In the early 1990s, evidence gathered pointed towards suboptimal performance of the screening program. [53-55] Based on a request from the Ministry of Health for possible solutions, new protocols and guidelines were implemented nationally in 1996.[56] The screening interval was lengthened from 3 to 5 years, the age range was broadened from 35-54 to 30-60 years, and the invitational coverage was made more complete than in the old program. The changes have resulted in increased coverage and efficiency of the screening program, and in a decrease of negative side effects.[57] Recent developments are the introduction of Human Papillomavirus (HPV) vaccination for 12-year old girls in 2009 and the positive advice of the Health Council of the Netherlands for using HPV DNA test as the primary screen test in the cervical screening program.[58]

Colorectal cancer screening

Despite the high incidence of colorectal cancer in the Netherlands there is no organized national screening program. Since 2005, several feasibility projects were started to examine and compare different tests for screening (e.g. immunochemical fecal occult blood test (iFOBT), sigmoidoscopy, coloscopy, CT-colography). Based on the first results and the positive advice of the Health Council of the Netherlands, the Minister of Health decided recently to start colorectal cancer screening using the immunochemical fecal occult blood test (iFOBT). From 2013, all persons aged 55-75 will be invited every 2 years for this national screening program.[59,60]

Prostate cancer screening

In the early 1990s, opportunistic case finding of prostate cancer by testing serum prostate-specific antigen level (PSA) was introduced in the Netherlands.[61] First mainly used by urologists and later on also by general practitioners. However, the introduction of PSA testing was relatively slow in the Netherlands compared to other high-income countries.[62] According to a survey by Statistics Netherlands in 2001, only 14% of men aged 45 and over had a PSA test in the previous five years.[63] Until now, PSA testing is not routine practice in the Netherlands because of the high risk of overdiagnosis and overtreatment. This outweighs the 20% decrease in prostate cancer mortality as an effect of population-based PSA testing as shown by the European Randomised Study of Screening for Prostate Cancer (ERSPC).[64]

Skin cancer screening

In 1989, clinicians in the western part of the Netherlands took the initiative to do a screening campaign on skin cancer in four seaside resorts (Noordwijk, Katwijk, Scheveningen and Kijkduin) using a mobile examination room, which was continued until 1995. The so-called 'sproetenbus' campaign had two aims: firstly to inform the population about the risks of excessive sun exposure and the risk of skin cancer and secondly to see if screening for skin cancer could be effective. During and after the campaign the number of consultations for skin lesions increased as well as the number of diagnoses of malignant lesions. The positive predictive value of the clinical examination was 83%.[65] Based on the results of this screening campaign and the literature, clinicians advocated a screening among high risk groups in the Netherlands. A dermatologist at the Sint Anna hospital in Oss also took an initiative and organized a screening day in 1989. However, these dermatologists doubted

about the added value of a national screening program for skin cancer and pointed out the increasing workload for general practitioners, dermatologists, surgeons and pathologists.[66] At the end of the 1990s, Van der Rhee and Coebergh[40] advocated a secondary prevention by instructing high-risk groups how to check their own skin and getting annual check-ups. About 9% of the total population belongs to this high-risk group, which has a 40 times higher risk of getting skin melanoma. Recently, a 'Skin monitor app' was launched, which can compare suspected lesions with examples of melanomas.[42]

Main changes in cancer management

Detection and staging

Since the 1970s, detection and staging of cancer continuously improved by the availability of and improved access to new diagnostic techniques. For example, the widespread use of flexible endoscopy since the 1980s caused that stomach cancer was slightly more often detected in earlier disease stages. For esophageal and colorectal cancer no change in stage distribution was seen probably due to treatment of benign Barrett's lesions or polyps.[11] Introduction of new diagnostic techniques can also cause an increase in cancer incidence which was observed for pancreatic cancer during the 1970s and early 1980s caused by the introduction of ultrasound and computed tomography (CT-scan) in combination with cytology. A strong increase in incidence was also observed for kidney cancer which is probably due to increased use of ultrasound and CT-scan.[11,67] Diagnosis of lung cancer improved (detection and histological verification) by introduction of flexible bronchoscopy and cytology in the 1970s. Since 2000, staging of lung cancer improved by introduction of Positron Emission Tomography (PET-scan) and immunohistochemistry.[11,67] These new diagnostic techniques and Magnetic Resonance Imaging (MRI-scan) are useful for many other cancers particularly in finding cancers in an earlier stages of disease.[68]

Treatment

Surgery

Treatment of cancer patients underwent enormous developments in different areas, of which surgery is one of the oldest and one of the most important. One of the examples of developments of new surgical techniques is the total mesorectal excision (TME) technique in rectal cancer patients in the mid-1990s, which replaced conventional blunt dissection of the rectum.[69] The introduction of TME resulted

in a decreased local recurrence rate.[70] Other examples are the breast-conserving surgery for breast cancer patients introduced in the 1980s,[71] radical prostatectomy for prostate cancer patients which became more common since the late 1980s. In time, removal of affected organs became more precise and more surrounding tissue/organs could be saved, which improved the quality of life of cancer patients. For example, the introduction of the sentinel lymph node biopsy, which was already described for penile cancer at the end of the 1970s, was used as a model for breast cancer introduced at the end of the 1990s. In case of a negative sentinel lymph node, breast cancer patients could be spared a lymph node dissection and avoiding lymph edema. The introduction of the subspecialism 'surgery oncology' was an important step in the aforementioned developments in oncologic surgery. In 1981, the Dutch Association for Surgical Oncology was founded.[11,72]

More recent, there is a lot of discussion about the centralisation of surgical treatment of rare tumours, like cancer of the stomach, oesophagus, pancreas, lung, rectal stage IV cancer, thyroid and bladder. In September 2011, guidelines for sarcoma, breast, oesophagus, colorectal, pancreatic, endocrinal, lung and liver cancer were introduced by the Dutch Association for Surgery (Surgical Oncology included) including the numbers of surgeries needed for a good quality of cancer care.[73]

Chemotherapy

Since the 1970s, chemotherapy became increasingly important. Particularly a combination of different cytostatics appeared to be effective in treating cancer patients. Another milestone in cancer treatment was the introduction of the multi-disciplinary approach using chemotherapy in combination with other therapies, like surgery and radiotherapy. One of the examples is breast cancer where from the second half of the 1970s and 1980s adjuvant chemotherapy and hormonal therapy was introduced as addition to surgery. Since the mid-1990s, adjuvant chemotherapy was also more given to late stage colon cancer patients. Unfortunately, chemotherapy is also harmful for healthy tissue and causes many unintended side-effects, although in time improvements were made and nowadays this treatment has become more patient friendly. In 1992, the subspecialism 'medical oncology' was introduced and in 1997 the Netherlands Association for Medical Oncology was founded, both having been important for quality improvement of chemotherapy.[11,72]

Radiotherapy

From the 1930s, radiotherapy developed from being a palliative therapy to a more curative therapy. The first breakthroughs took place after the Second World War, firstly for patients with Hodgkin lymphoma. Later on, good survival results were obtained for seminomas and early stages of cancer of the head and neck, larynx, endometrium, bladder, prostate, thyroid and cervical cancer. In the 1970s, new radiation equipments became available which enables radiation with less side-effects for cancer patients. At the end of the 20th century, radiotherapy developed further because of new ICT possibilities. Clinicians became more accurate in fixing the target and surrounding areas by using computer tomography (CT). Besides, radiotherapy was more often given in combination with surgery and chemotherapy. Radiotherapy in combination with hyperthermia became also popular (e.g. cervical cancer patients), because hyperthermia increases the sensitivity of tissue for radiation. Important for all these developments was the recognition of radiotherapy as separate specialism in the early 1970s.[11, 72]

Targeted therapies

Since the beginning of the 21st century, targeted therapies were introduced. These targeted therapies indicate small molecules and monoclonal anti-bodies, blocking specific transcription and signal ways, which are essential for tumour growth. Examples of these therapies are the hormonal therapies for breast and prostate cancer, blocking specific hormone receptors, blockers of the epidermal growth factor receptor (EGFR), blockers of proteins and enzymes who are involved in invasion and metastasis, and anti-angiogenesis agents. These are better known as the '-mabs' and '-nibs'. For example, breast cancer patients with an overexpression of Her2neu are often treated with Trastuzumab and for colorectal patients Cetuximab and Bevacizumab are common targeted therapies. Rituximab is used in patients with non-Hodgkin lymphoma, Sunitinib and Sorafenib in kidney cancer patients and so on. At the moment targeted therapy is often given in combination with chemotherapy. The hope is that these targeted therapies will replace chemotherapy in the future and a lot of research is going on into new monoclonal anti-bodies.[11,72]

RESEARCH QUESTIONS

After all the efforts that are made an important question arises:
How much progress did we make against cancer in the Netherlands since the late 1980s?

To get an answer to this important question the project 'Progress against cancer in the Netherlands since the 1970s' was started in 2007 by the department of Public Health, Erasmus MC in cooperation with epidemiologists of seven Comprehensive Cancer Centres (CCC; constitute CCC The Netherlands from 2010) and Comprehensive Cancer Centre South in Eindhoven. The project was funded by the Dutch Cancer Society. Within this project 17 working groups were started to study time trends of incidence, survival and mortality in relationship with previous changes in risk factors, prevention, screening and cancer management. In total 25 tumour types were studied within this project. Part of all this work is presented in this thesis.

The two main research questions in this thesis were:

a. What is the impact of changes in risk factor prevalence, primary and secondary prevention, and cancer management on cancer trends?
b. How can we optimize the assessment of progress against cancer and what are the pitfalls?

METHODS

Data sources

The studies in this thesis are performed using population-based incidence data from the nationwide Netherlands Cancer Registry (NCR), which has a national coverage since 1989 and is maintained and hosted by the Comprehensive Cancer Centre the Netherlands (IKNL) and the Comprehensive Cancer Centre South (IKZ). The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathology archive (PALGA). An additional source is the national registry of hospital discharges, which accounts for up to 8% of newly diagnosed cases. Information on patient and tumour characteristics is obtained routinely from the medical records six to nine months after diagnosis. The quality of the data is high, due to thorough training of the administrators and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[74] The

information on vital status was actively obtained from the municipal registries and from the database of deceased persons of the Central Bureau for Genealogy. The vital status was used to calculate follow-up time for each cancer patient. Mortality data was derived from Statistics Netherlands.

To get an overview of the progress against cancer achieved in the Netherlands compared to other European countries we described cancer incidence, mortality and survival trends of 21 European countries using data from national or regional cancer registries.

Methods to measure progress against cancer

Many parameters may indicate progress, such as less false positive and false negative screening exams, more effective therapies with fewer associated side effects, better quality of life, and improved organization of palliative care. All of these are difficult to measure and monitor through the standard surveillance instruments, mainly cancer registries. However, several of these parameters will influence incidence of, survival and/or mortality from cancer, which can be monitored over time. We chose to focus on these three measures of cancer burden (i.e. incidence, survival, and mortality) combined in order to achieve a more objective assessment of progress against cancer, while avoiding over-interpreting findings from one of these measures only.

CONTENTS OF THIS THESIS

The main aim of this thesis is to determine whether or not we have made progress against cancer in the Netherlands since the late 1980s after spending so much time, energy and money. First of all, recent cancer trends in Europe and the Netherlands are described in **Chapter 2**.

In **Chapter 3** the impact of changes in risk factor prevalence and primary prevention are described by studying lung and ovarian cancer trends. The impact of changes in secondary prevention and cancer management was investigated for prostate, ovarian and esophageal cancer in **Chapter 4**.

A useful framework for measuring progress against cancer and pitfalls of using incidence, prognosis and mortality as measures for progress are presented in **Chapter 5**. This thesis concludes in **Chapter 6** with a general discussion of the main findings, their policy implications and recommendations for future research.

REFERENCES

1. Office of Government and Congressional Relations. National Cancer Act of 1971. *http://legislative.cancer.gov/history/phsa/1971* (accessed November 2011).
2. Begley S. We Fought Cancer… And Cancer Won. *Newsweek*Sep 5, 2008:7.
3. Cancer Plan 1987-1989. *Official Journal of the European Union.* C 50,26, 2, 1987.
4. Coebergh JW, Verhagen-Teulings MT, Crommelin MA, Bakker D, van der Heijden L. [Trends in incidence of cancer in southeast North Brabant and North Limburg during 1975-1986; report from the IKZ/SOOZ cancer registration (Integrated Cancer Center South/Cooperative Organization Oncology Hospitals)]. *Ned Tijdschr Geneeskd.* 1990;134(15):754-760.
5. Harmse NS, de Waard F. [Trends of cancer incidence in The Netherlands]. *T Soc Geneesk.* 1973;51:670-679.
6. Siesling S, van Dijck JA, Visser O, Coebergh JW. Trends in incidence of and mortality from cancer in The Netherlands in the period 1989-1998. *Eur J Cancer.* 2003;39(17):2521-2530.
7. van Dijck JAAM, Coebergh JWW, Siesling S, Visser O, eds. *Trends of cancer in the Netherlands 1989-1998*. Utrecht: Comprehensive Cancer Centres Netherlands; 2002.
8. Janssen-Heijnen ML, Louwman WJ, van de Poll-Franse LV, Voogd AC, Houterman S, Coebergh JW. [Trends in the incidence and prevalence of cancer and in the survival of patients in southeastern Netherlands, 1970-1999]. *Ned Tijdschr Geneeskd.* 2003;147(23):1118-1126.
9. Siesling S, Visser O, Van Dijk JAAM, Coebergh JWW. [Trends in incidence of and mortality from cancer in the Netherlands during 1989-2006]. *Ned Tijdschr Geneeskd.* 2006;150(45):2490-2496.
10. Coebergh JW, Verhagen-Teulings MT, Crommelin MA, van der Heijden LH, Hop WC. [Survival chances of patients diagnosed with cancer in 1975-1985 in southeast Noord-Brabant and north Limburg]. *Ned Tijdschr Geneeskd.* 1991;135(21):938-943.
11. Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW, eds. *Van meten naar weten: 50 jaar kankerregistratie.* Eindhoven: Comprehensive Cancer Center South; 2005.
12. Lemmens V, van Steenbergen L, Janssen-Heijnen M, Martijn H, Rutten H, Coebergh JW. Trends in colorectal cancer in the south of the Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. *Acta Oncol.* 2010;49(6):784-796.
13. Louwman WJ, Voogd AC, van Dijck JA, et al. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. *Cancer Causes Control.* 2008;19(1):97-106.
14. Balvert-Locht HR, Coebergh JW, Hop WC, et al. Improved prognosis of ovarian cancer in The Netherlands during the period 1975-1985: a registry-based study. *Gynecol Oncol.* 1991;42(1):3-8.
15. Post PN, Kil PJ, Coebergh JW. Trends in survival of prostate cancer in southeastern Netherlands, 1971-1989. *Int J Cancer.* 1999;81(4):551-554.
16. Verhoeven RH, Coebergh JW, Kiemeney LA, 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(17):2553-2558.
17. de Vries E, Houterman S, Janssen-Heijnen ML, et al. Up-to-date survival estimates and historical trends of cutaneous malignant melanoma in the south-east of The Netherlands. *Ann Oncol.* 2007;18(6):1110-1116.
18. van Spronsen DJ, Dijkema IM, Vrints LW, et al. Improved survival of Hodgkin's patients in south-east Netherlands since 1972. *Eur J Cancer.* 1997;33(3):436-441.

19. Pinheiro PS, van der Heijden LH, Coebergh JW. Unchanged survival of gastric cancer in the southeastern Netherlands since 1982: result of differential trends in incidence according to Lauren type and subsite. *Int J Cancer.* 1999;84(1):28-32.
20. Dassen AE, Lemmens VE, van de Poll-Franse LV, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. *Eur J Cancer.* 2010;46(6):1101-1110.
21. Aben KK, Luth TK, Janssen-Heijnen ML, Mulders PF, Kiemeney LA, van Spronsen DJ. No improvement in renal cell carcinoma survival: a population-based study in the Netherlands. *Eur J Cancer.* 2008;44(12):1701-1709.
22. Verhoef C, Visser O, de Man RA, de Wilt JH, JN IJ, Janssen-Heijnen ML. Hepatocellular carcinoma in the Netherlands incidence, treatment and survival patterns. *Eur J Cancer.* 2004;40(10):1530-1538.
23. Korteweg R. [Cancer mortality in the Netherlands]. *Ned Tijdschr Geneeskd.* 1930;74:5017-5023.
24. Hoogendoorn D. [Observations on cancer mortality during the past 50 years]. *Ned Tijdschr Geneeskd.* 1955;99(23):1631-1644.
25. Hoogendoorn D. [Trends in cancer mortality]. *Ned Tijdschr Geneeskd.* 1983;127(37):1661-1668.
26. Statistics Netherlands. Mortality data. *http://statline.cbs.nl* (accessed March 2011).
27. STIVORO. *http://www.stivoro.nl* (accessed April 2011).
28. Health Canada. Health Concerns: Tobacco. *www.hc-sc.gc.ca* (accessed November 2011).
29. Better Health Channel. Healthy Living: Tobacco. *www.betterhealth.vic.gov.au* (accessed November 2011).
30. Janssen-Heijnen ML, Coebergh JW, van Reek J. Very high male lung cancer incidence in areas with tobacco industries. *Eur J Cancer.* 1996;32A(13):2372-2373.
31. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst.* 2009;101(5):296-305.
32. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer.* 2002;87(11):1234-1245.
33. Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med.* 2004;38(5):613-619.
34. World Cancer Research Fund / American Institute for Cancer Research. *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective.* Washington D.C.: AICR; 2007.
35. Knibbe RA, Drop MJ, Van Reek MJ, Saenger G. The development of alcohol consumption in the Netherlands: 1958-1981. *Br J Addict.* 1985;80(4):411-419.
36. van Laar MW, Cruts AAN, Verdurmen JEE, van Ooyen-Houben MMJ, Meijer RW. [*National Drug Monitor: annual report 2005*]. Utrecht: Trimbos Institute; 2006.
37. Statistics Netherlands. Health and welfare. *http://statline.cbs.nl* (accessed November 2011).
38. Garretsen HF, Knibbe RA. Alcohol consumption and alcohol control policy: the case of the Netherlands. *Health Policy.* 1985;5(2):151-158.
39. Dutch Institute for Alcohol Policy. *www.stap.nl* (accessed November 2011).
40. van der Rhee HJ, Coebergh JW. [Prevention of cutaneous melanoma]. *Ned Tijdschr Geneeskd.* 1999;143(26):1356-1359.
41. KWF Zonkracht App. *http://itunes.apple.com/nl/app/kwf-zonkracht/id375626891?mt=8 / https://play.google.com/store/apps/details?id=org.me.zonkracht&feature=search_result* (accessed June 2012).

42. Stichting Melanoom. Huidmonitor App. *http://itunes.apple.com/nl/app/huidmonitor/id519040410?mt=8 / https://play.google.com/store/apps/details?id=com.popappfactory.melanoom.* (accessed June 2012).
43. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008;371(9612):569-578.
44. Stumphius J. Asbest in een bedrijfsbevolking. *Een onderzoek naar het voorkomen van asbestlichaampjes en mesotheliomen op een scheepswerf en machinefabriek*. Assen: Van Gorcum & Comp N.V.; 1969:280.
45. Burdorf A, Swuste P, van der Maas P. [Asbestos and health: from patient presentation to recognition of occupational diseases in The Netherlands]. *Ned Tijdschr Geneeskd.* 19 1988;132(47):2162-2167.
46. Burdorf A, Barendregt JJ, Swuste PH, Heederik DJ. [Future increase of the incidence of mesothelioma due to occupational exposure to asbestos in the past]. *Ned Tijdschr Geneeskd.* 1997;141(22):1093-1098.
47. Burdorf A, Dahhan M, Swuste PH. [Pleural mesothelioma in women is associated with environmental exposure to asbestos]. *Ned Tijdschr Geneeskd.* 2004;148(35):1727-1731.
48. Sinninghe Damste HE, Siesling S, Burdorf A. [Environmental exposure to asbestos in the area around Goor has been established as the cause of pleural mesothelioma in women]. *Ned Tijdschr Geneeskd.* 2007;151(44):2453-2459.
49. Verbeek AL, Hendriks JH, Holland R, Mravunac M, Sturmans F, Day NE. Reduction of breast cancer mortality through mass screening with modern mammography. First results of the Nijmegen project, 1975-1981. *Lancet.* 1984;1(8388):1222-1224.
50. Collette HJ, Day NE, Rombach JJ, de Waard F. Evaluation of screening for breast cancer in a non-randomised study (the DOM project) by means of a case-control study. *Lancet.* 1984;1(8388):1224-1226.
51. Tabar L, Fagerberg CJ, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet.* 1985;1(8433):829-832.
52. Peeters PHM, Beex LVAM, Kiemeney LA. The role of early studies in Nijmegen and Utrecht in preventing 1000 women per year from dying of breast cancer In: Terwee C, Dekker F, Burdorf L, eds. *Inspiratie in de epidemiologie. Een bloemlezing van Nederlandse epidemiologische studies van het eerste uur*. Rotterdam: Vereniging voor Epidemiologie; 2011:37-43.
53. Giard RW, Hermans J, Doornewaard H. [National results of cervix cytology diagnosis in 1992; efficacy of screening could be improved]. *Ned Tijdschr Geneeskd.* 1994;138(26):1325-1330.
54. van Ballegooijen M, Habbema JD, van Oortmarssen GJ, Koopmanschap MA, Lubbe JT, van Agt HM. Preventive Pap-smears: balancing costs, risks and benefits. *Br J Cancer.* 1992;65(6):930-933.
55. van Elven E, Griffioen H, Wiegman H. [*Survey into bottlenecks of the organised cervical cancer screening programme*]. KPMG. 1990.
56. National Health Insurance Council. [*Starting points for the restructering of the organised cervical cancer screening programme - final decision*]. Amstelveen: Ziekenfondsraad; 1993.
57. Rebolj M, van Ballegooijen M, Berkers LM, Habbema D. Monitoring a national cancer prevention program: successful changes in cervical cancer screening in the Netherlands. *Int J Cancer.* 2007;120(4):806-812.
58. Health Council of the Netherlands*. [Population screening for cervical cancer]*. The Hague: Health Council of the Netherlands; 2011.

59. Health Council of the Netherlands. *[Population screening for colorectal cancer]*. The Hague: Health Council of the Netherlands; 2009.
60. Schippers EI. [*Final decision of introduction national colorectal cancer screening*]. Letter of the ministry of Public Health, Welfare and Sport (PG/OGZ 3065362). June 1, 2011.
61. Post PN, Kil PJ, Crommelin MA, Schapers RF, Coebergh JW. Trends in incidence and mortality rates for prostate cancer before and after prostate-specific antigen introduction. A registry-based study in southeastern Netherlands, 1971-1995. *Eur J Cancer.* 1998;34(5):705-709.
62. Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. *BJU Int.* 2002;90(2):162-173.
63. Statistics Netherlands. POLS data-nog uitschrijven. *http://statline.cbs.nl* (accessed January 2010).
64. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med.* 2009;360(13):1320-1328.
65. Krol AD, van der Rhee HJ, Dieleman M, Welvaart K. [The 'freckle bus' campaign; an unhealthy phenomenon or a sensible experiment?]. *Ned Tijdschr Geneeskd.* 1990;134(42):2047-2050.
66. Groenendal H, Rampen FH, Broekman JM. [Mass screening for skin cancer; experiences in Oss]. *Ned Tijdschr Geneeskd.* 1990;134(42):2057-2058.
67. Coebergh JWW, van der Heijden LH, Janssen-Heijnen MLG, eds. *Cancer Incidence and Survival in the Southeast of the Netherlands 1955-1994.* Eindhoven: Comprehensive Cancer Center South; 1995.
68. Rijnsburger AJ, Obdeijn IM, Kaas R, et al. BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study. *J Clin Oncol.* 2010;28(36):5265-5273.
69. den Dulk M, Krijnen P, Marijnen CA, et al. Improved overall survival for patients with rectal cancer since 1990: the effects of TME surgery and pre-operative radiotherapy. *Eur J Cancer.* 2008;44(12):1710-1716.
70. Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg.* 1995;181(4):335-346.
71. Siesling S, van de Poll-Franse LV, Jobsen JJ, Repelaer van Driel OJ, Voogd AC. [Trends and variation in breast conserving surgery in the southeast and east of the Netherlands over the period 1990-2002]. *Ned Tijdschr Geneeskd.* 2005;149(35):1941-1946.
72. Wagener DJT. *[The history of the oncology]*. Houten: Bohn Stafleu van Loghum; 2008.
73. Nederlandse Vereniging voor Heelkunde. [*Report: Guidelines surgical treatment (2.0)*]. 2011.
74. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol.* 1993;22(3):369-376.

CHAPTER 2

Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s

Henrike E. Karim-Kos
Esther de Vries
Isabelle Soerjomataram
Valery Lemmens
Sabine Siesling
Jan Willem W. Coebergh

Eur J Cancer 2008 Jul;44(10):1345-89

ABSTRACT

Background. We present a comprehensive overview of most recent European trends in population-based incidence of, mortality from and relative survival for patients with cancer since the mid 1990s.

Methods. Data on incidence, mortality and 5-year relative survival from the mid 1990s to early 2000 for the cancers of the oral cavity and pharynx, oesophagus, stomach, colorectum, pancreas, larynx, lung, skin melanoma, breast, cervix, corpus uteri, ovary, prostate, testis, kidney, bladder, and Hodgkin's disease were obtained from cancer registries from 21 European countries. Estimated annual percentages change in incidence and mortality were calculated. Survival trends were analyzed by calculating the relative difference in 5-year relative survival between 1990-1994 and 2000-2002 using data from EUROCARE-3 and -4.

Results. Trends in incidence were generally favourable in the more prosperous countries from Northern and Western Europe, except for obesity related cancers. Whereas incidence of and mortality from tobacco-related cancers decreased for males in Northern, Western and Southern Europe, they increased for both sexes in Central Europe and for females nearly everywhere in Europe. Survival rates generally improved, mostly due to better access to specialized diagnostics, staging and treatment. Marked effects of organised or opportunistic screening became visible for breast, prostate and melanoma in the wealthier countries. Mortality trends were generally favourable, except for smoking related cancers.

Conclusions. Cancer prevention and management in Europe is moving in the right direction. Survival increased and mortality decreased through the combination of earlier detection, better access to care and improved treatment. Still, cancer prevention efforts have much to attain, especially in the domain of female smoking prevalence and the emerging obesity epidemic.

INTRODUCTION

Cancer has become a major public health problem in Europe with an estimated prevalence of about 3%, increasing to 15% at old age. Almost 50% of deaths at middle age is caused by cancer, partly resulting from lowering mortality from other causes of death. In 2002, 26% of all cancer cases in the world were diagnosed in Europe.[1] **Figures 2.1** and **2.2** show the distribution of estimated cancer incidence and mortality for 2006; breast, colorectal, prostate and lung cancers were the most important cancer types in Europe.[2]

The progress against cancer is often focussed on survival of individual cancer patients. The recent paper on trends in survival of cancer across Europe up to 2002 by the EUROCARE group clearly showed that the most marked improvements occurred among patients with colorectal, breast, prostate and thyroid cancer and lymphomas, both Hodgkin's and non-Hodgkin's.[3] Little explicit clarification was given for the observed differences between the countries. These differences may be due to variation in the baseline characteristics of the covered populations, e.g. selective areas in a country or state with large proportions of inhabitants having a high socio-economic status. Other explanations are the potentially selective incompleteness of cases at time of detection or diagnosis and during follow-up.

In the US, survival improvements were also revealed and largely determined by marked improvements in detection, thereby introducing lead time and length bias, together with shifts in classification, subtype, and subsite resulting in pseudo-improvements of survival rates.[4] To circumvent these problems, it is preferred to study simultaneously trends in cancer incidence and survival, also because both affect mortality.[5,6] Survival improvements are more often preceded by rises in incidence than followed by decreases in mortality. **Table 2.1** summarizes possible explanations for changes in incidence, survival, and mortality.

In this article we present the most recent trends in incidence, mortality, and survival over the last decade across Europe of 17 tumour sites, derived from cancer registries and mortality statistics.

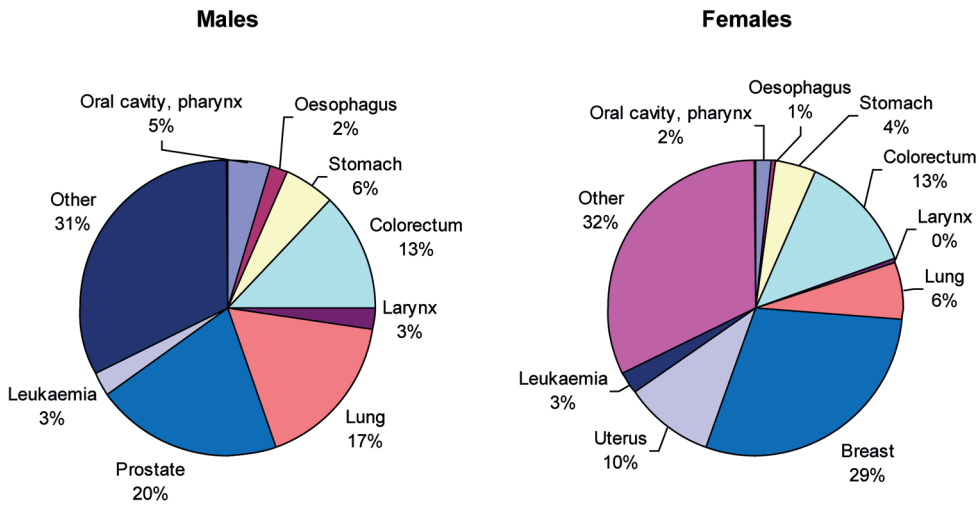


Figure 2.1 | Distribution of new cancer cases in Europe by gender, 2006 (Source: Ferlay et al.[2])

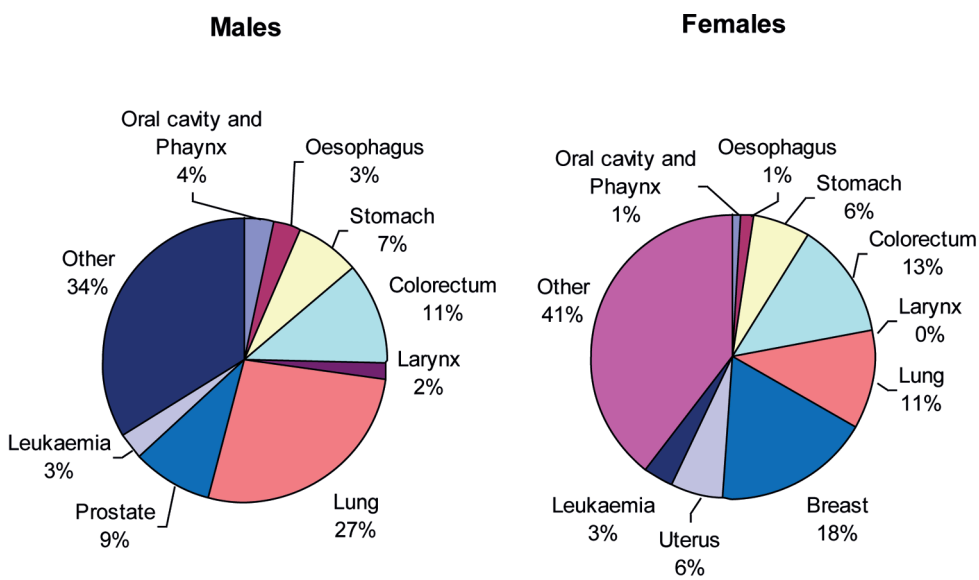


Figure 2.2 | Distribution of cancer deaths in Europe by gender, 2006 (Source: Ferlay et al.[2]).

Table 2.1 | Possible explanations for combined changes in trends in incidence of, survival for and mortality from cancer

Incidence	Survival	Mortality	Plausible explanation(s) for changes
↑	↑	↑	• Higher prevalence of risk factors, earlier diagnosis and/or shifts to unfavourable subsites/-types. If incidence increased faster than survival, mortality rates also increase.
↑	↑	=	• 'Artificial' increases in incidence due to e.g. screening, leading to increased survival rates due to lead time bias, but not resulting in any changes in mortality. • Higher prevalence of risk factors, favourable shifts in stage-distribution and/or subsites/-types and/or improved treatment. The net result is no changes in mortality.
↑	↑	↓	'Artificial' increase in incidence due to e.g. screening, increased survival due to favourable shifts in stage-distribution and/or subsites/-types and effective early treatment, resulting in decreasing mortality after 5-10 years.
↑	=	↑	Higher prevalence of risk factors for aggressive tumours.
↑	↓	↑	Higher prevalence of risk factors, unfavourable shifts in stage-distribution and/or subsites/-types.
=	↑	↓	Improved treatment.
=	=	=	No changes.
=	↓	↑	Worsening case-mix, e.g. when screening manages to detect most if not all slow growing tumours.
↓	↑	↓	Lower risk factor prevalence and/or pre-malignant screening, more favourable case-mix and/or better staging or treatment.
↓	=	↓	Lower risk factor prevalence and/or more restrictive classification and/or pre-malignant screening – without changes in survival will result in decreasing mortality rates.
↓	↓	=	Lower risk factor prevalence and/or more restrictive classification, resulting in worsening survival.
All other combinations of incidence, survival mortality trends			Probably registrion artefacts or problems (e.g. missing cases, incomplete follow-up, coding errors).

METHODS

Data of the following 17 tumour sites (and corresponding ICD-10 code) were collected: oral cavity and pharynx (C00-14), oesophagus (C15), stomach (C16), colorectal (C18-21), pancreas (C25), larynx (C32), lung (C33-34), skin melanoma (C43), female breast (C50), cervix (C53), corpus uteri (C54-55), ovary (C56), prostate (C61), testis (C62), kidney (C64-66/C68), bladder (C67), and Hodgkin's disease (C81). They were derived from 21 European cancer registries, grouped into four regions: Northern Europe (Denmark, Finland, Norway, Sweden, Ireland, and the United Kingdom), Western

Europe (Austria, France, Germany, The Netherlands, and Switzerland), Southern Europe (Croatia, Italy, Malta, Slovenia, and Spain) and Central Europe (Czech Republic, Lithuania, and Poland). The sources of age-standardised (World Standard Population) incidence, mortality and survival for each country and their coverage are summarised in **Table 2.2**.

Five-year relative survival estimates were collected from the EUROCARE-3,[7-9] the EUROCARE-4 study,[3] and from a variety of national or regional cancer registry websites or annual reports. Trends in incidence and mortality between 1994 and 2006 (for details, see **Table 2.2**) were analyzed by calculating the estimated annual percentage change (EAPC) based on the published age-standardised rates per year, using the Joinpoint Regression Program (version 3.0) from the Surveillance Research Program of the US National Cancer Institute (http://srab.cancer.gov/joinpoint). If the EAPC was significantly different from zero it was termed an increasing or decreasing trend. The EAPCs for incidence for Switzerland and Lithuania were based on periods and not on annual rates.

Survival trends were analyzed by calculating the relative difference in 5-year relative survival estimates for patients diagnosed between 1990-1994 and 2000-2002. For cancers of the oral cavity and pharynx, larynx, oesophagus, pancreas, ovary, testis and bladder, survival data were retrieved from literature and individual cancer registries or consortia of cancer registries, because for these tumours data of 2000-2002 were not yet available from EUROCARE.

A survival trend was determined as an increasing or decreasing trend if the 5-year survival rate changed more than one percent-points in cancers with a poor prognosis (5-year relative survival <20%) and more than two percent-points in other cancers.

RESULTS & COMMENTS

Results are presented in the accompanying tables, figures and text. Annual incidence and mortality rates per registry are provided on-line, and can be accessed at:
http://www.eurocadet.org/documents/index.php?map=%2FEurocadet+publications%2FOnline+tables+trends+in+Europe+2008%2F.

Table 2.2 | Data sources of cancer incidence, mortality and 5-year relative survival

	Country	Serving population of cancer registration (in millions)	proportion of national population covered by cancer registration, %	Incidence		Mortality		5-year relative survival[a]	
				period of diagnosis	source	period of death	source	period	source
Northern Europe	Denmark	5.4	100	1994-2003	NORDCAN database[76]	1994-2001	NORDCAN database[76]	-	-
	Finland	5.3	100	1994-2005	NORDCAN database[76]	1994-2005	NORDCAN database[76]	2003-2005	Website Finnish Cancer Registry[77]
	Norway	4.7	100	1994-1995	NORDCAN database[76]	1994-2004	NORDCAN database[76]	1956-2000	Report 'Cancer in Norway 2005'
				1996-2005[1]	Report 'Cancer in Norway 2005'[78]				
	Sweden	9.1	100	1994-2005[2]	Report 'Cancer Incidence in Sweden 2005'[79]	1994-2004	NORDCAN database[76]	-	-
	Ireland	4.3	100	1994-2005	Website National Cancer Registry Ireland[80]	1994-2002[3]	Website National Cancer Registry Ireland [80]	1994-2001	Report 'Patterns of care and survival of cancer patients in Ireland 1994 to 2001'[81]
						2003-2004	Website Central Statistics Office Ireland[82,83]		
	UK England & Wales	53	100	1995-2004[4]	Website National Statistics[84]	1995-1998	WHO mortality database[85]	1971-2001	Website Cancer Research UK[86]
						1999-2005	Website National Statistics[87]		
	UK Northern Ireland	1.7	100	1994-2005	Website Northern Ireland Cancer Registry[88]	1994-2005[5]	Website Northern Ireland Cancer Registry[88]	1993-2004	Report 'Survival of cancer patients in Northern Ireland 1993-2004'[89]
	UK Scotland	5.1	100	1994-2004	Website Scottish Cancer Registry [90]	1994-2006	Website Scottish Cancer Registry [90]	1977-2001	Website Scottish Cancer Registry [90]

Table 2.2 | *Continued*

	Country	Serving population of cancer registration (in millions)	proportion of national population covered by cancer registration, %	Incidence		Mortality		5-year relative survival[a]	
				period of diagnosis	source	period of death	source	period	source
Western Europe	Austria (Tyrol)	0.7	8	1994/5-2003	Website Tyrol Cancer Registry[91]	1994-1997[6]	WHO mortality database[85]	-	-
						1998-2003	Website of the Tyrol Cancer Registry[91]		
	France	8	13	1995-2000[7]	Website of the French Institute for Public Health Surveillance[92]	1995-2002	WHO mortality database[85]	1989-1997	Report 'Survie des patients atteints de cancer en France'[93]
	Germany (Saarland)	1.1	1.3	1994-2005	Website Saarland Cancer Registry[94]	1994-2005	Website Saarland Cancer Registry[94]	2000-2002	Gondos, A et al.[73]
	Netherlands	16	100	1994-2003	Website of the Comprehensive Cancer Centres[95]	1994-2003	Website of the Comprehensive Cancer Centres[95]	1988-2003	Website of the Comprehensive Centre Amsterdam[96]
								1955-2002	Website of the Comprehensive Centre Eindhoven[97]
	Switzerland	7.5	58	1993-2003[8]	Report 'Cancer in Switzerland (volume 1)'[98]	1995-2004[9]	WHO mortality database[85]	-	Website Geneva Cancer Registry[99]
Southern Europe	Croatia	4.4	100	1994-2004	Croatian National Cancer Registry	1994-2004	WHO mortality database[85]	-	-
	Italy (Modena)	0.7	1.2	1994-2005	Website Modena Cancer Registry[100]	1994-2005	Website Modena Cancer Registry[100]	1988-2005	Report 'Cancer in Modena 1988-2005'[101]
								1995-1999	Report 'Italian cancer figures, report 2007: Survival'[102]
	Malta	0.4	100	1994-2005	Website Malta National Cancer Registry[103]	1994-2006[10]	Website Malta National Cancer Registry [103]	-	-

Table 2.2 | *Continued*

	Country	Serving population of cancer registration (in millions)	proportion of national population covered by cancer registration, %	Incidence		Mortality		5-year relative survival[a]	
				period of diagnosis	source	period of death	source	period	source
Southern Europe	Slovenia	2.0	100	1994-1997	EUROCIM version 4.0 [75]	1994-2003	WHO mortality database[85]	1993-2002	Reports 'Cancer incidence in Slovenia 2001-2003'[104-106]
				2001-2003	Reports 'Cancer incidence in Slovenia 2001-2003'[104-106]				
	Spain	3.5	8	1994-1997[11] 2002[12]	EUROCIM version 4.0[75]	1994-2003	WHO mortality database[85]	-	-
Central Europe	Czech Republic	10	100	1994-2004	Website Czech National Oncological Register[107]	1994-2004[13]	Website Czech National Oncological Register[107]	1995-1999	Report 'Cancer Incidence 2004 in the Czech Republic'[108]
	Lithuania	3.4	100	1993-2004	Website Lithuanian Cancer Registry[109]	1993-2004	WHO mortality database [85]	-	-
	Poland	38	100	1994-1997[14]	EUROCIM version 4.0[75]	1994-1996	WHO mortality database [85]	-	-
				1999-2004	Website National Cancer Registry Poland[110]	1999-2005	Website National Cancer Registry Poland[110]		

[a] If available data were used from the EUROCARE-3 [7, 9] and the EUROCARE-4 project [3]; [1] Data of ovarian, kidney, and bladder cancer from NORDCAN database[76]; [2] Data of corpus uteri, kidney, and bladder cancer from NORDCAN database[76]; [3] Data of oral cavity&pharyngeal, laryngeal, oesophageal, ovarian, testicular, and bladder cancer from WHO mortality database[85]; [4] Only available for England; [5] Data of laryngeal cancer from the WHO mortality database[85]; [6] Data of stomach, colorectal, lung, breast, and prostate cancer from the Tyrol cancer registry [111-115]; [7] Data from the FRANCIM network (Bas-Rhin, Calvados, Doubs, Gironde, Haut-Rhin, Hérault, Isère, Loire-Atlantique, Manche, Somme, Tarn, Vendée). For cancers of the digestive tract also the specialised registries of Côte-d'Or, Saône et Loire, Calvados, Finistère and for haematologic tumours also from Côte-d'Or, Gironde and Basse Normandie. The registry of Côte d'Or also provided information on gynaecologic and breast cancers; [8] Used incidence rates are estimates for total Switzerland; [9] Data of testicular, kidney cancer, and Hodgkin's disease from the report 'Cancer in Switzerland (volume 2)' [116]; [10] Data of oral cavity&pharyngeal, oesophageal, and testicular cancer until 2004 from WHO mortality database[85]; [11] Data from Spanish cancer registries of: Albacete, Asturias, Basque Country, Canary Islands, Cantabria, Catalonia (Tarragona), Cuenca, Girona, Granada, Mallorca, Murcia, Navarra, Zaragoz; [12] Data of 2002 from Spanish cancer registries of: Catalonia (Tarragona), Girona and Guipúzcoa; [13] Data of Hodgkin's disease from WHO mortality database[85]; [14] Data from Polish cancer registries of: Lower Silesia (Dolnoslaskie), (Kujawsko-Pomorskie), Lubelskie, Lubuskie, Lodzkie, Malopolskie, Mazowieckie, Opolskie, Podkarpackie, Podlaskie, Pomorskie, Slaskie, Swieto-Krzyskie, Warminsko-Mazurskie, Wielkopolskie, Zachodniopomorskie

Oral cavity and pharyngeal cancer (C00-14)

Within Europe incidence among males in the most recent period varied substantially between 5.9 (Finland) and 32 (France) per 100,000. Mortality rates varied considerably less and were highest in countries where incidence was moderate, e.g. in Croatia and Lithuania. Incidence rates among females were highest in Northern and Western Europe and were consistently lower than those for males. The male-to-female ratio decreased during the last 10 years and recently varied between 1.5 and 2.5 in Northern Europe to 7.7 in Lithuania. During the past decade incidence and mortality rates were stable in most European countries, except for a decrease in incidence in Northern Europe and France, Spain, and Slovenia among males, and an increase in incidence among females in some Northern and Western European countries (**Table 2.3a**). Five-year relative survival rates improved during the past decade in Europe, especially for oro- and nasopharyngeal cancer (**Table 2.3b**, **2.3c**).

As smoking is one of the main risk factors for these tumours, the observed trends in incidence largely reflect changes in smoking rates, which decreased amongst European males and increased among females in many Southern and Central European countries. For cancers of the oral cavity, alcohol consumption, especially in combination with smoking, is also an important risk factor, as are Epstein-Barr virus and Human papillomavirus infections [10].

Oesophageal cancer (C15)

Oesophageal cancer is relatively uncommon in Western societies with varying incidence and mortality patterns during the past decade in Europe. Highest incidence and mortality rates were observed in Ireland and the UK. Rates were low in Southern and Central Europe, especially among females. Increases in incidence and mortality rates were observed among males in Sweden, England, and the Netherlands, and among females in Norway, France and Slovenia. Trends were decreasing in French, German, Slovenian, and Spanish males and in Finnish, Scottish and Croatian females (**Table 2.4a**). Five-year relative survival improved or remained stable varying between 7 (Slovenian males) and 23% (Germany), except for Italian and Slovenian males, where survival decreased (**Table 2.4b**, **2.4c**).

Table 2.3a | Trends in incidence of and mortality from oral cavity and pharyngeal cancer (C00-14) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR End	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark[a]	1994-2003[1]	12.1	12.1	0.4 (-0.8, 1.7)	3.7	5.0	**3.0** (0.7, 5.4)	4.6	4.6	0.8 (-2.0, 3.7)	1.5	1.5	-0.0 (-3.6, 3.7)
	Finland[a]	1994-2005	7.4	5.9	**-1.5** (-2.7, -0.3)	3.4	3.7	0.6 (-1.1, 2.4)	2.1	1.9	0.0 (-2.2, 2.3)	0.9	0.8	-2.2 (-4.5, 0.1)
	Norway[a]	1994-2005[2]	7.8	6.6	**-1.4** (-2.5, -0.3)	3.5	4.1	0.3 (-1.7, 2.4)	3.1	2.4	-2.0 (-4.0, 0.0)	1.0	0.7	-3.0 (-6.8, 0.9)
	Sweden[b]	1994-2005[2]	7.4	6.4	-0.7 (-1.6, 0.2)	3.2	4.1	1.5 (-0.1, 3.1)	2.2	2.3	0.4 (-1.4, 2.3)	0.8	1.0	0.6 (-2.5, 3.8)
	Ireland	1994-2005[2]	10.9	9.0	**-3.1** (-5.2, -0.9)	2.5	3.4	1.2 (-1.2, 3.7)	4.2	3.0	**-3.8** (-5.5, -2.0)	1.3	1.3	-1.5 (-4.3, 1.3)
	UK England & Wales[c]	1995-2004[3]	5.9	7.6	**2.7** (2.0, 3.4)	2.8	3.5	**2.0** (0.8, 2.3)	2.6	2.6	-0.5 (-1.4, 0.4)	1.0	1.0	-0.2 (-1.3, 1.0)
	UK Northern Ireland	1994-2005	10.3	7.4	**-2.9** (-4.8, -0.8)	3.4	3.9	-0.6 (-3.4, 2.4)	2.9	2.3	**-2.6** (-5.5, 0.4)	1.1	1.4	-1.9 (-7.3, 4.0)
	UK Scotland	1994-2004[4]	10.5	11.8	0.6 (-0.4, 1.6)	3.9	4.8	1.3 (-0.7, 3.4)	4.3	3.9	-1.0 (-2.1, 0.2)	1.7	1.5	**-2.2** (-4.3, -0.2)
Western Europe	Austria (Tyrol)	1995-2003	12.6	9.3	-0.4 (-7.9, 7.8)	3.0	4.5	-1.5 (-10.1, 7.9)	6.5	5.8	-3.5 (-13.5, 7.6)	1.0	1.3	5.7 (-3.0, 15.1)
	France	1994-2000[5]	34.7	32.2	**-1.2** (-1.3, -1.2)	4.3	4.7	**1.6** (1.2, 2.0)	11.3	8.8	**-3.6** (-4.5, -2.7)	1.3	1.4	0.5 (-1.1, 2.2)
	Germany (Saarland)	1994-2005	18.3	17.2	-1.0 (-2.2, 0.3)	4.0	4.4	1.2 (-3.1, 5.7)	10.1	8.6	-1.0 (-4.3, 2.4)	1.3	1.7	2.7 (-2.3, 7.8)
	Netherlands	1994-2003	9.4	9.3	-0.3 (-1.6, 1.0)	4.1	4.8	**1.5** (0.4, 2.6)	2.9	3.1	0.6 (-0.6, 1.8)	1.1	1.4	1.9 (-0.4, 4.2)
	Switzerland	1993-2003[6]	14.1	12.9	-1.2 (-7.4, 5.5)	4.4	5.2	2.2 (-2.3, 7.0)	4.9	4.4	**-1.8** (-3.4, -0.1)	1.0	1.0	1.7 (-1.8, 5.3)

Table 2.3a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR End	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	17.7	18.8	-0.1 (-3.8, 3.7)	1.8	3.2	3.8 (-1.7, 9.6)	11.7	10.0	-1.8 (-3.6, 0.2)	1.1	1.0	0.4 (-3.3, 4.2)
	Italy (Modena)	1994-2005	7.7	6.3	-1.0 (-4.4, 2.7)	1.5	2.7	7.8 (-6.5, 24.3)	4.3	1.3	-5.5 (-12.2, 1.7)	1.0	0.6	5.0 (-4.0, 14.8)
	Malta	1994-2005[2]	No data			No data			1.8	3.3	-2.4 (-12.9, 9.3)	1.6	1.3	-6.6 (-19.7, 8.7)
	Slovenia	1994-2003	21.9	16.0	**-3.0** (-4.1, -1.9)	2.1	2.9	4.1 (-0.1, 8.5)	10.9	7.6	**-3.3** (-6.4, -0.1)	1.1	1.2	2.5 (-3.8, 9.3)
	Spain[d]	1994-2002[7]	20.8	12.7	**-6.4** (-8.2, -4.6)	2.2	1.8	-2.7 (-6.0, 0.8)	7.1	5.8	**-2.0** (-2.8, -1.2)	0.9	0.8	-0.7 (-2.2, 0.8)
Central Europe	Czech Republic	1994-2004	11.8	12.3	**0.8** (0.0, 1.5)	2.4	2.8	1.1 (-0.5, 2.6)	7.3	7.4	0.6 (-0.3, 1.5)	0.9	1.1	0.5 (-1.8, 2.8)
	Lithuania	1993-2004[8]	14.1	15.3	1.1 (-2.2, 4.5)	1.8	2.0	3.2 (-22.7, 37.8)	9.2	10.3	**2.3** (0.3, 4.2)	0.9	0.7	-0.4 (-4.0, 3.4)
	Poland	1994-2004[3]	10.2	9.2	-1.1 (-2.2, 0.1)	2.0	2.4	0.9 (-0.6, 2.5)	6.1	5.8	-0.6 (-1.3, 0.2)	1.0	1.1	0.2 (-1.5, 1.9)

[a] Inclusive C46.2; [b] Mortality inclusive C46.2; [c] Incidence only for England; [d] Incidence data valid for C00-06 + C10-14; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.3b | Trends in 5-year relative survival for oral cavity and pharyngeal cancer in Europe[1]

			5-year relative survival			5-year relative survival		
	Country	**Period**	**males**	**females**	**Period**	**males**	**females**	**Trend in survival**
Northern Europe	UK England & Wales[2]	1991-1995	45.0	55.5	1996-1999	47.2	55.4	↑/ =
	UK Northern Ireland	1993-1996	49.3	50.9	2001-2004	53.9	57.1	↑
	UK Scotland[2]	1992-1996	42.4	49.9	1997-2001	47.5	56.1	↑
Western Europe	France[3]	1992-1994	31.0	46.0	1995-1997	32.0	49.0	= / ↑
	Germany (Saarland)	-	-		2000-2002		51.9	?
	Netherlands (Amsterdam)[2]	1993-1996		50.0	2001-2005		61.0	↑
	Netherlands (Amsterdam)[4]	1993-1996		40.0	2001-2005		45.0	↑
	Netherlands (Eindhoven)[2]	1990-1994		55.0	2000-2002		58.0	↑
	Netherlands (Eindhoven)[4]	1990-1994		25.0	2000-2002		37.0	↑
	Switzerland (Geneva)	1990-1994	44.0	53.0	1994-1998	47.0	59.0	↑
Southern Europe	Italy (Modena)[5]	1990-1997	44.0	58.0	1999-2005	56.0	65.0	↑
	Italy[6]	-	-	-	1995-1999	58.0	58.0	?
Total Europe								
oral cavity		1990-1994[7]		44.4	1995-1999[8]		48.5	↑
oropharynx		1990-1994[7]		31.0	1995-1999[8]		39.8	↑
nasopharynx		1990-1994[7]		42.2	1995-1999[8]		50.2	↑
hypopharynx		1990-1994[7]		24.2	1995-1999[8]		25.5	=

[1] Data reported by individual cancer registries or consortia of cancer registries (sources are shown in Table 1); [2] Data valid for oral cavity cancer (C01-06); [3] Data valid for C01-06 + C09-13; [4] Data valid for pharyngeal cancer (C09-14); [5] Data valid for head&neck cancer (C01-14, C30-32); [6] Data valid for head&neck cancer (C01-06, C09-13, C30-32); [7] Data reported by the EUROCARE-3 study [117]; [8] Data reported by the EUROCARE-4 study.

Table 2.3c | Overview of recent trends in incidence of, survival for and mortality from oral cavity and pharyngeal cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	↑	=	UK-England&Wales	France, Netherlands
↑	=	=	-	UK-England&Wales
↑	?	=	Czech Republic	Denmark
=	↑	=	UK-Scotland, Netherlands, Italy	UK-Northern Ireland, Switzerland, Italy
=	↑	↓	Switzerland	UK-Scotland
=	?	↑	Lithuania	
=	?	=	Denmark, Sweden, Austria, Germany, Croatia, Poland	Finland, Norway, Sweden, Ireland, Austria, Germany, Croatia, Slovenia, Spain, Czech Republic, Lithuania, Poland
↓	↑	↓	UK-Northern Ireland	-
↓	=	↓	France	-
↓	?	=	Finland, Norway	-
↓	?	↓	Ireland, Slovenia, Spain	-
?	?	=	Malta	Malta

Table 2.4a | Trends in incidence of and mortality from oesophageal cancer (C15) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	5.6	6.1	1.4 (-0.0, 2.9)	1.7	1.7	1.0 (-1.0, 3.1)	5.9	6.6	**2.0** (0.3, 3.9)	1.6	1.8	2.0 (-2.4, 6.6)
	Finland	1994-2005	3.8	3.4	0.3 (-1.3, 1.9)	1.3	1.1	**-2.6** (-4.7, -0.5)	2.5	2.9	-0.1 (-2.1, 2.0)	0.9	1.0	-2.6 (-5.7, 0.7)
	Norway	1994-2005[2]	2.3	3.5	2.1 (-0.4, 4.6)	1.0	1.2	**2.8** (0.2, 5.5)	2.8	3.5	1.2 (-1.5, 3.8)	0.8	1.1	3.1 (-0.5, 6.9)
	Sweden	1994-2005[2]	3.0	3.9	**1.8** (0.8, 2.9)	1.0	0.9	0.1 (-2.5, 2.8)	2.9	3.5	1.6 (-0.4, 3.6)	0.8	0.9	2.0 (-0.4, 4.4)
	Ireland	1994-2005[2]	7.7	8.1	0.4 (-1.3, 2.1)	4.1	3.5	-0.9 (-2.3, 0.6)	8.6	7.4	-0.8 (-2.3, 0.9)	4.0	3.3	-1.9 (-4.2, 0.5)
	UK England & Wales[a]	1995-2004[3]	8.3	9.2	**1.3** (1.0, 1.6)	3.6	3.4	-0.3 (-1.1, 0.5)	8.3	8.7	**0.6** (0.3, 0.9)	3.3	3.1	-0.5 (-1.0, 0.1)
	UK Northern Ireland	1994-2005	9.5	8.9	-0.9 (-3.6, 2.0)	2.9	2.5	-2.0 (-5.0, 1.1)	8.0	8.2	0.3 (-1.5, 2.1)	3.4	2.6	-1.7 (-3.7, 0.4)
	UK Scotland	1994-2004[4]	11.5	12.1	0.3 (-0.5, 1.1)	5.4	5.1	**-1.8** (-3.3, -0.2)	10.5	10.7	0.1 (-0.5, 0.7)	4.8	3.8	**-1.7** (-3.1, -0.3)
Western Europe	Austria (Tyrol)	1995-2003	3.1	4.7	0.3 (-8.1, 9.5)	0.7	0.6	-1.0 (-14.6, 14.9)	1.9	2.5	0.4 (-10.4, 12.5)	1.0	0.2	-13.9 (-31.2, 7.7)
	France	1994-2000[5]	10.9	9.3	**-2.6** (-2.8, -2.5)	1.3	1.5	**2.6** (1.5, 3.6)	9.7	7.4	**-3.4** (-4.1, -2.6)	1.0	1.1	1.1 (-0.2, 2.4)
	Germany (Saarland)	1994-2005	8.5	5.6	**-2.6** (-4.3, 1.0)	0.9	1.7	2.8 (-1.5, 7.4)	4.8	4.8	-0.7 (-2.8, 1.4)	0.8	2.1	6.9 (-1.8, 16.3)
	Netherlands	1994-2003	6.3	8.0	**3.0** (2.0, 4.0)	2.2	2.5	0.7 (-0.9, 2.3)	6.2	7.5	**1.8** (0.6, 3.0)	2.0	2.1	0.6 (-0.9, 2.1)
	Switzerland	1993-2003[6]	5.5	5.8	0.7 (-7.2, 9.3)	1.5	1.5	-0.0 (-12.6, 14.4)	5.2	4.5	-0.2 (-1.7, 1.3)	1.1	0.8	-1.1 (-4.4, 2.2)

Table 2.4a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	6.0	5.3	**-2.1** (-4.1, -0.1)	1.0	0.6	-5.3 (-10.3, 0.1)	5.1	4.5	-1.2 (-4.0, 1.6)	0.8	0.5	**-5.0** (-7.2, -2.7)
	Italy (Modena)	1994-2005	1.7	0.8	-0.7 (-8.0, 7.1)	0.6	0.5	4.3 (-7.6, 17.6)	2.6	1.6	-1.5 (-7.7, 5.3)	0.6	0.8	-3.0 (-16.0, 12.0)
	Malta	1994-2005[2]	No data			No data			4.5	0.9	**-9.1** (-16.8, -0.7)	1.9	0.4	-9.7 (-21.1, 3.4)
	Slovenia	1994-2003	7.0	5.4	-2.0 (-4.1, 0.2)	0.6	0.9	**5.0** (2.4, 7.7)	7.5	3.9	**-5.0** (-9.0, -0.6)	0.6	0.7	3.2 (-5.2, 12.4)
	Spain	1994-2002[7]	7.5	5.6	-1.5 (-11.3, 9.5)	0.7	0.8	4.1 (-7.8, 17,4)	5.6	4.8	**-2.2** (-2.7, -1.6)	0.5	0.5	1.0 (-0.8, 2.7)
Central Europe	Czech Republic	1994-2004	5.4	5.1	-0.1 (-1.9, 1.8)	0.5	0.8	1.4 (-2.6, 5.6)	4.4	4.3	-0.4 (-1.7, 1.0)	0.3	0.6	3.0 (-1.8, 7.9)
	Lithuania	1993-2004[8]	6.0	6.6	1.1 (-2.0, 4.4)	0.6	0.5	-3.4 (-14.4, 9.0)	6.3	7.0	1.5 (-0.4, 3.3)	0.6	0.4	-1.6 (-6.0, 3.1)
	Poland	1994-2004[3]	4.3	4.3	-0.1 (-0.8, 0.6)	0.8	0.8	-2.2 (-4.4, 0.1)	4.9	4.6	0.2 (-1.1, 0.8)	0.8	0.8	-0.9 (-2.6, 0.9)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality available until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.4b | Trends in 5-year relative survival for oesophageal cancer in Europe[1]

			5-year relative survival			5-year relative survival		
	Country	Period	males	females	Period	males	females	Trend in survival
Northern Europe	Finland	-	-	-	2003-2005	10.0	19.0	?
	Norway	1991-1995	5.4	-	1996-2000	7.3	-	↑
	UK England&Wales	1991-1995	7.0	8.0	2000-2001	8.0	8.0	=
	UK Northern Ireland	1993-1996	5.7	14.4	2001-2004	10.3	17.9	↑
	UK Scotland	1992-1996	7.7	8.4	1997-2001	10.4	9.3	↑/ =
Western Europe	France	1992-1994	10.0	12.0	1995-1997	9.0	13.0	=
	Germany (Saarland)	-	-		2000-2002	22.6		?
	Netherlands (Amsterdam)	1993-1996	13.0		2001-2001	13.0		=
	Netherlands (Eindhoven)[2]	1990-1994	10.0		2000-2002	10.0		=
	Switzerland (Geneva)	1990-1994	13.0	-	1994-1998	13.0	-	=
Southern Europe	Italy (Modena)	1990-1997	3.0	17.0	1998-2005	14.0	8.0	↑ / ↓
	Italy	-	-	-	1995-1999	11.0	14.0	?
	Slovenia	1993-1997	3.0	17.0	1998-2002	7.0	9.0	↑/ ↓
Total Europe		1990-1994[3]	9.0		1995-1999[4]	12.3		↑

[1] Data reported by individual cancer registries or consortia of cancer registries (sources are shown in table 1); [2]3-year relative survival; [3] Data reported by the EUROCARE-3 study [117]; [4]Data reported by the EUROCARE-4 study [9]

Table 2.4c | Overview of recent trends in incidence of, survival for and mortality from oesophageal cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	=	↑	UK-England&Wales, Netherlands	-
↑	=	=	-	France
↑	↓	=	-	Slovenia
↑	?	=	Sweden	Norway
=	↑	=	Norway, UK-Northern Ireland / Scotland, Italy	UK-Northern Ireland, Netherlands
=	↑	↓	Slovenia	-
=	=	=	Switzerland	UK- England&Wales
=	↓	=	-	Italy
=	?	↑	Denmark	-
=	?	=	Finland, Ireland, Austria, Czech Republic, Lithuania, Poland	Denmark, Sweden, Ireland, Austria, Germany, Switzerland, Spain, Czech Republic, Lithuania, Poland
=	?	↓	Spain	Croatia
↓	↑	↓	-	UK-Scotland
↓	=	↓	France	-
↓	?	=	Germany, Croatia	Finland

The diverging trends are probably due to geographical variation in the two major subgroups that constitute oesophageal cancer: adenocarcinoma and squamous cell carcinoma and their risk factors. In the Western world, the incidence of adenocarcinoma was mainly rising, while the incidence of squamous cell carcinomas remained stable [11]. Smoking and alcohol consumption are known to be associated with an increased risk of squamous cell carcinoma, while Barrett's oesophagus, largely related to increasing weight and obesity and resulting reflux, is an important risk factor for adenocarcinoma.[12] Modest improvements in survival seem to have occurred during the last decade, most likely related to the increased incidence of adenocarcinoma and the increasing regionalization of surgery.[13,14] The decreases in survival among Italian and Slovenian males are probably due to increasing completeness of data.

Stomach cancer (C16)

Incidence and mortality rates of stomach cancer varied considerably within Europe, being generally higher in Southern and Central Europe and always twice as high in males compared with females. In most European countries, incidence and mortality rates have been dropping, while 5-year relative survival slowly improved (**Table 2.5a**, **2.5b** and **Figure 2.3**).

A combination of improved methods of fresh food preservation with higher vitamin C content and reduced salting,[15] decreased smoking prevalence and, more importantly, decreasing infection rates of Helicobacter Pylori,[16] has probably resulted in the observed decreases in incidence and, subsequently, mortality. Contrary to the downward trends for non-cardia cancers, incidence rates for cancers of the cardia, initially representing less than 20% of all gastric cancers, have been reported to increase or remain stable.[17,18] Differences in gastric cancer survival are largely related to age, subsite and histological type, with few changes over time[19] regardless of the country. On one hand the shift from the pylorus to the cardia has negative implications for survival because of the worse prognosis of cardia tumours. This may be countered however, by earlier detection due to larger availability of endoscopy, especially when followed by adequate surgery.[20]

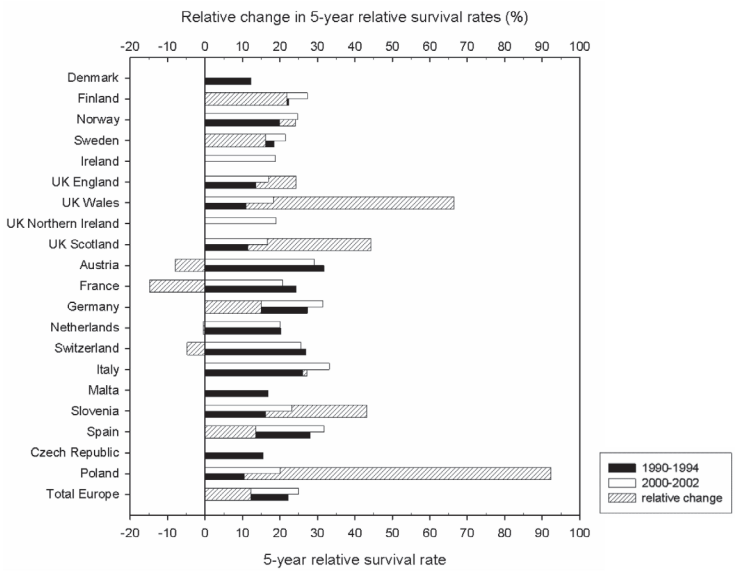


Figure 2.3 | Trends in 5-year age-adjusted relative survival for stomach cancer in Europe (Sources: EUROCARE-3[7] and EUROCARE-4[3])

Table 2.5a | Trends in incidence of and mortality from stomach cancer (C16) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR End	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	8.7	7.1	**-2.3** (-3.4, -1.2)	3.7	3.5	-1.8 (-4.4, 0.9)	6.4	5.2	**-4.1** (-6.7, -1.4)	3.0	2.7	**-3.7** (-7.1, -0.1)
	Finland	1994-2005	13.6	8.3	**-4.3** (-5.3, -3.3)	7.5	4.5	**-4.0** (-4.9, -3.1)	10.8	6.5	**-4.6** (-5.4, -3.7)	4.6	3.7	**-2.9** (-4.4, -1.3)
	Norway	1994-2005[2]	12.0	6.7	**-4.3** (-5.4, -3.3)	6.0	4.2	**-2.9** (-4.3, -1.6)	9.6	5.6	**-4.8** (-6.5, -3.0)	4.7	2.9	**-4.9** (-6.4, -3.4)
	Sweden	1994-2005[2]	9.1	6.2	**-3.1** (-3.8, -2.4)	4.1	2.9	**-2.9** (-4.1, -1.6)	7.0	4.9	**-3.5** (-4.2, -2.7)	3.7	2.7	**-2.6** (-3.7, -1.5)
	Ireland	1994-2005[2]	13.4	10.5	**-2.6** (-3.2, -1.9)	6.0	5.1	**-1.7** (-2.5, -0.9)	10.3	7.0	**-4.5** (-5.5, -3.6)	5.5	2.8	**-4.8** (-6.6, -3.0)
	UK England & Wales[a]	1995-2004[3]	13.0	8.9	**-4.1** (-5.0, -3.2)	5.0	3.7	**-3.4** (-4.1, -2.7)	9.4	5.9	**-4.8** (-5.2, -4.4)	3.9	2.5	**-4.0** (-4.6, -3.4)
	UK Northern Ireland	1994-2005	15.0	8.4	**-4.0** (-6.2, -1.8)	5.7	4.7	**-2.7** (-4.4, -1.1)	11.7	6.3	**-3.9** (-6.0, -1.8)	4.1	3.3	-2.4 (-4.8, 0.1)
	UK Scotland	1994-2004[4]	15.5	11.2	**-3.2** (-4.0, -2.5)	6.9	5.0	**-3.7** (-4.6, -2.7)	10.7	6.8	**-3.3** (-4.0, -2.7)	4.9	3.0	**-4.4** (-6.1, -2.7)
Western Europe	Austria (Tyrol)	1994-2003	22.8	14.4	**-4.5** (-7.2, -1.7)	10.4	7.1	**-3.5** (-5.9, -1.1)	16.1	8.1	**-7.3** (-8.7, -5.9)	8.8	4.9	**-4.9** (-7.9, -1.9)
	France	1994-2000[5]	10.3	9.0	**-2.2** (-2.4, -2.0)	4.0	3.4	**-2.7** (-2.7, -2.6)	7.3	5.9	**-2.7** (-3.1, -2.2)	2.8	2.3	**-2.4** (-2.8, -1.9)
	Germany (Saarland)	1994-2005	15.9	14.1	**-1.8** (-2.6, -1.0)	9.2	6.0	**-3.8** (-5.7, -1.9)	11.2	9.4	**-3.7** (-5.9, -1.6)	6.5	3.7	**-4.7** (-5.8, -3.6)
	Netherlands	1994-2003	13.7	9.7	**-3.8** (-4.3, -3.3)	5.7	4.2	**-2.3** (-3.4, -1.1)	10.8	7.3	**-4.4** (-5.1, -3.6)	4.4	3.2	**-2.8** (-4.2, -1.4)
	Switzerland	1993-2003[6]	10.7	8.5	-3.0 (-12.9, 8.0)	4.9	4.0	-2.6 (-14.5, 10.9)	7.1	4.6	**-4.4** (-5.7, -3.2)	3.1	2.1	**-4.9** (-5.7, -4.0)

Table 2.5a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR End	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	26.0	19.2	**-3.0** (-5.2, -0.9)	10.0	8.1	**-2.6** (-4.3, -0.8)	20.9	16.4	**-2.8** (-4.6, -1.1)	8.3	6.2	**-3.0** (-4.1, -1.8)
	Italy (Modena)	1994-2005	27.8	15.2	**-4.4** (-6.6, -2.2)	12.6	8.2	**-4.0** (-6.8,-1.1)	22.5	8.8	**-5.0** (-8.4, -1.5)	11.2	4.6	**-5.9** (-8.6, -3.2)
	Malta	1994-2005[4]	14.3	10.5	-2.9 (-7.6, 2.2)	5.6	4.2	-2.4 (-5.7, 0.9)	10.3	6.7	**-5.1** (-7.7, -2.3)	5.8	3.4	-1.4 (-5.8, 3.2)
	Slovenia	1994-2003	24.9	19.1	**-2.9** (-4.1, -1.8)	10.6	8.1	**-3.6** (-4.9, -2.3)	21.2	12.9	**-4.2** (-6.2, -2.3)	7.8	5.6	**-4.7** (-6.8, -2.5)
	Spain	1994-2002[7]	17.0	12.5	-3.1 (-6.4, 0.4)	6.8	6.5	0.3 (-4.7, 5.4)	13.2	9.2	**-3.7** (-4.1, -3.3)	5.8	4.2	**-3.8** (-4.5, -3.1)
Central Europe	Czech Republic	1994-2004	17.8	12.1	**-3.9** (-4.6, -3.2)	9.3	6.2	**-3.9** (-4.6, -3.2)	15.2	9.5	**-4.8** (-5.5, -4.1)	7.1	4.6	**-4.5** (-5.1, -3.8)
	Lithuania	1993-2004[8]	29.7	24.7	**-2.1** (-3.3, -0.9)	12.6	10.6	-1.4 (-11.4, 9.7)	28.5	21.1	**-3.0** (-3.7, -2.3)	12.1	8.0	**-2.5** (-3.6, -1.4)
	Poland	1994-2004[3]	23.1	13.8	**-5.8** (-7.0, -4.5)	8.0	5.0	**-5.4** (-6.7, -4.2)	19.7	13.6	**-3.2** (-3.5, -2.9)	7.0	4.9	**-3.2** (-3.6, -2.8)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004;
* EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.5b | Overview of recent trends in incidence of, survival for and mortality from stomach cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
=	↑	↓	Spain	Spain
=	=	↓	Switzerland	Switzerland
=	?	=	-	Malta
=	?	↓	Malta	Denmark, Lithuania
↓	↑	=	-	UK-Northern Ireland[1]
↓	↑	↓	Finland, Norway, Sweden, UK[1], Germany, Italy, Slovenia, Poland	Finland, Norway, Sweden, UK-England&Wales / Scotland, Germany, Italy, Slovenia, Poland
↓	=	↓	Netherlands	Netherlands
↓	↓	↓	Austria, France	Austria, France
↓	?	↓	Denmark, Ireland, Croatia, Czech Republic, Lithuania	Ireland, Croatia, Czech Republic

[1] Survival trends of UK-Northern Ireland are based on a report of the North-Ireland Cancer Registry[89]

Colorectal cancer (C18-21)

Incidence of colorectal cancer among males increased modestly in most countries and markedly in Austria, Croatia, Slovenia, Spain, and the Czech Republic. Among females, the incidence rates were stable with some decreases in Scotland, Northern Ireland, and Poland, contrasting a clear increase in Spain. The male to female ratio remained stable at 1.5. Mortality rates decreased across Europe but remained very high in Denmark, Norway, and Ireland in comparison with other Northern and Western European countries (**Table 2.6a**). Five-year relative survival increased, especially in Poland, Slovenia, and the Czech Republic (**Figure 2.4**, **Table 2.6b**).

The increasing incidence rates may be due to a relatively late, but rapid transition towards a life style being increasingly rich in sugar, red and processed meat, poor in fiber consumption and physical activity, resulting in increasing body mass index [21-23]. Improvement of survival, especially in younger patients, is probably due to positive changes in detection and treatment of colorectal cancer since the mid 1990s. This includes a widespread availability of endoscopy, either or not as part of screening activities, Total Mesorectal Excision (TME) surgery for rectal cancer, and more widespread use of (pre-operative) radiotherapy.[24-26] The high mortality rate in some Northern European countries is possibly caused by deficient access to endoscopic care, and less effective patient management.[27]

Table 2.6a | Trends in incidence of and mortality from colorectal cancer (C18-21) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	38.6	40.4	**1.0** (0.4, 1.7)	29.3	29.4	0.2 (-0.7, 1.1)	23.8	21.0	**-1.8** (-2.8, -0.8)	15.5	15.2	-0.0 (-1.7, 1.7)
	Finland	1994-2005	25.3	27.8	0.6 (-0.0, 1.2)	19.1	20.4	0.5 (-0.1, 1.1)	13.0	10.7	**-1.1** (-1.9, -0.2)	8.1	7.5	**-1.1** (-2.2, -0.1)
	Norway	1994-2005[2]	39.1	42.8	**1.0** (0.5, 1.5)	33.7	33.7	0.4 (-0.0, 0.7)	19.8	18.4	**-0.8** (-1.4, -0.2)	13.9	12.4	-1.0 (-2.2, 0.2)
	Sweden	1994-2005[2]	31.0	31.2	**0.5** (0.1, 0.9)	24.5	26.9	**0.8** (0.2, 1.3)	13.3	12.6	-0.4 (-1.0, 0.3)	10.1	9.6	**-0.7** (-1.3, -0.2)
	Ireland	1994-2005[2]	44.2	44.3	-0.0 (-0.5, 0.5)	27.5	27.5	0.2 (-0.6, 0.9)	22.0	19.6	**-1.7** (-2.9, -0.6)	13.2	10.3	**-2.3** (-3.9, -0.7)
	UK England & Wales[a]	1995-2004[3]	34.8	35.6	-0.2 (-0.8, 0.4)	22.8	23.0	-0.5 (-1.3, 0.3)	18.1	14.6	**-2.1** (-2.3, -1.8)	11.5	9.2	**-2.3** (-2.7, -1.9)
	UK Northern Ireland	1994-2005	44.1	42.9	-0.4 (-1.6, 0.8)	28.6	23.5	**-1.6** (-2.5, -0.7)	19.7	16.0	-1.2 (-3.0, 0.6)	13.3	10.4	**-2.3** (-4.0, -0.5)
	UK Scotland[b]	1994-2004[4]	41.4	42.0	0.0 (-0.8, 0.8)	28.7	25.8	**-0.9** (-1.8, -0.1)	21.5	17.2	**-1.7** (-2.1, -1.3)	13.6	10.0	**-2.7** (-3.4, -2.0)
Western Europe	Austria (Tyrol)	1994-2003	38.8	45.0	**2.3** (0.0, 4.7)	23.9	26.1	1.1 (-0.3, 2.6)	18.6	16.5	-1.0 (-7.3, 5.7)	8.4	8.5	-1.3 (-4.0, 1.5)
	France	1994-2000[5]	37.6	39.1	**0.7** (0.6, 0.7)	24.0	24.6	**0.4** (0.3, 0.5)	16.5	15.6	**-0.6** (-1.3, -0.0)	9.7	8.8	**-1.0** (-1.7, -0.2)
	Germany (Saarland)	1994-2005	53.6	51.0	0.4 (-0.4, 1.1)	34.2	31.9	-0.1 (-0.9, 0.8)	23.1	18.7	**-2.3** (-2.8, -1.9)	16.3	10.2	**-3.1** (-4.8, -1.4)
	Netherlands	1994-2003	37.2	40.6	**0.9** (0.5, 1.3)	27.7	29.4	**0.8** (0.3, 1.3)	17.7	16.9	**-0.7** (-1.3, -0.0)	12.5	11.7	**-1.1** (-1.7, -0.5)
	Switzerland	1993-2003[6]	35.4	36.3	0.3 (-1.7, 2.4)	22.9	23.6	0.4 (-0.7, 1.5)	15.7	12.6	**-2.4** (-3.2, -1.5)	9.2	7.4	**-1.6** (-2.6, -0.6)

Table 2.6a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	32.2	44.0	**2.6** (0.1, 5.2)	19.1	22.2	2.4 (-0.3, 5.2)	19.6	24.0	2.0 (-0.4, 4.4)	11.3	11.5	0.6 (-1.3, 2.5)
	Italy (Modena)	1994-2005	46.3	47.2	1.0 (-0.2, 2.3)	31.0	29.9	1.2 (-1.1, 3.5)	23.2	15.7	**-1.9** (-3.8, -0.0)	8.9	8.1	-1.2 (-4.4, 2.1)
	Malta[b]	1994-2005[4]	35.7	32.5	0.9 (-1.5, 3.4)	23.8	18.6	-0.9 (-3.6, 1.9)	23.1	15.2	**-3.1** (-5.1, -0.9)	11.8	12.1	-0.1 (-2.0, 1.9)
	Slovenia	1994-2003	37.7	45.2	**2.6** (1.9, 3.4)	22.5	25.1	1.0 (-0.0, 2.1)	21.5	25.3	0.5 (-1.1, 2.1)	13.2	13.0	**-2.1** (-3.9, -0.3)
	Spain	1994-2002[7]	34.3	46.3	**4.4** (0.1, 9.0)	20.5	27.3	**3.5** (0.5, 6.5)	16.1	17.6	**0.9** (0.6, 1.3)	10.3	9.4	**-1.0** (-1.4, -0.6)
Central Europe	Czech Republic	1994-2004	53.4	58.4	**1.1** (0.4, 1.8)	28.5	29.9	0.3 (-0.3, 0.9)	34.4	30.7	**-0.8** (-1.6, -0.0)	16.5	14.8	**-1.1** (-1.7, -0.4)
	Lithuania	1993-2004[8]	25.6	29.2	1.9 (-2.2, 6.2)	16.8	20.0	2.7 (-12.6, 20.7)	17.1	18.6	0.5 (-0.2, 1.2)	11.7	10.4	**-1.2** (-2.2, -0.3)
	Poland	1994-2004[3]	26.7	27.8	-0.2 (-1.6, 1.3)	17.9	16.8	**-1.1** (-2.2, -0.0)	16.0	18.8	**1.6** (1.3, 2.0)	10.8	10.8	0.2 (-0.7, 1.0)

[a] Incidence only for England; [b] Data valid for C18-20; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

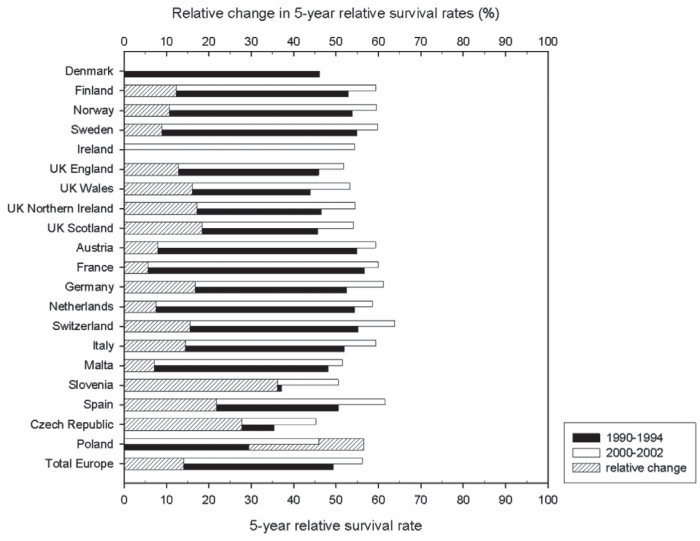


Figure 2.4 | Trends in 5-year age-adjusted relative survival for colorectal cancer in Europe (Sources: EUROCARE-3[9] and EUROCARE-4[3])

Table 2.6b | Overview of recent trends in incidence of, survival for and mortality from colorectal cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	↑	↑	Spain	-
↑	↑	=	Austria, Slovenia	-
↑	↑	↓	Norway, France, Netherlands, Czech Republic	France, Netherlands, Spain
↑	?	=	Croatia	
↑	?	↓	Denmark	-
=	↑	↑	Poland	-
=	↑	=	UK-Northern Ireland	Norway, Austria, Italy, Malta
=	↑	↓	Finland, Ireland[1], UK-England&Wales / Scotland, Germany, Switzerland, Italy, Malta	Finland, Ireland[1], UK-England&Wales, Germany, Switzerland, Slovenia, Czech Republic
=	?	=	Lithuania	Denmark, Croatia
=	?	↓	-	Lithuania
↓	↑	=	-	Poland
↓	↑	↓	-	UK-Northern Ireland / Scotland

[1] Survival trends are based on a report of the Ireland Cancer Registry[81]

Pancreatic cancer (C25)

Incidence and mortality rates of pancreatic cancer were similar across Europe and quite stable over time. However, in Denmark and France, incidence and mortality increased, and they decreased in Sweden and Poland (**Table 2.7a**). Rates were higher among males than females (male-to-female ratio 1.5). Five-year relative survival remained very low varying between 2 and 8% (**Table 2.7b**, **2.7c**).

Pancreatic mortality rates have increased throughout Europe between the late 1950s and the 1980s among males, and the 1990s among females followed by a leveling off which is confirmed by our data.[28] This leveling off is partly due to the decline in smoking which is the main risk factor for pancreatic cancer.[15,29,30] Factors related to obesity, such as type 2 diabetes and high blood glucose levels[31] also seem to be important risk indicators, as well as occupational exposures to pesticides or dyes.[32,33] Previously postulated associations with coffee and alcohol consumption were not confirmed.[34] No major improvements in treatment have occurred, causing the survival rates to remain stable. Centralisation of surgery may contribute to future improvement in survival of pancreatic cancer.

Table 2.7c | Overview of recent trends in incidence of, survival for and mortality from pancreatic cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	Females
↑	↑	↑	France	-
↑	=	↑	-	France
↑	?	=	Denmark	Denmark
=	=	=	Norway, UK, Netherlands, Italy	Norway, UK, Netherlands
=	=	↓	-	Italy
=	?	↑	Spain	Austria
=	?	=	Finland, Austria, Germany, Switzerland, Croatia, Malta, Slovenia, Czech Republic, Lithuania	Finland, Ireland, Germany, Switzerland, Croatia, Malta, Slovenia, Spain, Czech Republic, Lithuania
=	?	↓	Ireland	-
↓	?	=	Sweden, Poland	Sweden, Poland

Table 2.7a | Trends in incidence of and mortality from pancreatic cancer (C25) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR Start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	7.2	8.3	**2.0** (0.9, 3.2)	6.0	6.6	**1.9** (0.2, 3.6)	8.0	7.1	0.3 (-2.7, 3.4)	6.2	6.8	1.5 (-0.7, 3.8)
	Finland	1994-2005	8.9	8.7	0.1 (-1.0, 1.2)	6.3	6.9	0.7 (-0.4, 1.9)	8.4	8.5	0.3 (-0.8, 1.4)	6.3	6.2	1.0 (-0.6, 2.6)
	Norway	1994-2005[2]	7.7	7.0	-0.1 (-1.0, 0.8)	6.1	5.2	-0.3 (-1.5, 0.9)	7.6	7.4	0.1 (-1.2, 1.4)	5.6	5.9	0.2 (-1.0, 1.6)
	Sweden	1994-2005[2]	6.7	5.0	**-2.2** (-3.4, -0.9)	5.4	4.4	**-1.3** (-2.4, -0.3)	7.5	7.1	-0.4 (-1.3, 0.4)	6.7	6.6	-0.2 (-1.0, 0.6)
	Ireland	1994-2005[2]	6.9	6.6	-0.0 (-1.3, 1.2)	5.4	5.5	-0.4 (-2.0, 1.3)	8.5	6.6	**-1.5** (-2.8, -0.1)	4.9	5.0	0.3 (-1.2, 1.8)
	UK England & Wales[a]	1995-2004[3]	6.8	6.7	-0.2 (-0.6, 0.3)	5.0	5.2	0.3 (-0.7, 1.4)	6.4	6.3	-0.2 (-0.6, 0.2)	4.8	5.1	0.6 (-0.1, 1.2)
	UK Northern Ireland	1994-2005	5.7	7.3	0.5 (-2.8, 4.0)	5.0	3.8	0.3 (-2.8, 3.4)	6.2	6.6	-0.4 (-2.7, 2.1)	5.0	4.4	0.4 (-2.0, 2.8)
	UK Scotland	1994-2004[4]	6.9	6.3	-1.0 (-2.5, 0.6)	5.3	4.9	-0.1 (-1.6, 1.4)	6.1	5.8	-0.3 (-1.3, 0.7)	4.8	4.6	0.2 (-0.9, 1.3)
Western Europe	Austria (Tyrol)	1995-2003	7.3	5.9	0.1 (-6.5, 7.3)	4.5	4.6	1.7 (-5.6, 9.6)	10.0	6.9	-2.2 (-6.8, 2.6)	4.0	5.8	**6.8** (2.5, 11.2)
	France	1994-2000[5]	5.4	5.8	**1.2** (0.9, 1.4)	2.9	3.2	**1.9** (1.4, 2.4)	7.4	7.6	**0.7** (0.1, 1.3)	3.9	4.5	**1.8** (1.1, 2.4)
	Germany (Saarland)	1994-2005	7.5	7.1	2.6 (-0.3, 5.6)	4.7	6.0	1.6 (-1.2, 4.4)	9.1	8.0	1.0 (-1.1, 3.1)	5.7	5.2	0.1 (-2.5, 2.7)
	Netherlands	1994-2003	6.3	5.3	-1.0 (-2.6, 0.6)	4.6	4.3	-1.0 (-2.3, 0.4)	7.3	6.8	-0.5 (-1.5, 0.5)	5.2	5.4	0.3 (-0.6, 1.2)
	Switzerland	1993-2003[6]	7.4	7.6	0.3 (-5.0, 6.0)	5.0	4.7	-0.8 (-3.3, 1.7)	7.0	6.7	-0.1 (-0.7, 0.5)	5.2	4.6	-0.5 (-1.9, 1.0)

Table 2.7a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR Start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	8.3	9.1	0.5 (-1.5, 2.5)	3.7	4.9	1.3 (-1.4, 4.2)	7.7	7.3	0.7 (-1.9, 3.3)	3.5	4.8	1.4 (-1.3, 4.2)
	Italy (Modena)	1994-2005	9.8	8.0	1.5 (-2.0, 5.0)	7.8	6.4	-0.8 (-4.6, 3.2)	10.3	8.5	-1.1 (-4.0, 2.0)	5.9	4.6	**-1.5** (-2.7, -0.2)
	Malta	1994-2005[4]	9.9	5.7	-1.5 (-5.6, 2.8)	3.7	3.4	1.9 (-4.0, 8.2)	10.4	6.9	-3.1 (-6.3, 0.2)	4.2	5.1	0.6 (-2.0, 3.3)
	Slovenia	1994-2003	8.4	8.5	1.2 (-2.2, 4.6)	4.1	4.7	1.9 (-1.6, 5.6)	7.6	8.2	1.1 (-0.2, 2.4)	4.1	4.9	1.5 (-2.0, 5.2)
	Spain	1994-2002[7]	6.6	7.1	2.1 (-5.2, 10.0)	4.0	4.4	2.0 (-2.3, 6.3)	6.0	6.6	**1.3** (0.7, 1.9)	3.7	3.7	0.8 (-0.2, 1.9)
Central Europe	Czech Republic	1994-2004	11.1	10.7	-0.0 (-1.0, 0.9)	7.0	6.8	0.3 (-0.6, 1.2)	10.5	9.4	-0.7 (-1.6, 0.2)	6.3	6.1	-0.2 (-0.8, 0.5)
	Lithuania	1993-2004[8]	11.2	9.4	-1.4 (-7.4, 5.1)	5.0	4.5	-0.2 (-10.2, 10.9)	9.9	9.9	-0.6 (-1.5, 0.4)	4.7	4.4	-0.6 (-2.2, 1.0)
	Poland	1994-2004[3]	8.8	6.4	**-3.9** (-5.4, -2.4)	6.4	4.1	**-4.2** (-6.4, -1.8)	8.1	8.2	-0.1 (-0.6, 0.4)	5.0	4.9	0.0 (-0.4, 0.5)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004;
* EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.7b | Trends in 5-year relative survival for pancreatic cancer in Europe by gender

			5-year relative survival			5-year relative survival		
	Country	Period	males	females	Period	males	females	Trend in survival
Northern Europe	Finland	-	-	-	2003-2005	4.0	2.0	?
	Norway	1991-1995	2.5	3.2	1996-2000	3.4	3.2	=
	UK England&Wales	1991-1995	2.0	2.0	2000-2001	2.0	2.0	=
	UK Northern Ireland	1993-1996	2.9		1997-2000	2.5		=
	UK Scotland	1992-1996	2.9	2.6	1997-2001	2.8	3.3	=
Western Europe	France	1992-1994	3.0	7.0	1995-1997	8.0	6.0	↑ / =
	Germany (Saarland)	-		-	2000-2002		5.3	?
	Netherlands (Amsterdam)	1996-1999		3.0	2000-2003		3.0	=
	Netherlands (Eindhoven)[2]	1990-1994		7.0	2000-2002		3.0	↓
Southern Europe	Italy (Modena)	1990-1997	3.0	3.0	1998-2005	3.0	4.0	=
	Italy	-	-	-	1995-1995	5.0	6.0	?
	Slovenia	-	-	-	1998-2002	5.0	5.0	?
Central Europe	Czech Republic	-	-	-	1995-1999	4.3	-	?
Total Europe		1990-1994[3]		4.2	1995-1999[4]		5.5	↑

[1] Data reported by individual cancer registries or consortia of cancer registries (sources are shown in table 1); [2] 3-year relative survival; [3] Data reported by the EUROCARE-3 study [117]; [4] Data reported by the EUROCARE-4 study [9]

Laryngeal cancer (C32)

Incidence and mortality rates of cancer of the larynx varied considerably throughout Europe, especially among males. Lowest rates were observed in the Scandinavian countries, except in Denmark, and highest rates in Southern and Central Europe (**Table 2.8a**). This cancer was 4 (Scotland) to 49 (Spain) times more common among males than females. In all European regions, both incidence and mortality rates declined over the past decade, especially among males, for incidence more markedly in Northern Europe, and mortality in Southern Europe. However, in most countries, 5-year relative survival did not show marked improvements, except for Northern Irish, Scottish and Swiss males (**Table 2.8b**, **2.8c**).

The most important environmental risk factors are smoking and alcohol consumption.[35,36] The relative risks of smokers seem to be higher for supraglottic than glottic cancer, which is in accordance with the anatomical location of supraglottic tissue, being more readily exposed to tobacco smoke than the other laryngeal subsites. The decreasing smoking prevalences among (mainly) European males will therefore have contributed strongly to the decreases in incidence and mortality. Heavy alcohol use is also related to laryngeal cancer, and marked dose-response curves have been observed.[37] More importantly, there is a strong interaction between the effects of smoking and alcohol consumption and their combined effect may result in very high relative risks.

Table 2.8a | Trends in incidence of and mortality from laryngeal cancer (C32) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	5.8	4.4	**-3.4** (-5.6, -1.1)	1.1	0.7	-3.7 (-7.0, 0.0)	2.2	1.6	**-3.5** (-8.3, -1.7)	0.5	0.4	-2.4 (-12.1, 8.3)
	Finland	1994-2005	3.4	2.1	**-3.7** (-5.0, -2.4)	0.2	0.2	-2.7 (-7.4, 2.2)	0.9	0.7	-2.6 (-6.3, 1.2)	0.1	0.1	33.9 (-39.5, 196.8)
	Norway	1994-2005[2]	3.2	2.5	**-2.3** (-4.3, -0.3)	0.9	0.5	-4.1 (-8.5, 0.5)	0.8	0.9	-0.5 (-3.3, 2.4)	0.2	0.1	-6.0 (-13.0, 1.6)
	Sweden	1994-2005[2]	2.3	2.1	-0.9 (-2.7, 0.9)	0.2	0.3	**4.7** (0.4, 9.3)	0.8	0.6	-1.7 (-5.4, 2.1)	0.1	0.1	-19.7 (-56.9, 49.6)
	Ireland	1994-2005[2]	4.4	4.8	0.7 (-1.4, 2.8)	0.9	0.8	-1.8 (-6.6, 3.2)	1.9	1.4	-0.7 (-4.8, 3.6)	0.7	0.2	-7.1 (-15.6, 2.3)
	UK England & Wales[a]	1995-2004[3]	4.0	3.5	**-1.8** (-2.8, -0.7)	0.8	0.6	**-2.0** (-3.5, -0.5)	1.5	1.1	**-2.9** (-3.7, -2.0)	0.3	0.2	**-5.0** (-7.7, -2.3)
	UK Northern Ireland	1994-2005[5]	No data			No data			1.8	1.8	-0.3 (-4.8, 4.3)	0.5	0.3	6.5 (-18.0, 38.2)
	UK Scotland	1994-2004[4]	6.6	5.9	-0.8 (-2.7, 1.1)	1.4	1.4	-1.1 (-4.3, 2.2)	2.0	1.6	-2.0 (-4.4, 0.5)	0.6	0.4	-1.4 (-3.9, 1.1)
Western Europe	Austria (Tyrol)	1995-2003	5.0	4.4	-1.2 (-6.5, 4.3)	0.5	0.4	-3.8 (-28.9, 30.2)	3.2	2.3	**-3.7** (-6.4, -1.0)	0.3	0.2	-44.1 (-83.1, 85.6)
	France	1994-2000[5]	10.6	9.3	**-2.1** (-2.2, -2.0)	0.7	0.7	0.0 (-, -)	5.7	3.2	**-6.7** (-8.2, -5.2)	0.3	0.2	**-4.6** (-8.4, -0.7)
	Germany (Saarland)	1994-2005	8.2	6.2	-0.5 (-3.4, 2.6)	0.7	0.9	-0.3 (-3.9, 3.4)	4.1	3.4	-3.5 (-8.0, 1.2)	0.3	0.3	-5.5 (-15.2, 5.4)
	Netherlands	1994-2003	6.0	4.6	**-3.2** (-3.8, -2.7)	0.9	0.8	-2.3 (-4.8, 0.2)	1.9	1.6	-1.8 (-4.2, 0.6)	0.3	0.3	3.3 (-3.3, 10.2)
	Switzerland	1993-2003[6]	4.8	4.5	-0.8 (-10.9, 10.4)	0.5	0.8	6.4 (-6.9, 21.6)	1.7	1.5	-1.3 (-3.8, 1.3)	0.2	0.2	4.7 (-4.4, 14.7)

Table 2.8a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	12.2	9.5	-1.7 (-4.4, 1.1)	0.7	0.7	-0.6 (-5.7, 4.9)	8.1	6.2	-3.0 (-6.5, 0.7)	0.4	0.4	-0.6 (-7.3, 6.5)
	Italy (Modena)	1994-2005	9.4	7.3	-2.4 (-5.2, 0.6)	1.4	0.2	-5.2 (-17.2, 8.5)	3.4	1.7	**-5.8** (-10.8, -0.5)	0.5	0.1	-16.8 (-64.9, 97.4)
	Malta	1994-2005[4]	6.7	4.3	-3.1 (-6.4, 0.5)	0.0	0.0	3.9 (-55.4, 142.0)	3.3	3.9	-4.7 (-12.3, 3.5)	0.0	0.0	-36.8 (-74.0, -53.5)
	Slovenia	1994-2003	8.3	6.5	-1.2 (-3.9, 1.7)	0.7	0.4	0.4 (-9.9, 11.9)	5.1	3.1	**-5.4** (-8.1, -2.5)	0.3	0.2	-0.5 (-11.7, 12.1)
	Spain	1994-2002[7]	15.9	9.9	**-5.1** (-8.6, -1.4)	0.3	0.2	-5.8 (-22.3, 14.1)	6.4	4.7	**-3.4** (-4.2, -2.6)	0.1	0.2	**7.4** (0.3, 15.1)
Central Europe	Czech Republic	1994-2004	7.5	6.8	**-1.3** (-2.6, -0.0)	0.4	0.5	-0.1 (-3.9, 3.9)	4.6	3.3	**-3.0** (-4.0, -2.0)	0.2	0.1	-1.0 (-8.6, 7.3)
	Lithuania	1993-2004[8]	9.9	9.0	-1.4 (-4.1, 1.3)	0.4	0.2	-5.0 (-29.1, 27.3)	7.7	5.6	**-4.1** (-5.6, -2.5)	0.3	0.2	-3.6 (-9.7, 3.1)
	Poland	1994-2004[3]	12.1	8.8	**-3.7** (-4.6, -2.8)	1.4	1.0	-1.7 (-4.6, 1.2)	7.5	6.1	**-2.2** (-2.7, -1.6)	0.6	0.5	0.4 (-2.4, 3.3)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004;
* EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.8b | Trends in 5-year relative survival for laryngeal cancer in Europe[1]

			5-year relative survival			5-year relative survival		
	Country	Period	males	females	Period	males	females	Trend in survival
Northern Europe	Finland[2]	-	-	-	2003-2005	58.0	60.0	?
	UK England&Wales	1991-1995	62.0	-	2000-2001	65.0	-	↑
	UK Northern Ireland	1993-1996	62.0	59.9	2001-2004	76.6	56.6	↑ / ↓
	UK Scotland	1992-1996	60.4	56.3	1997-2001	64.3	54.1	↑ / ↓
Western Europe	France	1992-1994	52.0		1995-1997	53.0		=
	Germany (Saarland)	-	-		-	61.3		?
	Netherlands (Amsterdam)	1993-1996	74.0		2001-2004	81.0		↑
	Netherlands (Eindhoven)[3]	1990-1994	85.0		2000-2002	86.0		=
	Netherlands (Eindhoven)[4]	1990-1994	44.0		2000-2002	44.0		=
	Switzerland (Geneva)	1990-1994	66.0	56.0	1994-1998	74.0	57.0	↑ / =
Southern Europe	Italy	-	-	-	1995-1999	71.0	73.0	?
	Slovenia	1993-1997	60.0	65.0	1998-2002	60.0	64.0	=
Northern Europe	Czech Republic	-	-	-	1995-1999	49.9	-	?
Total Europe		1990-1994[5]	60.6		1995-1999[6]	63.1		↑

[1] Data reported by individual cancer registries or consortia of cancer registries (sources are shown in Table 1); [2] Data valid for epiglottis; [3] Data valid for glottis; [4] Data valid for supraglottis; [5] Data reported by the EUROCARE-3 study [117]; [6] Data reported by the EUROCARE-4 study [9]

Table 2.8c | Overview of recent trends in incidence of, survival for and mortality from laryngeal cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	?	=	-	Sweden
=	↑	=	UK-Scotland, Switzerland	-
=	=	=	-	Netherlands, Switzerland, Slovenia
=	=	↓	Slovenia	France
=	↓	=	-	UK-Scotland
=	?	↑	-	Spain
=	?	=	Sweden, Ireland, Germany, Croatia, Malta	Denmark, Finland, Norway, Ireland, Austria, Germany, Croatia, Italy, Malta, Czech Republic, Lithuania, Poland
=	?	↓	Austria, Italy, Lithuania	-
↓	↑	↓	UK-England&Wales	-
↓	↑	=	Netherlands	-
↓	=	↓	France	-
↓	?	=	Finland, Norway	-
↓	?	↓	Denmark, Spain, Czech Republic, Poland	UK-England&Wales
?	↑	=	UK-Northern Ireland	-
?	↓	=	-	UK-Northern Ireland

Lung cancer (C33-34)

In most European countries incidence and mortality rates decreased among males in the last decade, except in Norway, Sweden, Austria (Tyrol), Switzerland, Croatia, Spain, and Lithuania where the rates remained stable. The variation in recent incidence among males was about 3-fold, with highest rates in Poland (63 per 100,000) and lowest in Sweden (22 per 100,000). In contrast to males, incidence and mortality rates have increased rapidly among females, except in Denmark and the UK (where rates were already very high), Austria, Croatia, Malta, Spain, and Lithuania. Recent incidence rates varied 7-fold, with lowest rates in Spain and Lithuania (5 and 6 per 100,000) and highest rates in Scotland and Denmark (37 and 33 per 100,000). The male-to-female ratio decreased and varied from 1.3 to 1.8 in Northern Europe (except in Finland with 3.5) to 10 in Spain in the most recent period (**Table 2.9a**). Five-year relative survival of lung cancer slightly improved over time from 9 to 11% in Europe with a marked relative increase of 107% in Poland (**Figure 2.5**, **Table 2.9b**).

Geographical variations in lung cancer risk are influenced by past exposure to tobacco smoking. There are however indications that rates are starting to decline among younger females in some countries, which will translate into declining incidence and mortality rates in females in the near future.[38]

Improvement in survival such as in Poland is likely caused by better access to care and treatment if there were no changes in data completeness.

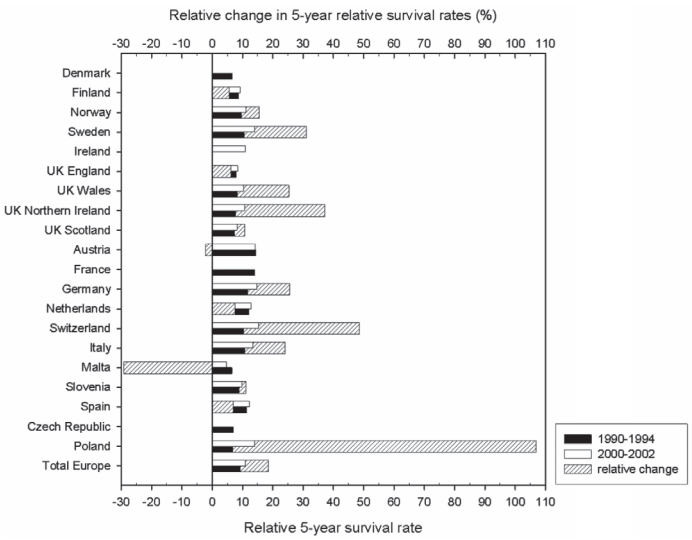


Figure 2.5 | Trends in 5-year age-adjusted relative survival for lung cancer in Europe (Sources: EUROCARE-3[9] and EUROCARE-4[3])

Table 2.9a | Trends in incidence of and mortality from lung cancer (C33-34) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	50.5	44.1	**-1.0** (-1.7, -0.4)	31.3	32.6	1.1 (0.4, 1.8)	49.1	42.3	**-2.4** (-3,3, -1,4)	28.2	27.9	-0.3 (-1.2, 0.7)
	Finland	1994-2005	48.1	33.5	**-3.4** (-3.9, -2.9)	8.8	9.7	**1.2** (0.5, 2.0)	40.6	29.2	**-3.4** (-3.7, -3.0)	6.8	8.2	**1.8** (0.9, 2.7)
	Norway	1994-2005[2]	36.8	33.7	-0.4 (-1.0, 0.1)	15.8	21.3	**3.1** (2.0, 4.3)	32.0	30.0	-0.4 (-0.9, 0.2)	13.5	17.3	**2.4** (1.1, 3.7)
	Sweden	1994-2005[2]	24.9	22.0	-0.5 (-1.1, 0.1)	13.6	16.7	**2.7** (1.7, 3.6)	22.9	20.1	**-1.2** (-1.5, -0.8)	11.1	15.3	**2.6** (1.7, 3.4)
	Ireland	1994-2005[2]	47.7	38.5	**-1.3** (-1.9, -0.7)	18.4	22.7	**2.3** (1.7, 3.0)	45.4	35.3	**-2.2** (-3.1, -1.3)	18.6	18.7	-0.1 (-1.4, 1.3)
	UK England & Wales[a]	1995-2004[3]	51.5	39.2	**-3.1** (-3.5, -2.7)	22.7	22.5	-0.2 (-0.5, 0.2)	46.3	33.1	**-3.3** (-3.5, -3.1)	19.8	19.1	**-0.4** (-0.6, -0.2)
	UK Northern Ireland	1994-2005	59.3	40.2	**-2.6** (-3.7, -1.5)	22.7	21.9	-0.0 (-0.8, 0.5)	47.2	34.9	**-2.3** (-3.0, -1.7)	17.4	18.0	0.3 (-0.7, 1.3)
	UK Scotland	1994-2004[4]	74.2	55.4	**-2.9** (-3.4, -2.5)	34.2	36.9	0.0 (-0.9, 1.0)	66.4	44.6	**-3.1** (-3.5, -2.7)	29.6	30.8	-0.1 (-0.5, 0.4)
Western Europe	Austria (Tyrol)	1994-2003	42.8	42.0	-1.3 (-3.3, 0.7)	12.4	12.8	2.0 (-1.6, 5.7)	37.5	36.9	-1.3 (-3.0, 0.5)	10.4	12.1	3.4 (-0.8, 7.8)
	France	1994-2000[5]	50.9	52.2	**0.4** (0.4, 0.5)	6.7	8.6	**4.2** (4.0, 4.3)	46.3	44.1	**-0.6** (-1.1, -0.2)	5.8	8.3	**4.1** (3.1, 5.2)
	Germany (Saarland)	1994-2005	63.4	52.7	**-2.2** (-2.8, -1,6)	15.7	17.8	**3.4** (1.2, 5.6)	57.8	47.4	**-2.5** (-3.4, -1.7)	11.7	15.0	**2.8** (1.6, 4.0)
	Netherlands	1994-2003	67.4	47.7	**-3.7** (-4.0, -3,4)	15.6	21.8	**3.7** (3.3, 4.2)	62.7	46.0	**-3.3** (-3.7, -2.9)	13.3	18.8	**4.0** (3.6, 4.4)
	Switzerland	1993-2003[6]	46.3	41.7	-1.4 (-3.2, 0.5)	13.0	15.7	**2.6** (2.2, 2.9)	36.9	31.2	**-1.9** (-2.6, -1.2)	9.4	11.7	**3.3** (2.1, 4.5)

Table 2.9a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	70.3	60.4	-1.8 (-4.0, 0.4)	10.0	12.1	2.2 (-0.0, 4.4)	63.0	58.0	-1.2 (-3.3, 1.0)	8.3	10.8	**2.7** (0.7, 4.8)
	Italy (Modena)	1994-2005	71.9	48.9	**-3.0** (-4.3, -1.6)	10.5	15.0	**2.9** (0.3, 5.5)	68.7	42.6	**-3.9** (-4.9, -2.9)	11.2	10.6	0.4 (-2.2, 3.1)
	Malta[b]	1994-2005[4]	45.1	29.9	**-4.0** (-6.0, -1.9)	4.8	7.0	1.9 (-0.4, 4.2)	42.5	35.1	**-2.3** (-3.8, -0.7)	6.1	5.3	0.5 (-4.4, 5.6)
	Slovenia	1994-2003	62.4	58.9	**-2.1** (-4.0, -0.2)	9.7	14.9	**5.0** (3.4, 6.6)	61.0	49.6	**-2.7** (-3.2, -2.2)	8.5	12.4	**3.8** (2.5, 5.3)
	Spain	1994-2002[7]	52.6	52.6	0.4 (-1.6, 2.3)	4.6	5.3	2.2 (-1.0, 5.6)	48.5	45.5	**-0.8** (-1.1, -0.4)	3.8	5.3	**3.8** (3.4, 4.3)
Central Europe	Czech Republic	1994-2004	74.1	60.1	**-2.4** (-2.9, -1.8)	12.5	15.4	**1.9** (1.2, 2.7)	65.3	51.9	**-2.7** (-3.2, -2.2)	10.1	11.6	**1.5** (0.8, 2.3)
	Lithuania	1993-2004[8]	65.8	54.4	-1.9 (-5.9, 2.3)	6.3	6.4	0.6 (-9.3, 11.5)	63.3	51.6	**-1.8** (-2.3, -1.3)	6.3	5.6	-0.3 (-2.1, 1.6)
	Poland	1994-2004[3]	85.6	63.1	**-3.7** (-4.6, -2.8)	15.6	13.9	**-2.4** (-4.8, -0.1)	71.3	64.6	**-0.9** (-1.1, -0.6)	10.7	14.3	**2.6** (2.0, 3.2)

[a] Incidence only for England; [b] Data valid for C34; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.9b | Overview of recent trends in incidence of, survival for and mortality from lung cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	↑	↑	-	Norway, Sweden, Germany, Switzerland
↑	↑	=	-	Italy
↑	=	↑	-	Finland, France[1], Netherlands, Slovenia
↑	=	=	-	Ireland[2]
↑	=	↓	France[1]	-
↑	?	↑	-	Czech Republic
=	↑	↑	-	UK-England&Wales
=	↑	=	Norway	UK-Northern Ireland
=	↑	↓	Sweden, Switzerland	-
=	=	↑	-	Spain
=	=	=	Austria	UK-Scotland, Austria
=	=	↓	Spain	-
=	↓	=	-	Malta
=	?		-	Croatia
=	?	=	Croatia	Denmark, Lithuania
=	?	↓	Lithuania	-
↓	↑	↑	-	Poland
↓	↑	↓	UK-Northern Ireland, Germany, Italy, Poland	-
↓	=	↓	Finland, Ireland[2], UK-England&Wales / Scotland, Netherlands, Slovenia	-
↓	↓	↓	Malta	-
↓	?	↓	Denmark, Czech Republic	-

[1] Survival trends are based on a report of FRANCIM[93]; [2] survival trends are based on a report of the Ireland Cancer Registry[8]

Skin melanoma (C43)

In some European countries incidence rates for skin melanoma continued to increase in others, they started to stabilize. In contrast with incidence, mortality rates have stabilized in most countries, except for the English, French, Dutch and Polish males and Swedish females (**Table 2.10a**). Over the past decade, 5-year relative survival rates improved in most countries with a relative increase varying from 1 to 30%. Improvements in survival were often stronger in countries with markedly increasing incidence rates (**Figure 2.6**, **Table 2.10b**).

Table 2.10a | Trends in incidence of and mortality from melanoma (C43) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	10.8	13.6	**2.1** (0.6, 3.6)	14.6	16.9	1.2 (-1.2, 3.7)	2.8	3.0	0.3 (-2.8, 3.5)	2.1	2.3	1.3 (-5.6, 8.6)
	Finland	1994-2005	8.4	10.3	**2.0** (1.0, 3.1)	6.1	8.5	**2.7** (2.0, 3.5)	2.3	2.5	0.2 (-1.8, 2.2)	1.1	0.9	-1.5 (-3.7, 0.7)
	Norway	1994-2005[2]	15.3	16.1	-0.1 (-1.2, 1.1)	15.8	15.7	-0.3 (-1.8, 1.3)	4.3	3.8	0.3 (-1.9, 2.5)	2.3	2.9	0.9 (-3.0, 4.9)
	Sweden	1994-2005[2]	11.9	13.7	**1.4** (0.5, 2.4)	12.2	13.9	**1.6** (0.6, 2.7)	2.6	2.4	-0.0 (-1.4, 1.3)	1.6	1.9	**2.5** (0.7, 4.3)
	Ireland	1994-2005[2]	6.2	9.3	**4.4** (2.9, 5.8)	10.5	13.1	**2.5** (1.1, 3.8)	1.4	1.7	1.4 (-3.6, 6.5)	1.0	1.7	4.4 (-0.0, 9.0)
	UK England & Wales[1]	1995-2004[3]	5.5	9.0	**5.9** (4.9, 6.9)	7.7	10.6	**4.1** (2.9, 5.4)	1.9	2.0	**1.1** (0.2, 2.1)	1.4	1.5	0.2 (-0.5, 0.9)
	UK Northern Ireland	1994-2005	7.2	8.7	**3.0** (0.7, 5.3)	10.1	10.9	**2.2** (0.5, 3.8)	1.3	2.2	**7.5** (4.6, 10.6)	1.7	0.9	**-3.5** (-6.6, -0.3)
	UK Scotland	1994-2004[4]	6.7	10.5	**3.4** (2.0, 4.8)	9.9	12.9	1.9 (-0.2, 4.1)	1.6	2.1	**2.0** (0.5, 3.5)	1.0	1.2	1.1 (-1.2, 3.5)
Western Europe	Austria (Tyrol)	1995-2003	8.2	21.5	**10.6** (3.9, 17.9)	7.5	17.5	**7.0** (1.3, 13.0)	2.3	2.0	-4.4 (-10.0, 1.6)	1.4	0.6	-1.9 (-23.2, 25.2)
	France	1994-2000[5]	5.4	7.6	**5.8** (5.5, 6.1)	7.2	9.5	**4.8** (4.6, 5.0)	1.5	1.6	**2.1** (0.6, 3.6)	1.1	1.1	-0.3 (-1.8, 1.1)
	Germany (Saarland)	1994-2005	7.0	7.7	2.1 (-0.1, 4.4)	4.9	9.0	**5.1** (3.0, 7.2)	1.8	1.6	0.1 (-3.3, 3.6)	0.9	0.7	1.4 (-5.8, 9.2)
	Netherlands	1994-2003	8.1	10.4	**3.5** (2.4, 4.5)	11.3	14.7	**3.2** (2.0, 4.3)	2.4	2.5	**2.1** (0.6, 3.7)	1.6	1.7	0.8 (-1.1, 2.8)
	Switzerland	1993-2003[6]	12.6	15.3	2.6 (-3.2, 8.8)	12.6	15.5	2.8 (-3.0, 9.0)	2.6	2.6	-2.6 (-5.1, 0.0)	1.3	1.6	0.4 (-2.5, 3.4)

Table 2.10a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	3.4	6.2	**5.8** (0.9, 10.9)	2.9	6.3	**7.4** (3.1, 11.9)	2.3	2.9	5.0 (-0.8, 11.0)	1.2	2.2	3.4 (-0.2, 7.1)
	Italy (Modena)	1994-2005	7.8	9.0	-0.3 (-5.9, 5.7)	6.7	7.0	-1.0 (-4.6, 2.8)	1.0	1.9	7.3 (-1.7, 17.1)	1.2	0.9	-0.9 (-8.5, 7.2)
	Malta	1995-2005[4]	3.0	4.5	**8.4** (2.8, 14.4)	5.5	10.3	4.1 (-1.4, 9.8)	0.8	1.7	4.0 (-9.0, 19.0)	0.3	0.4	-6.4 (-18.3, 7.2)
	Slovenia	1994-2003	7.7	11.7	5.0 (1.0, 9.2)	7.6	10.5	**5.4** (2.1, 8.8)	2.5	3.2	2.9 (-2.6, 8.7)	2.7	2.2	-4.8 (-9.6, 0.4)
	Spain	1994-2002[7]	No data			No data			1.1	1.2	0.3 (-2.3, 3.0)	0.9	0.8	-1.1 (-2.5, 0.4)
Central Europe	Czech Republic	1994-2004	8.1	11.0	**3.5** (2.6, 4.5)	7.2	9.5	**2.5** (1.0, 4.0)	2.8	3.0	-0.3 (-1.7, 1.1)	1.9	1.7	0.1 (-1.7, 2.0)
	Lithuania	1993-2004[8]	2.6	3.8	5.1 (-0.4, 10.8)	4.0	4.5	3.7 (-30.1, 53.8)	1.1	1.3	3.1 (-0.5, 6.8)	1.1	1.4	3.3 (-0.4, 7.2)
	Poland	1994-2004[3]	2.9	3.7	1.8 (-0.0, 3.6)	3.8	3.4	-1.2 (-3.5, 1.2)	1.6	2.0	**1.5** (0.5, 2.5)	1.3	1.2	-0.2 (-1.8, 1.3)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004;
* EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

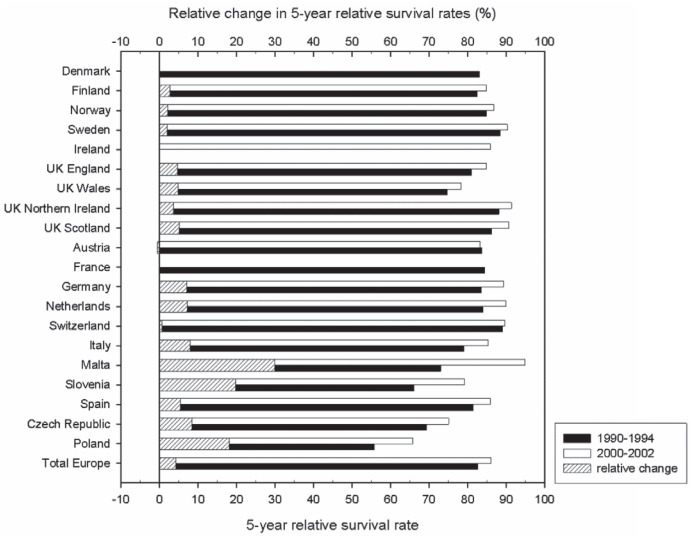


Figure 2.6 | Trends in 5-year age-adjusted relative survival for melanoma in Europe (Sources: EUROCARE-3[9] and EUROCARE-4[3])

Table 2.10b | Overview of recent trends in incidence of, survival for and mortality from melanoma in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	↑	↑	UK, Netherlands	-
↑	↑	=	Finland, Malta, Czech Republic	Finland, UK-England&Wales, Germany, Netherlands, Slovenia, Czech Republic
↑	↑	↓	-	UK-Northern Ireland
↑	=	↑	France[1]	Sweden
↑	=	=	Sweden, Austria	Austria, France[1]
↑	?	=	Denmark, Ireland, Croatia	Ireland, Croatia
=	↑	↑	Poland	-
=	↑	=	Germany, Italy, Slovenia	UK-Scotland, Italy, Malta, Poland
=	=	=	Norway, Switzerland	Norway, Switzerland
=	?	=	Lithuania	Denmark, Lithuania
?	↑	=	Spain	Spain

[1] Survival trends are based on a report of FRANCIM [93]

The increasing incidence rates of skin melanoma, reported since the 1960s has always been attributed to the ever increasing popularity of intensive sunbathing. Recently, the incidence rates started to level off or decrease starting among young people in the Nordic countries.[39] Possibly the efforts of campaigns, like EUROMELANOMA [40] which aimed to increase the awareness of skin melanoma and the risks of excessive sunbathing and sunburns, are starting to show an effect. Screening programs exist for people belonging to Familial Atypical Multiple Mole Melanoma (FAMMM) families, which are at increased risk of developing a melanoma. Melanomas occurring on the trunk generally have a worse prognosis than those occurring on the limbs or head and neck.

In absence of new treatment, the observed improvements of survival can be explained by earlier detection accompanied by a more adequate excision of early diagnosed melanomas.[41] The counterintuitive change in Austria suggest that data quality might have been imperfect, e.g. incompleteness of data.

Female breast cancer (C50)

Breast cancer incidence varied considerably in Europe with lowest rates in Central Europe, Croatia and Slovenia (41 to 64 per 100,000) and highest rates in the Netherlands and Italy (91 per 100,000). Both the highest and lowest mortality rates were observed in Northern Europe (in Denmark and Finland, respectively). In most European countries, incidence rates increased over the past decade, except in Germany, Switzerland, Croatia, Malta, Lithuania and Poland, where rates remained stable. Mortality rates decreased in most countries, except for the Danish, German, Croatian, Slovenian and Lithuanian females (**Table 2.11a**). Five-year relative survival rates have improved in all countries with a relative increase varying from 1% in Malta to 20% in Poland (**Figure 2.7**, **Table 2.11b**).

The rising breast cancer incidence and survival rates are partly influenced by the presence of organised breast cancer screening programmes or opportunistic screening through increased detection of smaller and less aggressive tumours resulting in a decreasing mortality after 5-8 years.[42] This is attributed to lead-time bias because of earlier detection of breast cancer and to length bias due to detection of slow growing tumours and possibly a real effect on mortality due to effective treatment of early detected cancers. However, before the introduction of mass screening, incidence rates were already increasing in most countries suggesting the role of other risk increasing factors.[43] Some of the risk factors, age at menarche, age

Table 2.11a | Trends in incidence of and mortality from female breast cancer (C50) in Europe

			Females					
			Incidence			Mortality		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	75.2	85.3	**1.6** (1.1, 2.1)	25.8	24.9	-1.6 (-3.4, 0.3)
	Finland	1994-2005	66.4	82.2	**1.8** (1.4, 2.2)	15.3	13.7	**-1.4** (-1.9, -0.9)
	Norway	1994-2005[2]	58.3	75.7	**2.3** (1.4, 3.1)	19.9	15.5	**-2.5** (-3.2, -1.8)
	Sweden	1994-2005[2]	78.6	87.1	**1.4** (1.1, 1.8)	16.6	15.6	**-1.1** (-1.9, -0.3)
	Ireland	1994-2005[2]	69.8	86.0	**2.3** (1.8, 2.8)	26.1	21.9	**-1.9** (-2.9, -0.8)
	UK England & Wales[a]	1995-2004[3]	75.5	88.0	**1.6** (1.1, 2.1)	25.1	19.6	**-2.3** (-2.6, -2.1)
	UK Northern Ireland	1994-2005	73.2	80.8	**1.1** (0.5, 1.8)	26.1	17.9	**-2.6** (-4.1, -1.0)
	UK Scotland	1994-2004[4]	76.2	87.5	**1.1** (0.5, 1.6)	26.8	19.4	**-2.3** (-2.8, -1.7)
Western Europe	Austria (Tyrol)	1994-2003	68.8	77.7	**1.6** (0.8, 2.5)	22.1	15.8	**-3.0** (-4.6, -1.4)
	France	1994-2000[5]	78.4	88.9	**2.1** (2.1, 2.2)	19.7	18.3	**-0.8** (-1.3, -0.3)
	Germany (Saarland)	1994-2005	73.2	73.8	0.4 (-0.3, 1.2)	21.5	19.8	-1.4 (-2.9, 0.2)
	Netherlands	1994-2003	88.2	90.6	**0.9** (0.3, 1.6)	26.7	21.8	**-2.0** (-2.7, -1.4)
	Switzerland	1993-2003[6]	77.3	84.8	1.3 (-5.4, 8.4)	23.0	17.5	**-2.4** (-3.7, -1.1)
Southern Europe	Croatia	1994-2004	45.7	52.9	1.6 (-1.2, 4.4)	18.1	17.9	-0.6 (-2.0, 1.0)
	Italy (Modena)	1994-2005	75.5	91.4	**1.6** (0.2, 2.9)	22.9	16.6	**-3.8** (-7.1, -0.4)
	Malta	1994-2005[4]	65.1	73.6	0.2 (-0.9, 1.2)	36.5	20.4	**-5.0** (-7.3, -2.7)
	Slovenia	1994-2003	47.8	64.4	**2.7** (1.5, 3.8)	21.3	18.7	-1.0 (-2.5, 0.5)
	Spain	1994-2002[7]	55.4	73.4	**4.0** (0.8, 7.3)	17.5	13.9	**-2.6** (-3.2, -2.1)
Central Europe	Czech Republic	1994-2004	55.0	62.5	**1.8** (1.0, 2.6)	23.5	19.0	**-2.1** (-2.6, -1.7)
	Lithuania	1993-2004[8]	37.7	43.2	3.3 (-26.5, 45.0)	19.7	17.4	-0.7 (-1.5, 0.0)
	Poland	1994-2004[3]	36.2	40.6	0.5 (-0.6, 1.6)	15.9	14.9	**-0.9** (-1.3, -0.5)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

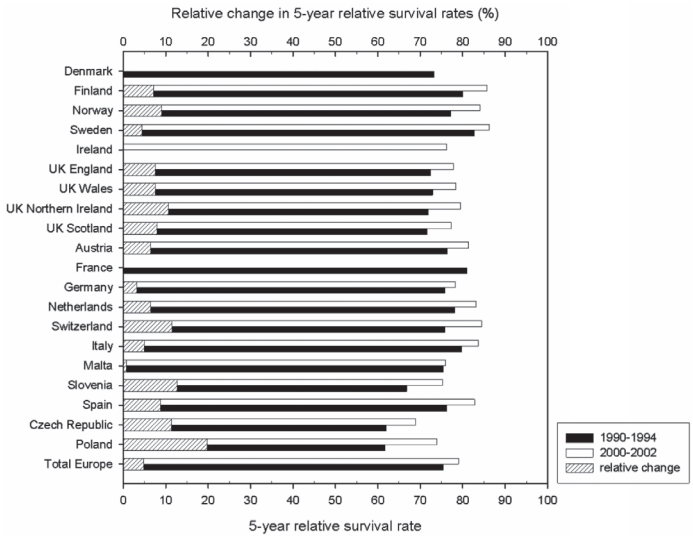


Figure 2.7 | Trends in 5-year age-adjusted relative survival for female breast cancer in Europe (Source: EUROCARE-3[9] and EUROCARE-4[3])

Table 2.11b | Overview of recent trends in incidence of, survival for and mortality from female breast cancer in Europe

Incidence	Survival	Mortality	Countries
			Females
↑	↑	=	Slovenia
↑	↑	↓	Finland, Norway, Sweden, Ireland[1], UK, Austria, France[2], Netherlands, Italy, Spain, Czech Republic
↑	?	=	Denmark
=	↑	=	Germany
=	↑	↓	Switzerland, Poland
=	=	↓	Malta
=	?	=	Croatia, Lithuania

[1] Survival trend is based on a report of the Ireland Cancer Registry [81]; [2] Survival trend is based on a report of FRANCIM[93]

at first childbirth, number of children and the proportion of nulliparous women, have all changed in an adverse way and had probably a negative impact on the trend of breast cancer.[44] However these risk factors are difficult to modify.[45] Other

lifestyle related risk factors are relatively more amenable to primary prevention interventions, including post-menopausal obesity, alcohol consumption and low physical activity.

Recent decreases in breast cancer incidence have been attributed to the decreased use of hormone replacement therapy, which will continue in the near future in countries where usage was high.[46,47]

The continuing rise in survival has also been observed before introduction of mass screening suggesting improved staging and treatment, such as application of tamoxifen in postmenopausal patients and chemotherapy in premenopausal patients.

Cervical cancer (C53)

Incidence and mortality rates of cervical cancer varied greatly throughout Europe with highest rates in Central Europe and Slovenia and lowest rates in Finland, Italy and Malta. In contrast with most European countries where incidence and mortality rates decreased, rates remained stable in Finland, Ireland, Austria (Tyrol), and Italy (Modena). Lithuania was the only country included in this study that showed increases in cervical cancer mortality (**Table 2.12a**). Five-year survival improved remarkably in Slovenia and Poland with a relative increase between 9 and 16%. In other parts of Europe, survival remained stable or decreased. In general the 5-year survival was between 60% and 70% (**Figure 2.8**, **Table 2.12b**).

The main cause of cervical cancer is sexually transmitted infection of human papilloma virus (HPV).[48] Geographical variations are mainly due to historical patterns of risk factors like sexual behaviour, age at first coitus, oral contraceptive use, the number of sexual partners, smoking, and, the influence of screening activities. Screening for cervical cancer can lower incidence rates up to 80%. Such low rates have indeed been accomplished in countries with long-running, effective screening programs, like Finland and the Netherlands.[49] In countries where organised screening programs have been recently introduced or improved, decreases in incidence and mortality are observed.[50-52] The improvement of survival in Slovenia and Poland is probably due to improvement of treatment and not yet an effect of screening. The decreasing survival rates in some European countries where mortality rates were already low can be explained by effective screening, causing a shift in the stage distribution by detection of pre-malignant lesions and slow growing tumours and leaving the more aggressive tumours with a worse prognosis.[53] This might be compensated again by advances in treatment that happened during the 1990s.

Table 2.12a | Trends in incidence of and mortality from cervical cancer (C53) in Europe

			Females					
			Incidence			Mortality		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR End	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	12.8	10.8	**-3.1** (-4.4, -1.7)	4.3	2.9	-4.2 (-8.2, 0.0)
	Finland	1994-2005	3.7	3.3	-0.8 (-2.4, 0.9)	1.2	1.0	-1.7 (-5.5, 2.3)
	Norway	1994-2005[2]	11.3	9.4	**-2.6** (-3.7, -1.5)	3.3	2.0	**-4.1** (-5.9, -2.2)
	Sweden	1994-2005[2]	7.8	6.6	**-1.1** (-2.1, -0.2)	2.0	1.9	-1.2 (-3.4, 1.0)
	Ireland	1994-2005[2]	8.4	9.9	0.6 (-1.4, 2.5)	2.7	3.3	-1.5 (-4.2, 1.3)
	UK England & Wales[a]	1995-2004[3]	8.2	6.4	**-2.8** (-3.2, -2.3)	3.1	1.9	**-4.8** (-5.4, -4.3)
	UK Northern Ireland	1994-2005	7.4	8.2	-1.6 (-3.7, 0.5)	3.2	1.1	**-4.9** (-9.6, -0.0)
	UK Scotland	1994-2004[4]	9.9	8.0	**-2.8** (-3.9, -1.6)	3.6	2.1	**-3.6** (-4.8, -2.4)
Western Europe	Austria (Tyrol)	1995-2003	13.7	10.0	0.1 (-4.0, 4.3)	5.5	2.8	-7.9 (-16.7, 2.0)
	France	1994-2000[5]	9.1	8.0	**-2.1** (-2.4, -1.8)	1.7	1.4	-1.4 (-3.7, 1.0)
	Germany (Saarland)	1994-2005	12.1	9.0	**-2.8** (-5.2, -0.3)	3.4	2.3	-1.6 (-5.8, 2.9)
	Netherlands	1994-2003	6.5	4.9	**-3.3** (-4.6, -1.9)	1.7	1.4	-2.1 (-5.1, 0.9)
	Switzerland	1993-2003[6]	6.9	5.6	-2.7 (-6.5, 1.2)	2.0	1.2	**-5.9** (-8.2, -3.4)
Southern Europe	Croatia	1994-2004	12.3	9.9	**-2.0** (-3.9, -0.2)	2.8	2.3	**-2.0** (-3.8, -0.3)
	Italy (Modena)	1994-2005	8.4	3.8	-4.5 (-9.0, 0.1)	1.1	0.1	-6.3 (-20.8, 10.9)
	Malta	1994-2005[4]	10.1	2.1	**-11.3** (-16.8, -5.5)	0.4	1.2	-1.2 (-9.6, 13.2)
	Slovenia	1994-2003	13.2	15.0	-0.4 (-3.1, 2.4)	3.3	3.0	**-4.0** (-7.0, -0.9)
	Spain	1994-2002[7]	No data			1.8	1.5	**-2.0** (-3.6, -0.5)
Central Europe	Czech Republic	1994-2004	17.3	13.9	**-1.8** (-2.6, -1.0)	5.8	4.8	**-2.1** (-3.1, -1.2)
	Lithuania	1993-2004[8]	14.6	20.1	5.4 (-21.5, 41.5)	7.5	8.7	**1.7** (0.5, 2.9)
	Poland	1994-2004[3]	17.2	11.9	**-3.4** (-4.2, -2.5)	7.5	5.7	**-2.4** (-3.0, -1.8)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004;
* EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

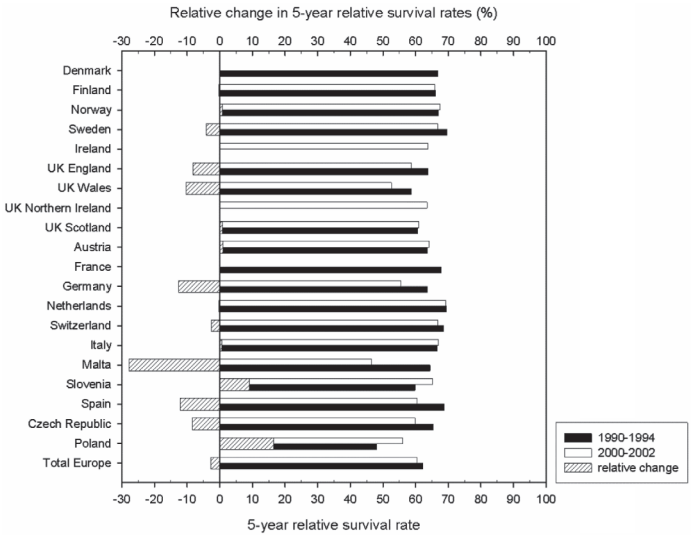


Figure 2.8 | Trends in 5-year age-adjusted relative survival for cervical cancer in Europ (Sources: EUROCARE-3 [7] and EUROCARE-4[3])

Table 2.12b | Overview of recent trends in incidence of, survival for and mortality from cervical cancer in Europe

Incidence	Survival	Mortality	Countries
			Females
=	↑	↓	UK-Northern Ireland[1]
=	=	=	Finland, Austria, Italy
=	=	↓	Switzerland
=	?	↑	Lithuania
=	?	=	Ireland
↓	↑	↓	Slovenia, Poland
↓	=	=	Netherlands, France[2]
↓	=	↓	Norway, UK-Scotland
↓	↓	=	Sweden, Germany, Malta
↓	↓	↓	UK-England&Wales, Czech Republic
↓	?	=	Denmark
↓	?	↓	Croatia
?	↓	↓	Spain

[1] Survival trend is based on a report of the Northern Ireland Cancer Registry[89]; [2] Survival trend is based on a report of FRANCIM[93]

Corpus uteri cancer (C54)

The recent incidence rate of corpus uteri cancer varied between 9.2 (France) and 18 (Czech Republic) per 100,000. In most countries incidence rates remained stable, except in Norway, Ireland, the UK and Slovenia where rates were increasing. Mortality rates were dropping mostly in Southern and Central Europe, but remained still higher than other parts of Europe (**Table 2.13a**). Consistently, in most countries, moderate improvements in 5-year survival were observed, except for Malta, where the relative improvement was 28% (**Figure 2.9**, **Table 2.13b**).

Geographical variation in cancer incidence of the corpus uteri across Europe can be due to variation in prevalence of risk factors like oestrogen replacement therapy, sequential oral contraceptives, nulliparity and obesity.[34,54] The higher mortality in Southern and Central Europe is probably indicating some disparity in the early diagnosis and treatment of patients.[54] However, the observed increased 5-year survival in these countries indicates improvements and probably the mortality will decrease further. The counterintuitive change of survival in Austria and Spain suggest that data quality might have been imperfect, e.g. incompleteness of (follow-up) data.

Ovarian cancer (C56)

Within Europe, incidence and mortality rates of ovarian cancer were largely similar and quite stable or decreasing over time (**Table 2.14a**). Five-year survival improved slightly over time in Europe from 37 to 42% (**Table 2.14b**, **2.14c**).

Ovarian cancer has different risk factors like personal or family history of breast or ovarian cancer, obesity, oestrogen replacement therapy, no oral contraceptive use, late age at last birth and more debatable is the use of fertility drugs and/or subfertility.[55] Five-year survival rates for ovarian cancer are largely determined by the stage at diagnosis: with early diagnosis and treatment, the 5-year relative survival rate is over 90%. Unfortunately, ovarian cancer has very non-specific symptoms and only a small percentage of cases are found at an early stage. In addition, age is also an important prognostic factor.[56] Five-year relative survival rates are substantially lower for females aged 70 and over compared with younger females (**Table 2.14b**). In the south-eastern Netherlands, improvements in survival were accomplished in the elderly since the late 90's only.[56] Surgical management of ovarian cancer and regionalisation of care were also reported to be related to improved survival.[57,58]

Table 2.13a | Trends in incidence of and mortality from corpus uteri cancer (C54) in Europe

			Females					
			Incidence			Mortality		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	13.4	12.5	-0.5 (-1.3, 0.4)	2.8	1.9	-3.5 (-8.6, 2.0)
	Finland	1994-2005	13.5	14.6	0.3 (-0.8, 1.5)	2.2	2.2	-0.1 (-1.6, 1.4)
	Norway	1994-2005[2]	12.3	16.2	**2.5** (1.7, 3.2)	2.6	1.6	-2.2 (-5.3, 1.0)
	Sweden	1994-2005[2]	13.5	14.7	0.3 (-0.4, 1.1)	1.4	1.1	-0.5 (-2.5, 1.6)
	Ireland	1994-2005[2]	8.0	10.7	**1.9** (0.5, 3.3)	1.7	1.3	-1.2 (-4.3, 1.9)
	UK England & Wales [a,b]	1995-2004[3]	9.6	11.7	**2.5** (1.8, 3.2)	2.2	2.4	**1.0** (0.0, 2.0)
	UK Northern Ireland	1994-2005	8.3	13.4	**5.5** (3.7, 7.3)	1.2	0.9	2.6 (-2.3, 7.7)
	UK Scotland	1994-2004[4]	8.9	11.1	**1.5** (0.4, 2.7)	1.9	1.6	0.8 (-2.1, 3.7)
Western Europe	Austria (Tyrol)	1995-2003	12.3	11.9	-1.2 (-4.7, 2.4)	1.5	1.8	-1.7 (-13.3, 11.4)
	France[c]	1994-2000[5]	9.8	9.2	**-1.1** (-1.1, -1.0)	3.5	2.9	**-2.1** (-3.0, -1.2)
	Germany (Saarland)	1994-2005	14.0	12.8	-1.5 (-3.1, 0.1)	1.2	1.1	-0.4 (-6.9, 6.5)
	Netherlands[b]	1994-2003	11.2	11.6	0.3 (-0.4, 1.0)	2.4	2.0	-0.3 (-1.9, 1.3)
	Switzerland[b]	1993-2003[6]	12.9	12.4	**-0.5** (-1.0, -0.1)	2.5	2.3	-1.5 (-3.6, 0.7)
Southern Europe	Croatia[b]	1994-2004	11.2	12.2	-0.3 (-2.5, 1.9)	4.2	3.1	**-3.8** (-6.8, -0.6)
	Italy (Modena)	1994-2005	12.9	16.4	2.8 (-0.7, 6.4)	1.2	1.1	-3.7 (-10.5, 3.7)
	Malta[b]	1994-2005[4]	18.4	16.5	-1.0 (-3.1, 1.2)	4.0	3.7	-1.8 (-5.4, 2.0)
	Slovenia[b]	1994-2003	14.9	17.1	**1.6** (0.5, 2.6)	5.0	3.7	**-4.2** (-7.6, -0.7)
	Spain[c]	1994-2002[7]	11.0	11.2	0.4 (-1.3, 2.0)	3.2	2.6	**-2.5** (-3.4, -1.6)
Central Europe	Czech Republic	1994-2004	17.9	18.2	-0.1 (-0.5, 0.4)	4.5	4.0	**-2.3** (-3.5, -0.9)
	Lithuania[b]	1993-2004[8]	14.0	16.6	5.2 (-41.4, 88.9)	5.4	3.5	**-3.4** (-4.9, -2.0)
	Poland[b]	1994-2004[3]	11.9	13.8	0.6 (-0.9, 2.1)	3.8	3.2	**-1.4** (-2.0, -0.7)

[a] Incidence only for England; [b] Data valid for C54-55; [c] Mortality data valid for C54-55; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

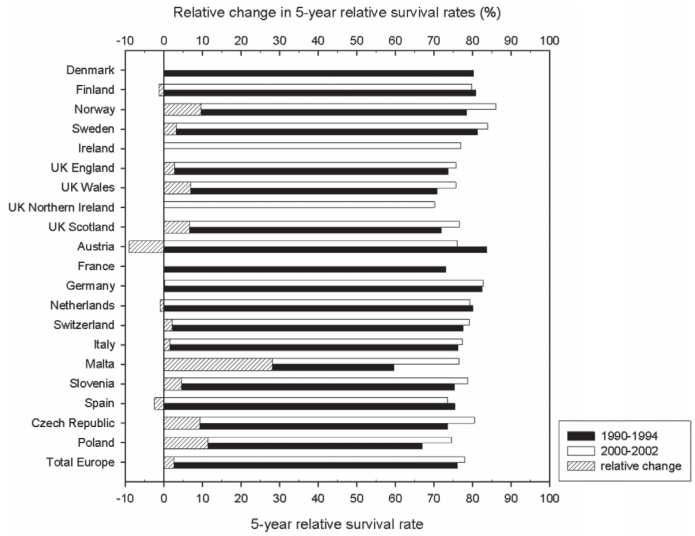


Figure 2.9 | Trends in 5-year age-adjusted relative survival for corpus uteri cancer in Europe (Source: EUROCARE-3 [7] and EUROCARE-4[3])

Table 2.13b | Overview of recent trends in incidence of, survival for and mortality from corpus uteri cancer in Europe

Incidence	Survival	Mortality	Countries
			Females
↑	↑	↑	UK-England&Wales
↑	↑	=	Norway, UK-Northern Ireland[1] / Scotland
↑	↑	↓	Slovenia
↑	?	=	Ireland
=	↑	=	Sweden, Malta
=	↑	↓	Czech Republic, Poland
=	=	=	Finland, Germany, Netherlands, Italy
=	=	↓	Spain
=	↓	=	Austria
=	?	=	Denmark
=	?	↓	Croatia, Lithuania
↓	↑	↓	France[2]
↓	=	=	Switzerland

[1] Survival trend is based on a report of the Northern Ireland Cancer Registry[89]; [2] Survival trend is based on a report of FRANCIM[93]

Table 2.14a | Trends in incidence of and mortality from ovarian cancer (C56) in Europe

			Females					
			Incidence			Mortality		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR End	EAPC* (95% CI)
Northern Europe	Denmark[a]	1994-2003[1]	13.7	11.9	-0.8 (-2.1, 0.4)	9.0	8.4	-0.8 (-3.1, 1.5)
	Finland[a]	1994-2005	11.2	9.0	-1.0 (-2.2, 0.2)	6.4	5.4	-1.7 (-3.1, -0.3)
	Norway[a]	1994-2005[2]	14.3	11.2	**-1.4** (-2.6, -0.3)	7.9	7.4	-1.2 (-2.9, 0.5)
	Sweden[a]	1994-2005[2]	12.9	9.4	**-2.3** (-3.0, -1.6)	7.4	6.6	-1.1 (-2.3, 0.1)
	Ireland[a]	1994-2005[2]	12.8	13.2	0.1 (-1.0, 1.3)	8.4	8.2	-0.4 (-2.1, 1.4)
	UK England & Wales[a,b]	1995-2004[3]	13.3	12.3	**-0.8** (-1.4, -0.2)	8.1	7.1	**-1.4** (-2.0, -0.7)
	UK Northern Ireland	1994-2005	13.4	13.4	0.8 (-0.9, 2.5)	6.7	8.3	1.3 (-0.8, 3.4)
	UK Scotland	1994-2004[4]	13.8	12.8	-0.7 (-2.0, 0.5)	9.1	7.1	**-1.5** (-2.4, -0.6)
Western Europe	Austria (Tyrol)[a]	1995-2003	16.9	11.4	**-4.2** (-7.1, -1.3)	6.1	6.7	-2.7 (-9.3, 4.4)
	France[a]	1994-2000[5]	9.1	9.0	**-0.2** (-0.4, -0.1)	5.5	5.5	-0.2 (-0.6, 0.2)
	Germany (Saarland)[a]	1994-2005	11.1	8.7	-0.7 (-2.6, 1.2)	6.2	6.1	0.7 (-1.8, 3.4)
	Netherlands	1994-2003	10.7	8.3	**-3.0** (-3.5, -2.4)	7.7	5.9	**-3.1** (-3.9, -2.3)
	Switzerland	1993-2003[6]	11.7	11.4	-0.3 (-7.7, 7.6)	5.8	5.7	-0.4 (-1.8, 1.1)
Southern Europe	Croatia[a]	1994-2004	11.1	10.8	0.6 (-2.2, 3.4)	6.0	6.2	1.2 (-0.5, 3.0)
	Italy (Modena)[c]	1994-2005	13.9	7.9	-1.6 (-4.6, 1.6)	7.1	4.5	-2.7 (-6.5, 1.2)
	Malta	1994-2005[4]	11.7	8.1	-1.9 (-5.6, 2.0)	9.2	5.7	-1.8 (-5.5, 2.0)
	Slovenia[a]	1994-2003	12.1	11.5	**-1.9** (-3.6, -0.1)	7.5	6.8	-1.0 (-3.1, 1.1)
	Spain[a]	1994-2002[7]	No data			4.1	4.5	0.7 (-0.0, 1.5)
Central Europe	Czech Republic	1994-2004	14.0	14.0	-0.1 (-0.7, 0.5)	7.8	7.1	-0.3 (-1.5, 0.9)
	Lithuania[a]	1993-2004[8]	13.8	13.3	0.8 (-16.5, 21.5)	9.8	8.3	**-1.8** (-3.3, -0.2)
	Poland[a]	1994-2004[3]	12.0	11.2	**-1.2** (-2.0, -0.4)	6.6	7.6	**1.5** (1.0, 2.1)

[a] Data valid for C56-57; [b] Incidence only for England; [c] Data until 1999 valid for 183 (ICD-9), and from 2000 valid for C56 (ICD-10); [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.14b | Trends in 5-year relative survival for ovarian cancer in Europe[1]

	Country	Period	5-year relative survival	Period	5-year relative survival	Trend in survival
Northern Europe	Finland	-	-	2003-2005	49.0	?
	Norway	1991-1995	39.9	1996-2000	44.1	↑
	UK England&Wales	1991-1995	31.0	2000-2001	41.0	↑
	UK Northern Ireland	1993-1996	41.6	2001-2004	43.6	↑
	UK Scotland	1992-1996	32.8	1997-2001	40.6	↑
Western Europe	France	1992-1994	39.0	1995-1997	40.0	=
	Germany (Saarland)	-	-	2000-2002	48.0	?
	Netherlands (Amsterdam)	1993-1996	37.0	2001-2005	40.0	↑
	Netherlands (Eindhoven) (<70 years)	1990-1994	47.0	2000-2002	54.0	↑
	Netherlands (Eindhoven) (≥70 years)	1990-1994	18.0	2000-2002	24.0	↑
	Switzerland (Geneva)	1990-1994	39.0	1994-1998	48.0	↑
Southern Europe	Italy (Modena)	1990-1997	41.0	1998-2005	36.0	↓
	Italy	-	-	1995-1999	41.0	?
	Slovenia	1993-1997	37.0	1998-2002	46.0	↑
Central Europe	Czech Republic	-	-	1995-1999	45.0	?
Total Europe		1990-1994[2]	36.7	1995-1999[3]	41.6	↑

[1] Data reported by individual cancer registries or consortia of cancer registries (sources are shown in Table 1); [2] Data reported by the EUROCARE-3 study [8]; [3] Data reported by the EUROCARE-4 study [9]

Table 2.14c | Overview of recent trends in incidence of, survival for and mortality from ovarian cancer in Europe

Incidence	Survival	Mortality	Countries
			Females
=	↑	=	UK-Northern Ireland, Switzerland
=	↑	↓	UK-Scotland
=	↓	=	Italy
=	?	=	Denmark, Finland, Ireland, Germany, Croatia, Malta, Czech Republic
=	?	↓	Lithuania
↓	↑	=	Norway, Slovenia
↓	↑	↓	UK-England&Wales, Netherlands
↓	=	=	France
↓	?	↑	Poland
↓	?	=	Sweden, Austria
?	?	=	Spain

Prostate cancer (C61)

In contrast to mortality, incidence of prostate cancer varied largely across Europe with highest incidence rates in Finland, Sweden and Austria (Tyrol) (114, 112 and 106 per 100,000 respectively) and lowest rate in Poland (25 per 100,000). A dramatically increasing incidence trend was observed in all European countries except for The Netherlands and Austria (Tyrol), where rates already increased in previous periods. In Slovenia, Lithuania and Poland mortality rates increased while rates were decreasing or stable in other European countries (**Table 2.15a**). Relative improvements in five-year survival rates from 1990-2002 varied between 10% in Germany and the Czech Republic to 83% in Poland, resulting in 5-year survival rates of 58% (Czech Republic) to 87% (Switzerland) in 2000-2002 (**Figure 2.10**, **Table 2.15b**).

The dramatic increase of incidence is mostly due to the introduction of (non-) organized PSA-testing, leading to detection of many latent cancers and artificially high survival rates. Differences in intensity of the use of PSA screening and the registration of these latent cancers make interpretation of incidence and survival complicated.

Testicular cancer (C62)

Recent incidence rates of testicular cancer in Europe varied between 1.9 per 100,000 in Lithuania to 11 per 100,000 in Norway. Mortality rates were quite similar throughout Europe (**Table 2.16a**). In many countries an increased incidence trend was observed, in contrast with stable mortality trends. Five-year survival improved from 91 to 94% in Europe and varied between 94 and 100% (**Table 2.16b**, **2.16c**).

Previous studies observed that increases in incidence are largely due to increases in the incidence of localised tumours among men born after the 1930s.[59-61] Factors like low birth weight, older maternal age, low birth order, maternal smoking during pregnancy, cryptorchidism convey an increased risk.[62-64] In all member countries of the European Union, maternal age has been increasing since 1994 and family sizes have been decreasing, possibly explaining the observed increases in trends.[44] The increase in survival and the decreases in mortality are attributed to the introduction of cisplatin-containing chemotherapy, which has proven to be the most effective treatment for non-seminoma testicular cancer, constituting about half of testicular cancer cases.[61,65]

Table 2.15a | Trends in incidence of and mortality from prostate cancer (C61) in Europe

			Males					
			Incidence			Mortality		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	29.4	49.9	**6.2** (5.4, 7.1)	19.7	20.7	0.3 (-0.9, 1.4)
	Finland	1994-2005	57.7	114.0	**5.9** (5.1, 6.8)	17.1	14.8	**-1.6** (-2.6, -0.7)
	Norway	1994-2005[2]	60.5	91.7	**3.9** (2.5, 5.4)	23.6	20.5	**-1.5** (-2.2, -0.7)
	Sweden	1994-2005[2]	62.1	112.4	**6.4** (5.4, 7.4)	20.7	21.3	-0.2 (-1.0, 0.6)
	Ireland	1994-2005[2]	43.7	88.9	**8.0** (6.8, 9.2)	18.1	17.1	**-1.2** (-2.1, -0.2)
	UK England & Wales[a]	1995-2004[3]	39.7	64.0	**6.0** (4.7, 7.4)	17.1	14.9	**-0.9** (-1.5, -0.3)
	UK Northern Ireland	1994-2005	39.2	56.7	**4.6** (2.9, 6.2)	16.4	13.8	**-1.3** (-2.4, -0.3)
	UK Scotland	1994-2004[4]	42.8	56.3	**2.3** (1.0, 3.6)	16.6	14.1	**-1.1** (-1.7, -0.4)
Western Europe	Austria (Tyrol)	1994-2003	117.3	106.4	1.5 (-1.5, 4.5)	19.5	11.6	**-4.8** (-7.7, -1.7)
	France	1994-2000[5]	51.3	75.3	**6.7** (6.5, 6.8)	16.2	14.6	**-1.1** (-1.8, -0.4)
	Germany (Saarland)	1994-2005	52.0	71.0	**4.9** (3.0, 6.8)	12.5	15.0	-0.2 (-1.8, 1.4)
	Netherlands	1994-2003	55.4	61.4	0.6 (-0.0, 1.3)	19.2	16.3	**-2.2** (-2.7, -1.7)
	Switzerland	1993-2003[6]	66.0	86.1	**3.6** (1.4, 5.9)	20.0	16.3	**-2.0** (-2.7, -1.3)
Southern Europe	Croatia	1994-2004	21.6	35.1	**6.7** (4.7, 8.7)	13.4	15.4	1.8 (-0.4, 4.1)
	Italy (Modena)	1994-2005	43.8	91.3	**10.9** (6.8, 15.1)	17.5	7.4	**-5.1** (-7.8, -2.3)
	Malta	1994-2005[4]	23.3	45.9	**6.1** (3.9, 8.4)	13.6	7.8	**-3.7** (-6.0, -1.2)
	Slovenia	1994-2003	24.6	36.7	**4.2** (1.8, 6.8)	13.3	21.2	**3.7** (1.5, 6.0)
	Spain	1994-2002[7]	29.3	56.4	**8.9** (4.9, 13.1)	13.8	11.7	**-2.1** (-2.8, -1.3)
Central Europe	Czech Republic	1994-2004	30.4	52.3	**4.8** (3.6, 5.9)	16.3	17.1	0.1 (-0.6, 0.7)
	Lithuania	1993-2004[8]	26.0	71.1	**12.3** (5.7, 19.4)	15.5	19.2	**2.1** (1.4, 2.9)
	Poland	1994-2004[3]	16.7	24.5	**2.9** (1.4, 4.5)	10.8	12.9	**1.9** (1.3, 2.6)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

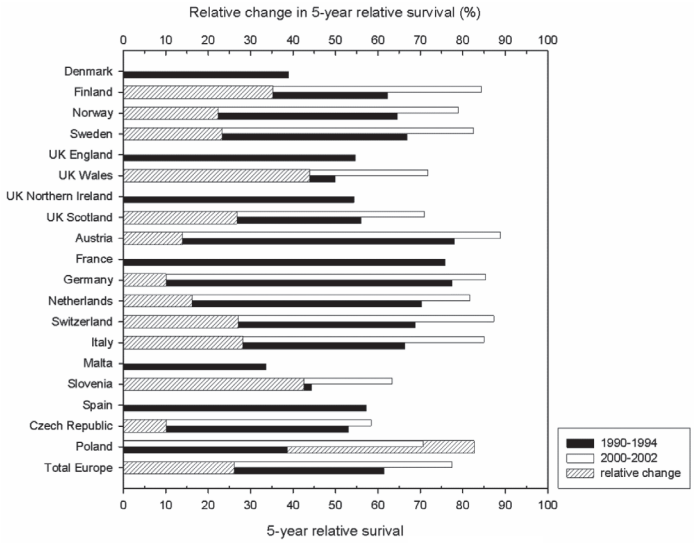


Figure 2.10 | Trends in 5-year age-adjusted relative survival for prostate cancer in Europe (Sources: EUROCARE-3[9] and EUROCARE-4[3])

Table 2.15b | Overview of recent trends in incidence of, survival for and mortality from prostate cancer in Europe

Incidence	Survival	Mortality	Countries
			Males
↑	↑	↑	Slovenia, Poland
↑	↑	=	Sweden, Germany, Czech Republic
↑	↑	↓	Finland, Norway, Ireland[1], UK[2], Switzerland, Italy
↑	?	↑	Lithuania
↑	?	=	Denmark, Croatia
↑	=	↓	France[3]
↑	?	↓	Malta, Spain
=	↑	↓	Austria, Netherlands

[1] Survival trend is based on a report of Ireland Cancer Registry[81]; [2] Survival trend of UK-Northern Ireland is based on a report of the Northern Ireland Cancer Registry [89]; [3] Survival trend is based on a report of FRANCIM[93]

Table 2.16a | Trends in incidence of and mortality from testicular cancer (C62) in Europe

			Males					
			Incidence			Mortality		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	10.6	9.3	-1.4 (-2.7, -0.0)	0.7	0.5	-7.5 (-15.4, 1.2)
	Finland	1994-2005	2.3	5.1	5.4 (3.1, 7.7)	0.1	0.2	1.4 (-6.8, 10.4)
	Norway	1994-2005[2]	8.3	10.5	2.4 (0.8, 4.1)	0.4	0.4	2.5 (-3.3, 8.7)
	Sweden	1994-2005[2]	5.3	6.2	2.3 (0.4, 4.1)	0.2	0.2	-0.1 (-8.1, 8.6)
	Ireland	1994-2005[2]	3.6	6.9	4.5 (2.1, 6.9)	0.4	0.1	-5.8 (-13.7, 2.9)
	UK England & Wales[a]	1995-2004[3]	5.3	6.1	1.7 (0.1, 3.2)	0.3	0.2	-3.3 (-5.9, -0.6)
	UK Northern Ireland	1994-2005	5.4	7.3	3.1 (1.0, 5.3)	0.5	0.0	-26.4 (-65.8, 58.4)
	UK Scotland	1994-2004[4]	6.9	6.4	1.4 (-0.8, 3.5)	0.3	0.5	1.7 (-2.6, 6.1)
Western Europe	Austria (Tyrol)	1995-2003	7.7	8.2	-0.1 (-2.9, 2.7)	0.8	0.7	-19.2 (-87.9, 439.9)
	France	1994-2000[5]	No data			0.3	0.3	1.0 (-2.0, 4.0)
	Germany (Saarland)	1994-2005	5.3	9.3	2.4 (-1.0, 5.9)	0.1	0.5	-30.4 (-55.5, 8.8)
	Netherlands	1994-2003	4.4	6.2	4.4 (2.8, 6.0)	0.2	0.3	2.5 (-4.7, 10.3)
	Switzerland	1993-2003[6]	9.1	9.8	1.0 (-4.5, 6.8)	0.4	0.3	-3.7 (-28.6, 30.0)
	Croatia	1994-2004	1.8	6.3	11.5 (4.9, 18.5)	0.1	0.6	6.8 (-4.9, 20.1)
	Italy (Modena)	1994-2005	4.1	7.5	3.8 (-0.2, 8.0)	0.1	0.0	-43.1 (-80.5, 66.2)
	Malta	1994-2005[2]	No data			0.8	0.3	14.5 (-58.3, 214.4)
	Slovenia	1994-2003	5.3	9.5	5.7 (1.7, 10.0)	0.4	0.7	0.8 (-14.0, 18.2)
	Spain	1994-2002[7]	No data			0.2	0.2	-2.9 (-11.0, 5.9)
Central Europe	Czech Republic	1994-2004	6.2	7.0	1.7 (0.6, 2.8)	1.0	0.5	-4.2 (-8.4, 0.2)
	Lithuania	1993-2004[8]	1.6	1.9	1.7 (-4.3, 8.0)	0.6	0.5	-3.4 (-6.0, -0.7)
	Poland	1994-2004[3]	2.9	3.9	3.0 (1.0, 5.1)	0.7	0.6	-2.3 (-5.3, 0.8)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence and mortality for periods 1993-1996, 1997-1999, and 2001-2003; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.16b | Trends in 5-year relative survival for testicular cancer in Europe[1]

	Country	Period	5-year relative survival	Period	5-year relative survival	Trend in survival
Northern Europe	Finland	-	-	2003-2005	94.0	?
	Norway	1991-1995	95.8	1996-2000	96.0	=
	UK England&Wales	1991-1995	93.0	2000-2001	98.0	↑
	UK Northern Ireland	1993-1996	92.4	2001-2004	94.0	=
	UK Scotland[2]	1992-1996	95.1	1997-2001	97.7	↑
Western Europe	France	1992-1994	95.0	1995-1997	96.0	=
	Germany (Saarland)	-	-	2000-2002	100.0	?
	Netherlands (Amsterdam)	1993-1996	97.0	2001-2005	95.0	=
	Netherlands (Eindhoven) (non-seminoma)	1990-1994	91.0	2000-2002	94.0	↑
	Netherlands (Eindhoven) (seminoma)	1990-1994	98.0	2000-2002	97.0	=
	Switzerland (Geneva)	1990-1994	98.0	1994-1998	95.0	↓
Southern Europe	Italy (Modena)	1990-1997	98.0	1998-2005	97.0	=
	Italy	-	-	1995-1999	94.0	?
	Slovenia	1993-1997	96.0	1998-2002	97.0	=
Total Europe		1990-1994[3]	91.4	1995-1999[4]	93.8	↑

[1] Data reported by individual cancer registries or consortia of cancer registries (sources are shown in Table 1); [2] Data were calculated for age group 15-74 year; [3] Data reported by the EUROCARE-3 study [8]; [4]Data reported by the EUROCARE-4 study [9]

Table 2.16c | Overview of recent trends in incidence of, survival for and mortality from testicular cancer in Europe

Incidence	Survival	Mortality	Countries
			Males
↑	↑	↓	UK-England&Wales
↑	=	=	Norway, UK-Northern Ireland, Netherlands, Slovenia
↑	?	=	Finland, Sweden, Croatia, Poland
↑	?	=	Czech Republic
=	↑	=	UK-Scotland
=	=	=	Italy
=	↓	=	Switzerland
=	?	=	Austria, Germany
=	?	↓	Lithuania
↓	?	=	Denmark
?	=	=	France
?	?	=	Malta, Spain

Another explanation of the improved survival is a shift toward seminomas, which have a better prognosis than non-seminomas (**Table 2.16b).** Prognosis is also influenced by stage and age at diagnosis, with younger patients exhibiting better survival than older patients.[66]

Kidney cancer (C64-66 / C68)

Incidence and mortality of kidney cancer was lowest in Northern Europe and highest in Central Europe, especially in the Czech Republic. This tumour was about twice as frequent in males compared with females. Trends have been rather diverse across Europe, with increasing or stable incidence trends in countries throughout Europe and decreases in the Czech Republic, Austria, Sweden, the Netherlands, Poland and Finland (**Table 2.17a**). Survival rates improved across Europe (**Figure 2.11**). This explains why, with the observed trends in incidence, mortality trends have been stable or decreasing in most countries, except for Irish and Slovenian males (**Table 2.1** and **2.20**).

The most important environmental risk factors for kidney cancer include smoking, obesity and possibly hypertension. The observed trends in incidence therefore reflect of the generally decreasing smoking prevalence rates of European males, and increasing rates of obesity prevalence. For females, the patterns of risk factor prevalence differ strongly by European region, explaining the large variation in incidence, mortality and survival patterns (**Table 2.17b**). Previously it was believed that coffee and tea consumption would increase the risk of kidney cancer, but this has not been confirmed, except possibly for cancers of the renal pelvis and urether.[37]

Bladder cancer (C67)

In the most recent period, incidence of bladder cancer varied across Europe from 10 (Northern Ireland) to 29 per 100,000 (Denmark, Austria, Italy and Spain). Trends in incidence are heavily influenced by changes in coding practices (including in situ carcinomas or not). These coding practices also influenced absolute levels of incidence and may explain part of the differences between countries. It is better to interpret trends in mortality rates, as these did not suffer from this problem.

Mortality trends decreased throughout Europe for males. Female mortality patterns differed throughout Europe, mostly decreasing or remaining stable with the exception of Poland, where mortality rates increased significantly (**Table 2.18a**). Five-year survival remained largely stable in Europe (**Table 2.18b**, **21.8c**).

Table 2.17a | Trends in incidence of and mortality from kidney cancer (C64-66, C68) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark[a]	1994-2003[1]	7.7	7.4	0.0 (-1.1, 1.2)	4.8	3.6	-1.7 (-4.5, 1.2)	4.6	4.6	-0.4 (-3.7, 3.0)	2.4	2.8	1.2 (-1.1, 3.4)
	Finland[a]	1994-2005	11.1	8.8	-2.1 (-3.1, -1.0)	6.3	5.7	-1.1 (-1.9, -0.2)	5.2	3.5	-2.4 (-3.8, -1.1)	2.1	2.1	-0.3 (-2.0, 1.4)
	Norway[a]	1996-2005[2]	8.0	9.3	2.3 (1.1, 3.5)	4.8	5.3	0.4 (-1.1, 1.9)	3.7	3.7	-1.8 (-4.1, 0.4)	2.1	1.8	-2.0 (-4.3, 0.3)
	Sweden[a]	1994-2005[2]	8.2	6.2	-1.6 (-2.6, -0.5)	4.9	3.9	-1.3 (-2.5, 0.0)	4.6	3.9	-1.1 (-2.6, 0.3)	2.3	2.3	-1.2 (-2.7, 0.3)
	Ireland	1994-2005[2]	7.6	9.0	2.8 (1.4, 4.2)	3.9	5.8	3.7 (2.4, 5.0)	3.3	4.9	4.1 (1.8, 6.5)	1.7	1.5	-0.3 (-3.1, 2.5)
	UK England & Wales[b]	1995-2004[3]	7.4	8.7	1.6 (1.0, 2.3)	3.6	4.6	2.0 (1.1, 3.0)	3.9	3.9	-0.2 (-0.8, 0.4)	1.9	1.7	-0.5 (-1.8, 0.7)
	UK Northern Ireland	1994-2005	11.1	8.0	-1.0 (-2.7, 0.7)	3.5	4.8	1.5 (-1.1, 4.0)	3.8	3.8	1.3 (-1.2, 3.9)	1.7	2.2	3.2 (-2.0, 8.6)
	UK Scotland[c]	1994-2004[4]	8.5	9.2	0.5 (-0.5, 1.4)	4.9	4.8	0.0 (-1.3, 1.4)	4.3	3.5	-1.1 (-2.5, 0.4)	2.1	2.1	0.7 (-1.0, 2.5)
Western Europe	Austria (Tyrol)	1995-2003	14.0	12.0	-1.6 (-6.2, 3.3)	7.1	6.5	-0.8 (-5.1, 3.7)	5.0	4.0	-2.9 (-5.0, -0.7)	2.5	1.9	-2.2 (-6.6, 2.3)
	France	1994-2000[5]	10.5	12.2	2.5 (2.4, 2.6)	4.7	5.7	3.3 (3.0, 3.6)	4.7	4.4	-0.7 (-1.1, -0.4)	1.9	1.7	-1.1 (-2.4, 0.1)
	Germany (Saarland)	1994-2005	15.4	13.3	-0.6 (-2.7, 1.5)	6.9	6.2	-2.1 (-4.5, 0.4)	6.4	4.1	-1.9 (-5.4, 1.7)	2.4	1.4	-2.3 (-6.7, 2.2)
	Netherlands	1994-2003	10.1	9.5	-0.8 (-1.4, -0.1)	5.7	5.0	-0.9 (-2.2, 0.4)	5.1	5.1	-0.7 (-1.7, 0.3)	2.8	2.3	-1.5 (-2.6, -0.3)
	Switzerland	1993-2003[6]	10.4	10.2	-0.3 (-5.7, 5.5)	5.1	4.5	-1.7 (-8.4, 5.6)	4.3	3.8	-1.7 (-12.1, 10.1)	3.0	3.0	-0.0 (-6.4, 6.8)

Table 2.17a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	7.7	9.8	4.2 (0.8, 7.6)	4.4	5.0	2.5 (-0.8, 5.8)	3.9	5.0	2.1 (-0.2, 4.5)	1.7	2.3	1.5 (-2.1, 5.3)
	Italy (Modena)	1994-2005	14.9	13.8	-0.2 (-2.6, 2.4)	6.6	5.5	0.6 (-3.8, 5.1)	5.7	4.6	-0.9 (-6.2, 4.8)	3.4	1.2	-5.6 (-11.9, 1.1)
	Malta[a]	1994-2005[4]	6.7	5.7	0.7 (-4.0, 5.6)	3.2	3.2	-5.7 (-11.0, -0.0)	3.5	5.6	-1.0 (-6.3, 4.7)	0.3	3.5	8.5 (-1.3, 19.3)
	Slovenia	1994-2003	9.5	9.3	0.5 (-1.1, 2.1)	4.1	4.3	-2.3 (-6.7, 2.4)	3.9	5.6	3.6 (0.2, 7.1)	2.4	1.6	-4.5 (-11.3, 2.8)
	Spain[d]	1994-2002[7]	7.4	8.4	2.3 (-2.1, 7.0)	3.1	3.9	3.8 (-5.3, 13.7)	3.2	3.2	-0.6 (-1.8, 0.7)	1.0	1.2	0.0 (-2.1, 2.2)
Central Europe	Czech Republic	1994-2004	21.8	23.2	0.5 (-0.5, 1.6)	11.9	11.5	-0.6 (-1.6, 0.4)	10.9	9.8	-0.9 (-1.8, -0.0)	5.1	4.3	-1.9 (-2.7, -1.0)
	Lithuania	1993-2004[8]	12.8	17.1	3.3 (0.5, 6.3)	6.6	7.4	3.5 (-28.2, 49.2)	7.6	7.2	-0.7 (-2.3, 1.1)	3.5	3.0	-0.6 (-2.4, 1.3)
	Poland	1994-2004[9]	11.4	9.3	-2.6 (-3.6, -1.5)	5.8	4.8	-2.9 (-4.5, -1.2)	6.0	6.0	-0.1 (-1.5, 1.3)	2.4	2.2	-1.4 (-3.7, 1.0)

[a] Data only valid for C64; [b] Incidence only for England; [c] Data only valid for C64-65; [d] Incidence data only valid for C64-65; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence and mortality for periods 1993-1996, 1997-1999, and 2001-2003; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; [9] Mortality for 1999-2005; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

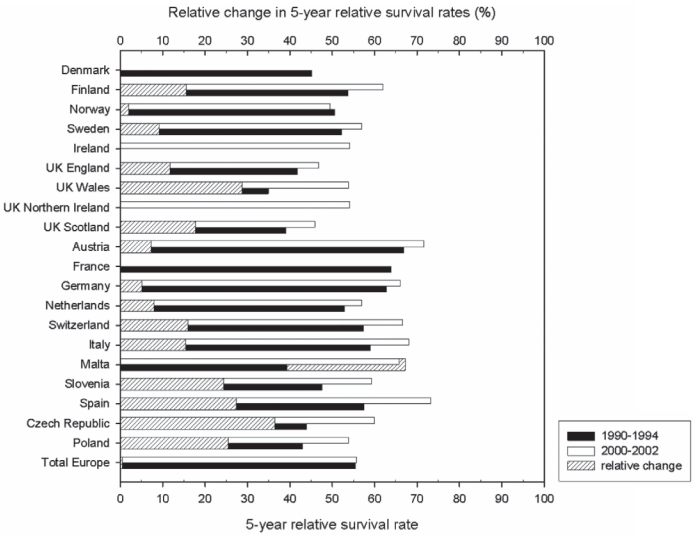


Figure 2.11 | Trends in 5-year age-adjusted relative survival for kidney cancer in Europe (Sources: EUROCARE-3[7] and EUROCARE-4[3])

Table 2.17b | Overview of recent trends in incidence of, survival for and mortality from kidney cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	↑	=	UK-England&Wales	UK-Enlgand&Wales, France[1]
↑	=	=	Norway	-
↑	=	↓	France[1]	-
↑	?	↑	Ireland	-
	?	=	Croatia, Lithuania	Ireland
=	↑	↑	Slovenia	-
=	↑	=	UK-Northern Ireland[2] / Scotland, Germany, Switzerland, Italy, Malta, Spain	Sweden, UK-Northern Ireland[2] / Scotland, Austria, Germany, Switzerland, Italy, Slovenia, Spain
=	=	=	-	Norway
=	?	=	Denmark	Denmark, Croatia, Lithuania
=	↑	↓	Austria, Czech Republic	Netherlands, Czech Republic
↓	↑	=	Sweden, Netherlands, Poland	Finland, Malta, Poland
↓	↑	↓	Finland	-

[1] Survival trend is based on a report of FRANCIM [93]; [2] Survival trend of UK-Northern Ireland is based on a report of the Northern Ireland Cancer Registry[89]

Table 2.18a | Trends in incidence of and mortality from bladder cancer (C67) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark[a]	1994-2003[1]	31.2	28.9	**-1.2** (-2.3, -0.0)	10.0	8.4	-0.6 (-2.1, 0.9)	9.6	7.6	-2.6 (-5.2, 0.1)	3.0	2.9	0.4 (-1.7, 2.6)
	Finland[a]	1994-2005	16.5	14.4	**-1.9** (-2.6, -1.2)	3.7	3.3	**-1.7** (-3.4, -0.0)	4.0	3.8	-0.8 (-1.8, 0.1)	1.3	0.9	-1.1 (-4.0, 1.9)
	Norway[a]	1996-2005[2]	23.8	21.3	-0.3 (-1.2, 0.5)	5.7	6.7	1.1 (0.2, 2.0)	6.0	6.0	-1.0 (-2.2, 0.2)	1.9	1.8	0.0 (-2.7, 2.8)
	Sweden[a]	1994-2005[2]	20.0	18.3	-0.2 (-0.9, 0.4)	5.2	5.1	0.4 (-0.6, 1.3)	4.5	4.3	0.2 (-0.9, 1.4)	1.6	1.6	1.1 (-0.2, 2.4)
	Ireland	1994-2005[2]	14.8	12.1	**-2.3** (-3.2, -1.4)	5.8	4.7	-0.5 (-2.9, 1.8)	4.6	3.3	**-2.4** (-4.6, -0.2)	1.8	1.3	-2.0 (-4.8, 1.0)
	UK England & Wales[b]	1995-2004[3]	19.4	11.9	**-5.6** (-6.7, -4.6)	5.4	3.5	**-5.3** (-6.7, -3.9)	6.7	4.8	**-2.8** (-3.3, -2.3)	2.0	1.7	**-1.0** (-1.6, -0.4)
	UK Northern Ireland	1994-2005	12.3	9.8	-2.1 (-4.3, 0.1)	2.9	2.9	-2.0 (-6.4, 2.6)	4.1	3.7	-2.2 (-5.3, 1.1)	1.5	1.4	-3.2 (-7.8, 1.7)
	UK Scotland	1994-2004[4]	24.9	11.9	**-8.6** (-11.0, -6.1)	7.3	4.3	**-7.9** (-11.2, -4.5)	6.9	5.3	**-2.8** (-3.6, -2.0)	2.5	1.8	**-2.9** (-4.2, -1.6)
Western Europe	Austria (Tyrol)[c]	1995-2003	29.1	29.5	1.7 (-4.8, 8.5)	6.8	5.6	3.8 (-4.7, 13.0)	5.3	4.2	-2.0 (-4.5, 0.6)	1.7	1.4	-2.1 (-10.5, 7.1)
	France	1994-2000[5]	17.8	18.3	**0.5** (0.4, 0.7)	2.4	2.3	**-0.9** (-1.5, -0.3)	6.6	5.9	**-1.4** (-2.7, -0.0)	1.1	1.0	-1.4 (-3.0, 0.3)
	Germany (Saarland)	1994-2005	14.3	14.1	0.4 (-1.7, 2.6)	4.0	3.9	0.1 (-2.6, 3.0)	6.2	3.4	**-5.7** (-9.1, -2.3)	1.3	0.9	-2.6 (-7.1, 2.0)
	Netherlands	1994-2003	15.1	13.5	**-1.1** (-1.9, -0.3)	3.1	3.2	0.9 (-0.7, 2.5)	6.3	5.6	**-1.3** (-2.3, -0.3)	1.6	1.7	1.0 (-0.9, 2.9)
	Switzerland	1993-2003[6]	13.2	12.6	-0.6 (-2.4, 1.3)	3.2	3.0	**-0.9** (-1.4, -0.3)	5.3	4.4	**-2.4** (-4.4, -0.4)	1.5	1.4	-1.5 (-4.3, 1.5)

Table 2.18a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	14.3	14.4	2.3 (-1.5, 6.3)	2.4	3.2	**4.6** (1.0, 8.4)	6.3	6.1	0.1 (-1.7, 1.9)	1.0	1.2	3.1 (-0.7, 6.9)
	Italy (Modena)	1994-2005	32.3	28.9	-0.8 (-2.1, 0.5)	6.7	6.9	0.1 (-5.5, 6.0)	9.8	5.0	**-5.7** (-9.3, -1.8)	2.0	2.2	-3.0 (-13.5, 8.7)
	Malta	1994-2005[4]	30.5	19.4	**-6.2** (-9.5, -2.9)	7.5	3.4	-5.6 (-11.6, 0.9)	10.2	7.9	-3.3 (-8.7, 2.3)	4.2	1.1	-10.1 (-48.4, 56.5)
	Slovenia	1994-2003	10.4	10.6	-1.9 (-5.1, 1.5)	2.7	2.9	-2.2 (-7.6, 3.4)	6.7	6.0	-0.0 (-2.4, 2.5)	1.3	1.8	-0.4 (-6.9, 6.5)
	Spain[d]	1994-2002[7]	29.7	29.4	-0.2 (-3.9, 3.7)	3.7	3.8	0.0 (-4.5, 4.8)	8.7	8.4	-0.2 (-0.9, 0.5)	1.2	1.1	-0.1 (-1.8, 1.6)
Central Europe	Czech Republic	1994-2004	18.0	21.5	**1.2** (0.6, 1.8)	4.3	6.1	**2.4** (1.4, 3.5)	7.5	6.8	-1.1 (-2.5, 0.2)	1.5	1.8	1.1 (-0.6, 2.8)
	Lithuania	1993-2004[8]	12.7	15.7	3.1 (-3.5, 10.1)	2.2	3.1	5.0 (-25.0, 47.0)	8.6	6.9	**-1.6** (-3.0, -0.2)	1.1	1.0	-0.3 (-2.9, 2.4)
	Poland	1994-2004[3]	15.6	16.0	-0.5 (-1.5, 0.5)	2.8	3.0	-0.2 (-2.0, 1.7)	8.3	8.0	0.2 (-0.6, 0.9)	1.1	1.3	**1.1** (0.3, 1.9)

[a] Data valid for C65-68 + D09.0 + D41.4; [b] Incidence only for England; [c] Inclusive in situ carcinomas; [d] Incidence data valid for C66-68; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence for periods 1993-1996, 1997-1999, and 2001-2003 and mortality for 1995-2004; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

Table 2.18b | Trends in 5-year relative survival for bladder cancer in Europe[1]

			5-year relative survival			5-year relative survival		
	Country	Period	males	females	Period	males	females	Trend in survival
Northern Europe	Finland[2]	-	-	-	2003-2005	73.0	73.0	?
	Norway[2]	1991-1995	73.7	63.5	1996-2000	73.3	65.6	= / ↑
	UK England&Wales[3]	1991-1995	64.0	59.0	2000-2001	66.0	57.0	=
	UK Northern Ireland[3]	1993-1996	57.5	41.5	2001-2004	59.3	47.2	= / ↑
	UK Scotland[3]	1992-1996	70.0	61.0	1997-2001	73.3	62.8	↑ / =
Western Europe	France[4]	1992-1994	56.0	55.0	1995-1997	57.0	54.0	=
	Germany (Saarland)	-		-	2000-2002		58.2	?
	Netherlands (Amsterdam)[4]	1993-1996		56.0	2001-2005		55.0	=
	Netherlands (Eindhoven)[5]	1990-1994		38.0	2000-2002		33.0	↓
	Switzerland (Geneva)[3]	1990-1994	58.0	58.0	1994-1998	58.0	51.0	= / ↓
Southern Europe	Italy (Modena)[3]	1990-1997	77.0	69.0	1998-2005	78.0	80.0	= / ↑
	Italy[3]				1995-1999	72.0	69.0	?
	Slovenia[3]	1993-1997	50.0	50.0	1998-2002	48.0	49.0	=
Northern Europe	Czech Republic[3]	-	-	-	1995-1999	73.0	-	?
Total Europe		1990-1994[6]		69.0	1995-1999[7]		65.8	↓

Data reported by individual cancer registries or consortia of cancer registries (sources are shown in Table 1); [2] Data valid for C66-68; [3] Data valid for C67; [4] Data valid for invasive bladder cancer (C67); [5] Data valid for C67, exclusive Ta/Tis; [6] Data reported by the EUROCARE-3 study [117]; [7] Data reported by the EUROCARE-4 study [9]

Table 2.18c | Overview of recent trends in incidence of, survival for and mortality from bladder cancer in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	=	↓	France	-
↑	?	=	Czech Republic	Croatia, Czech Republic
=	↑	=	-	Norway, UK-Northern Ireland, Italy
=	=	=	Norway, UK-Northern Ireland, Slovenia	Slovenia
=	=	↓	Switzerland, Italy	-
=	=/↓	=	-	Netherlands
=	?	↑	-	Poland
=	?	=	Sweden, Austria, Croatia, Spain, Poland	Denmark, Sweden, Ireland, Austria, Germany, Malta, Spain, Lithuania
=	?	↓	Germany, Lithuania	-
↓	↑	↓	UK-Scotland	
↓	=	=	-	France
↓	=	↓	UK-England&Wales	UK-England&Wales / Scotland
↓	↓	=	-	Switzerland
↓	=/↓	↓	Netherlands	-
↓	?	=	Denmark, Finland, Malta	Finland
↓	?	↓	Ireland	-

The favourable mortality trends in males are partly due to the declines in the smoking prevalence together with reduced occupational exposure to carcinogens. The decreases in females are more difficult to explain, as female smoking prevalence rates increased in many countries but mortality rates remained stable or decreased. Better control of urinary tract infections probably played a role, while the role of diet and other potential urinary tract carcinogens remains undefined.[67]

Despite small improvements in treatment, no improvements in survival were achieved, which is in line with earlier findings for Sweden since the 1970s.[68]

Hodgkin's disease (C81)

In most European countries, incidence and mortality rates of Hodgkin's disease have been stable or slightly decreasing, with the exception of Norwegian, Dutch, Croatian and Slovenian males and English, Croatian and Italian females (**Table 2.19a**). Five-year survival for Hodgkin's disease was between 70% and 80% and has improved in all countries (**Figure 2.12**, **Table 2.19b**).

Table 2.19a | Trends in incidence of and mortality from Hodgkin's disease (C81) in Europe by gender

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Northern Europe	Denmark	1994-2003[1]	2.5	2.9	1.0 (-2.4, 4.6)	1.7	1.8	1.5 (-2.3, 5.3)	0.5	0.2	**-16.4** (-28.5, -2.4)	0.3	0.2	-6.7 (-15.1, 2.5)
	Finland	1994-2005	3.0	2.4	-0.4 (-2.3, 1.4)	1.8	2.6	1.7 (-1.7, 5.2)	0.3	0.3	-3.2 (-9.6,	0.3	0.2	-2.3 (-6.6, 2.1)
	Norway	1994-2005[2]	1.8	2.7	**3.1** (0.5, 5.8)	1.7	2.0	3.0 (-1.5, 7.8)	0.4	0.3	-4.9 (-9.9, 0.5)	0.2	0.1	**-10.8** (-16.2, -5.0)
	Sweden	1994-2005[2]	2.2	1.8	**-1.6** (-2.7, -0.5)	1.4	1.8	1.6 (-0.4, 3.6)	0.4	0.3	-2.5 (-6.0, 1.1)	0.2	0.1	-4.5 (-10.1, 1.5)
	Ireland	1994-2005[2]	2.6	2.2	0.5 (-1.9, 3.0)	1.9	1.9	1.1 (-1.6, 3.8)	0.8	0.3	**-7.7** (-12.3, -3.0)	0.4	0.2	-6.9 (-16.2, 3.3)
	UK England & Wales[a]	1995-2004[3]	2.3	2.5	1.3 (-0.6, 3.3)	1.7	2.0	**1.3** (0.3, 2.4)	0.5	0.3	**-3.1** (-4.9, -1.2)	0.3	0.3	-1.5 (-5.5, 2.7)
	UK Northern Ireland	1994-2005	2.4	3.1	-0.1 (-6.2, 6.4)	1.8	1.8	2.7 (-0.5, 6.0)	0.6	0.4	-3.2 (-9.3, 3.3)	0.4	0.5	-2.9 (-15.4, 11.5)
	UK Scotland	1994-2004[4]	2.4	2.9	0.7 (-2.0, 3.4)	2.1	2.4	2.1 (-0.3, 4.5)	0.7	0.6	-2.4 (-8.6, 4.2)	0.5	0.4	-4.8 (-11.8, 2.7)
Western Europe	Austria (Tyrol)	1995-2003	1.7	1.6	0.2 (-12.3, 14.5)	1.3	1.1	-9.1 (-19.3, 2.4)	0.8	0.0	-68.1 (-92.0, 26.3)	0.0	0.4	**340.0** (57.7, 1129.4)
	France	1994-2000[5]	2.4	2.2	**-1.4** (-2.1, -0.7)	2.0	2.0	0.0 (-0.0, 0.0)	0.4	0.4	-1.1 (-3.3, 1.1)	0.3	0.2	-2.0 (-8.0, 4.4)
	Germany (Saarland)	1994-2005	3.0	2.7	-0.1 (-4.1, 4.2)	0.9	1.5	1.4 (-5.3, 8.6)	0.7	0.6	-1.4 (-13.7, 12.5)	0.0	0.2	4.1 (-33.0, 61.9)
	Netherlands	1994-2003	2.1	2.9	**3.2** (1.6, 4.8)	1.7	1.9	1.1 (-0.3, 2.5)	0.5	0.3	-3.0 (-8.2, 2.5)	0.4	0.1	**-9.1** (-16.0, -1.7)
	Switzerland	1993-2003[6]	2.8	2.7	-0.5 (-17.2, 19.5)	2.2	2.3	0.6 (-3.4, 4.8)	0.5	0.2	**-11.5** (-15.3, -7.6)	0.3	0.2	-5.4 (-34.6, 36.9)

Table 2.19a | *Continued*

			Incidence						Mortality					
			Males			Females			Males			Females		
	Country	Period	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)	WSR start	WSR end	EAPC* (95% CI)
Southern Europe	Croatia	1994-2004	1.2	2.6	**11.3** (3.4, 19.9)	1.3	2.0	**8.6** (0.0, 18.0)	0.7	0.3	-6.6 (-13.8, 1.1)	0.5	0.4	-3.0 (-14.9, 10.6)
	Italy (Modena)	1994-2005	1.8	2.8	3.5 (-4.3, 12.0)	2.4	3.4	**7.4** (1.6, 13.5)	0.9	0.3	-11.4 (-22.6, 1.6)	0.1	0.1	-17.8 (-64.4, 89.4)
	Malta	1994-2005[4]	5.1	2.7	-0.4 (-6.8, 6.4)	3.9	1.1	-1.5 (-13.7, 12.4)	0.5	1.0	-19.3 (-51.5, 34.4)	1.2	0.4	-1.2 (-56.2, 123.3)
	Slovenia	1994-2003	1.7	3.1	**5.0** (0.9, 9.2)	2.0	1.9	2.9 (-5.6, 12.2)	1.6	0.6	-8.6 (-22.6, 8.0)	0.2	0.2	-2.3 (-12.4, 9.0)
	Spain	1994-2002[7]	No data			No data			0.6	0.5	**-3.4** (-6.1, -0.7)	0.3	0.2	-2.9 (-7.2, 1.7)
Central Europe	Czech Republic	1994-2004	No data			No data			1.1	0.6	**-7.3** (-9.5, -5.1)	0.9	0.6	**-5.9** (-10.3, -1.2)
	Lithuania	1993-2004[8]	2.8	2.0	**-4.1** (-7.0, -1.2)	2.5	1.9	-1.4 (-32.0, 43.0)	1.3	0.9	**-6.7** (-10.3, -2.9)	1.0	0.4	**-7.3** (-12.4, -1.9)
	Poland	1994-2004[3]	2.2	2.0	-0.3 (-2.0, 1.4)	1.9	1.9	0.1 (-2.0, 2.1)	1.3	0.7	**-6.0** (-8.0, -4.0)	0.7	0.4	**-5.9** (-7.8, -4.0)

[a] Incidence only for England; [1] Mortality until 2001; [2] Mortality until 2004; [3] Mortality until 2005; [4] Mortality until 2006; [5] Mortality until 2002; [6] Only average incidence and mortality for periods 1993-1996, 1997-1999, and 2001-2003; [7] Mortality until 2003; [8] Only average incidence for periods 1993-1997, 1998-2000, 2001-2002, and 2003-2004; * EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

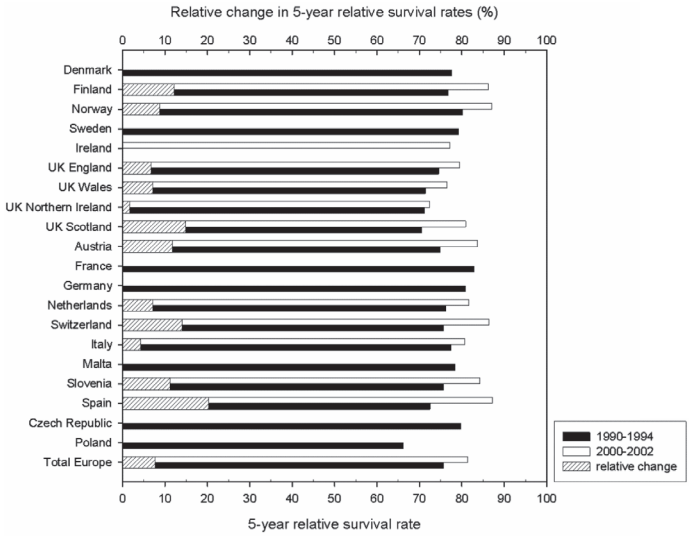


Figure 2.12 | Trends in 5-year age-adjusted relative survival for Hodgkin's disease in Europe (Sources: EUROCARE-3[9] and EUROCARE-4[3])

Table 2.19b | Overview of recent trends in incidence of, survival for and mortality from Hodgkin's disease in Europe

Incidence	Survival	Mortality	Countries	
			Males	**Females**
↑	↑	=	Norway, Netherlands, Slovenia	UK-England&Wales, Italy
↑	?	=	Croatia	Croatia
=	↑	↑	-	Austria
=	↑	=	Finland, UK-Scotland, Austria, Italy	Finland, UK-Scotland, Switzerland, Slovenia
=	↑	↓	UK-England&Wales, Switzerland	Norway, Netherlands
=	=	=	UK-Northern Ireland	UK-Northern Ireland, France[1]
=	?	=	Germany, Malta	Denmark, Sweden, Ireland, Germany, Malta
=	?	↓	Denmark, Ireland, Poland	Lithuania, Poland
↓	=	=	France[1]	-
↓	?	=	Sweden	-
↓	?	↓	Lithuania	-
?	↑	=	-	Spain
?	↑	↓	Spain	-
?	?	↓	Czech Republic	Czech Republic

[1] Survival trend is based on a report of FRANCIM[93]

Table 2.20 | Summary of factors which can influence trends in incidence, survival and mortality

Tumour site	Main risk factors	Early detection & screening	Classification	Subsite / subtype	Health care / treatment
Oral cavity & pharynx	smoking, alcohol, HPV infection	-	-	oral cavity, oro-, naso-, and hypopharynx	-
Oesophagus	smoking, alcohol, obesity	-	-	squamous cell carcinoma → adenocarcinoma, proximal → distal	regionalization of surgery, preoperative chemotherapy
Stomach	food preservation, smoking, vitamine C, HP infection	endoscopy	-	non-cardia → cardia, distal → proximal	-
Colorectum	diet: sugar-rich, fiber-poor, red and processed meat	endoscopy, polypectomy, screening - also of familial HNPCC	-	ascending ↑, sigmoid ↑, rectum =	patient management, TME surgery, (pre-operative) radiotherapy
Pancreas	smoking	-	-	-	regionalization
Larynx	smoking, alcohol	-	-	supraglottis vs. glottis	regionalization
Lung	smoking	screening	-	small cell vs. non-small cell, adenocarcinoma ↑	systemic treatment of small cell
Skin melanoma	intermittent sun exposure, light skin phototype	screening, familial (FAMMM), awareness ↑, skin self- examination	-	trunk ↑, limbs ↑, superficial spreading ↑	improved staging
Breast	age at first childbirth ↑, oral contraceptive use, hormone replacement therapy, physical activity, obesity, alcohol	screening – also for familial breast cancer	-	lobular =, ductal ↑, in situ ↑, stage I ↑	improved staging & treatment
Corpus uteri	menopausal status, obesity, tamoxifen use, estrogen replacement therapy, nulliparity, oral contraceptive use	screening of breast cancer patients	-	-	-
Cervix	HPV infection, obesity, oestrogen replacement therapy, nulliparity, oral contraceptive use	screening	-	adenocarcinoma =, squamous cell ↓	-

Table 2.20 | *Continued*

Tumour site	Main risk factors	Early detection & screening	Classification	Subsite / subtype	health care / treatment
Ovary	obesity, oestrogen replacement therapy, no oral contraceptive use, late age at last birth	-	-	-	surgery management and regionalization
Prostate	obesity	PSA testing	-	-	-
Testis	low birth weight, low birth order, maternal age ↑, maternal smoking during pregnancy, cryptorchidism	awareness ↑	-	seminoma → non-seminoma	cis-platin chemotherapy
Kidney	obesity, smoking, hypertension	echography ↑	-	parenchyma vs. pelvis	-
Bladder	smoking, occupational exposure to aromatic amines	surveillance among patients with superficial disease	changes in coding practices	-	-
Hodgkin's disease	poor immunity, EBV infection	-	-	-	better staging and treatment

The observed incidence and mortality trends are in accordance with previous reports on trends in Hodgkin's disease for all ages [69] and children.[70] Although there is much unclearness regarding the aetiology of Hodgkin's disease, some factors have been identified to contribute to the risk, including poor immunity (organ transplant patients, HIV patients) and Epstein Barr virus infection. Over time, new prognostic systems were developed stratifying patients into early stages (more or less favourable or intermediate), advanced stages and delivering effective chemotherapy suited for the individual tumour characteristics.[71] The combination of improved staging and more appropriate chemotherapy resulted in the observed improvements in survival rates.

DISCUSSION

This study provides the most recent available overview of the burden of cancer in Europe. It is one of the few publications combining incidence, mortality and survival statistics of cancer. This combination is important in order to correctly interpret (trends in) cancer rates: has real progress been made or are we looking at artefacts? Observed increases in cancer incidence for example, might be real, i.e. that there are more cancer patients because of increasing risks, or they might be due to improvements in the completeness of the cancer registry, changes in diagnostic criteria, or effects of early detection methods such as population screening (**Table 2.1**). Likewise, improving cancer survival could be due to better treatment, improvements in treatment effectiveness because of earlier diagnosis, diagnosis of patients that would otherwise have never had clinical disease (i.e. lead time bias), or better treatment of co-morbidity.[4-6]

We observed the highest incidence of breast, prostate, testicular cancer and melanomas in Northern and Western Europe. However, cancers of the lung, cervix and stomach were more common in the South and Central parts of Europe. Within Northern Europe, for many tumours, we observed a distinction between the Scandinavian countries (excluding Denmark), and the United Kingdom and Denmark, with higher rates for most cancers in the latter two countries.

During the past decade, many changes in the occurrence, survival and mortality of cancer have occurred. Some of the cancer types included in this study showed very mixed patterns for incidence, such as corpus uteri and kidney cancers. Rates

for colorectal cancer were either stabilising or increasing, presumably due to changing dietary habits, increasing obesity and decreasing physical activity levels. Prostate, testicular cancer, and melanomas, female lung and breast cancer showed persistently increasing trends in incidence throughout Europe, the latter two due to the increasing prevalence of smoking females and changing reproductive patterns. Incidence trends of pancreatic, laryngeal, ovarian and bladder cancer were stabilising or decreasing. The most consistent decreases in incidence were observed for gastric, cervical, and male lung cancer due to improved food preservation methods, screening and decreased male smoking rates.

Improvements of cancer survival were observed for oral cavity and pharyngeal, stomach, lung, corpus uteri, ovarian and kidney cancer and for Hodgkin's disease throughout Europe. For colorectal, melanoma, breast and prostate cancer improvements were seen in all countries, with the exception for Austrian melanoma patients. For Austria, this is probably due to problems with the data quality. Over time, the survival rates for patients with a cervical cancer have decreased in most countries. This is likely due to a worsening case-mix, leading to decreasing survival.[51] Conversely, survival improved in Poland where rates were historically very low and have recently been catching up to reach levels comparable with the other European countries. Possible explanations for changes in incidence, survival and mortality are described in the results section of this paper and summarized in **Table 2.20**.

Europe is a large continent, with large variations in lifestyle patterns and healthcare systems.[6,72] Variation in healthcare systems has large influence on the possibility of the population to attend programs for early detection (i.e. active/ voluntarily invitation) and access to care and treatment.

Some of the improvements in cancer survival may be due to earlier detection (breast, prostate) and/or increasing proportions of elderly patients receiving new or more aggressive treatment.[73] Cervical cancer screening, on the other hand, resulted in poorer survival rates: the effect of screening is that less cancers develop, but those which do develop are often more aggressive. For some tumours, such as rectal tumours and Hodgkin's lymphomas, staging procedures have improved treatment efficacy and survival rates. In many countries, cancer care has been regionalised, resulting in more specialised oncologists and, possibly, more optimal care for cancer patients and an improved survival.

As presented in **Table 2.2**, the results in this paper are based on many sources of information, national or (combinations of) regional data, different time periods,

and different population sizes. Some registries cover relatively small populations, causing fluctuating numbers of cancer patients and rates. Some registries seemed to have faced temporary problems with the completeness of the registry; in Lithuania for example, in the period 1998-2000 there seems to be an under-registration among females in comparison with the period(s) before and after these years (see on-line tables). In Croatia, it is known that the marked increase in incidence of most sites in 1999 was due to the introduction of a new (improved) population data source. The effects of these characteristics on cancer incidence, mortality and survival rates are extensively described elsewhere.[6]

We used world-standardised rates (WSR) because the available incidence and mortality rates are usually standardised to this population. This age-standardisation facilitates comparisons between countries, but the reader should keep in mind that the world standard population is a much younger population than the population of an average European country. The observed trends using WSRs therefore mainly represent changes in incidence and/or mortality in the middle-aged population groups. European standardised rates would better illustrate changes at older ages, although the currently used European standard population is already younger than many real European populations.

The presented estimated annual percentages change were based on joinpoint modelling of the rates – not on the original population numbers, since they were not readily available for each registry. The EAPCs and their confidence intervals should therefore be interpreted with caution.

Survival rates presented for oral cavity and pharyngeal, laryngeal, oesophageal, pancreatic, ovarian, testis and bladder cancer cannot be directly compared between countries. They were not standardised for age, or encompass different time periods.

CONCLUSIONS

The biggest achievement in cancer surveillance over the past 10 years, seems to have been the large reductions in smoking prevalence among males, hopefully soon to be followed by females.[38] Lung cancer is still a very commonly diagnosed cancer, with a very poor survival, hence primary prevention by anti-smoking measures remains of utmost importance. Obesity, an upcoming problem, should be the target for prevention of oesophageal, breast, corpus uteri, cervical, prostate, and kidney

cancer.[74] Substantial improvements in cancer survival have been achieved, mainly in Southern and Central Europe, where survival rates have been traditionally lagging behind compared to the rest of Europe.[6]

Variations in policies for (mass-) screening, other measures for early detection of cancer, access to health care, and treatment policies exist within Europe. These variations are largely reflected in the observed incidence, mortality and survival rates, which should be interpreted simultaneously in order to really understand whether increased survival is merely due to lead time bias, improvements in treatment, changing patient and tumour characteristics, or a combination of the above.[6] In order to plan health services, policy makers of each country or region should make a choice of the options for primary and secondary prevention, treatment and health care organisation based on results, available budgets and infrastructure.[74] The results of this study may serve as a basis for these decisions.

Acknowledgements

The authors thank M. Dalmas (Malta National Cancer Registry), A. Znaor (Croatian National Cancer Registry), J. Borras (Institut Catala d'Oncologia) for the information that they provided. Some of the data used in this paper were taken from the EUROCIM database of the European Network of Cancer Registries [75]. We thank the individual cancer registries for making their data publicly available; their work on collecting and presenting the data is gratefully acknowledged.

The work on this research was performed within the framework of the project 'Progress against cancer in the Netherlands since the 1970's?' (Dutch Cancer Society grant EMCR 2006-3489) and the Eurocadet project (European Commission FP-6 grant SP23-CT-2005-006528).

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55(2):74-108.
2. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol.* 2007;18(3):581-592.
3. Verdecchia A, Francisci S, Brenner H, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol.* 2007;8(9):784-96.
4. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? *Jama.* 2000;283(22):2975-2978.
5. Sant M, Francisci S, Capocaccia R, Verdecchia A, Allemani C, Berrino F. Should we use incidence, survival or mortality to assess breast cancer trends in European women? *Nat Clin Pract Oncol.* 2006;3(5):228-229.
6. Coleman MP, Gatta G, Verdecchia A, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann Oncol.* 2003;14 Suppl 5:v128-149.
7. EUROCARE-3. *http://www.eurocare.it/CDEu3/Index.htm "Survival of cancer patients in Europe: The EUROCARE-3 study".* (accessed October 2007).
8. Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990-94-results and commentary. *Ann Oncol.* 2003;14 Suppl 5:V61-V118.
9. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. *Lancet Oncol.* 2007;8(9):773-783.
10. Chin D, Boyle GM, Porceddu S, Theile DR, Parsons PG, Coman WB. Head and neck cancer: past, present and future. *Expert Rev Anticancer Ther.*2006;6(7):1111-1118.
11. Vizcaino AP, Moreno V, Lambert R, Parkin DM. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. *Int J Cancer.* 2002;99(6):860-868.
12. Crane LM, Schaapveld M, Visser O, Louwman MW, Plukker JT, van Dam GM. Oesophageal cancer in The Netherlands: Increasing incidence and mortality but improving survival. *Eur J Cancer.* 2007;43(9):1445-1451.
13. Levi F, Te VC, Randimbison L, La Vecchia C. Trends in survival for both histologic types of esophageal cancer in Switzerland. *Int J Cancer.* 2004;108(4):638-639.
14. van Lanschot JJ, Rutten HJ, Boom RP, Gouma DJ. [Importance of regional surgery networks]. *Ned Tijdschr Geneeskd.* 2000;144(24):1148-1152.
15. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. *Eur J Cancer.* 1997;33(7):1075-1107.
16. Prinz C, Schwendy S, Voland P. H pylori and gastric cancer: shifting the global burden. *World J Gastroenterol.* 2006;12(34):5458-5464.
17. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol.* 2006;20(4):633-649.
18. Remontet L, Esteve J, Bouvier AM, et al. Cancer incidence and mortality in France over the period 1978-2000. *Rev Epidemiol Sante Publique.* 2003;51(1 Pt 1):3-30.
19. Verdecchia A, Corazziari I, Gatta G, et al. Explaining gastric cancer survival differences among European countries. *Int J Cancer.* 2004;109(5):737-741.

20. Hartgrink HH, Bonenkamp HJ, van de Velde CJ. Influence of surgery on outcomes in gastric cancer. *Surg Oncol Clin N Am.* 2000;9(1):97-117, vii-viii.

21. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. *Int J Cancer.* 2001;91(3):421-430.

22. Lopez-Abente G, Pollan M, Vergara A, et al. Age-period-cohort modeling of colorectal cancer incidence and mortality in Spain. *Cancer Epidemiol Biomarkers Prev.* 1997;6(12):999-1005.

23. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer.* 2006;118(3):728-738.

24. Rougier P, Mitry E. Epidemiology, treatment and chemoprevention in colorectal cancer. *Ann Oncol.* 2003;14 Suppl 2:ii3-5.

25. Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, Manfredi S, Dancourt V, Faivre J. Colon cancer in France: evidence for improvement in management and survival. *Gut.* 2002;51(1):60-64.

26. Chessin DB, Guillem JG. Surgical issues in rectal cancer: a 2004 update. *Clin Colorectal Cancer.* 2004;4(4):233-240.

27. Engholm G, Kejs AM, Brewster DH, et al. Colorectal cancer survival in the Nordic countries and the United Kingdom: Excess mortality risk analysis of 5 year relative period survival in the period 1999 to 2000. *Int J Cancer.* 2007;121(5):1115-1122.

28. Levi F, Lucchini F, Negri E, La Vecchia C. Pancreatic cancer mortality in Europe: the leveling of an epidemic. *Pancreas.* 2003;27(2):139-142.

29. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control.* 2000;11(10):915-923.

30. Qiu D, Kurosawa M, Lin Y, et al. Overview of the epidemiology of pancreatic cancer focusing on the JACC Study. *J Epidemiol.* 2005;15 Suppl 2:S157-167.

31. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology.* 2007;132(6):2208-2225.

32. Lo AC, Soliman AS, El-Ghawalby N, et al. Lifestyle, occupational, and reproductive factors in relation to pancreatic cancer risk. *Pancreas.* 2007;35(2):120-129.

33. Michaud DS. Epidemiology of pancreatic cancer. *Minerva Chir.* 2004;59(2):99-111.

34. Higginson J, Muir CS, Muñoz N. *Human cancer: epidemiology and environmental causes*. Cambridge: Cambridge University Press; 1992.

35. Talamini R, Bosetti C, La Vecchia C, et al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. *Cancer Causes Control.* 2002;13(10):957-964.

36. Tuyns AJ, Esteve J, Raymond L, et al. Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). *Int J Cancer.* 1988;41(4):483-491.

37. Schottenfeld D, Fraumeni JF. *(eds). Cancer epidemiology and prevention*. 3 ed. New York, USA: Oxford University Press; 2006.

38. Bosetti C, Levi F, Lucchini F, Negri E, La Vecchia C. Lung cancer mortality in European women: recent trends and perspectives. *Ann Oncol.* 2005;16(10):1597-1604.

39. de Vries E, Bray F, Coebergh JWW, Parkin DM, ENCR. Changing Epidemiology of malignant cutaneous melanoma in Europe 1953-1997: rising trends in incidence and mortality, but recent stabilisations in Western Europe and decreases in Scandinavia. *Int J Cancer.* 2003;107(1):119-126.

40. Stratigos A, Nikolaou V, Kedicoglou S, et al. Melanoma/skin cancer screening in a Mediterranean country: results of the Euromelanoma Screening Day Campaign in Greece. *J Eur Acad Dermatol Venereol.* 2007;21(1):56-62.

41. de Vries E, Houterman S, Janssen-Heijnen M, et al. Up-to-date survival estimates and historical trends of cutaneous malignant melanoma in the south-east of The Netherlands. *Ann Oncol.* 2007;18:1110-1116.
42. International Agency for Research on Cancer. *IARC Handbooks of Cancer Prevention. Volume 7: Breast cancer screening.* Vol 7. Lyon: IARC*Press*; 2002.
43. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 European countries. *Eur J Cancer.* 2003;39(12):1718-1729.
44. Eurostat. A statistical view of the life of women and men in the EU25. *Eurostat News Release.* 2006(29).
45. Soerjomataram I, Pukkala E, Brenner H, Coebergh JW. On the avoidability of breast cancer in industrialized societies: older mean age at first birth as an indicator of excess breast cancer risk. *Breast Cancer Res Treat.* 2008;111(2):297-302.
46. Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. *Breast Cancer Res Treat.* 2008;107(3):427-430.
47. Glass AG, Lacey JV, Jr., Carreon JD, Hoover RN. Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst.* 2007;99(15):1152-1161.
48. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol.* 2002;55(4):244-265.
49. Arbyn M, Autier P, Ferlay J. Burden of cervical cancer in the 27 member states of the European Union: estimates for 2004. *Ann Oncol.* 2007;18(8):1423-1425.
50. Primic-Zakelj M, Repse-Fokter A. Cervical cancer screening: A Slovenian experience. *Coll Antropol.* Apr 2007;31 Suppl 2:23-26.
51. Nygard M, Daltveit AK, Thoresen SO, Nygard JF. Effect of an antepartum Pap smear on the coverage of a cervical cancer screening programme: a population-based prospective study. *BMC Health Serv Res.* 2007;7:10.
52. Berkers LM, van Ballegooijen M, van Kemenade FJ, et al. [The 1996 revision of the Dutch cervical cancer screening programme: increased coverage, fewer repeat smears and less opportunistic screening]. *Ned Tijdschr Geneeskd.* 9 2007;151(23):1288-1294.
53. Bielska-Lasota M, Inghelmann R, van de Poll-Franse L, Capocaccia R, Group EW. Trends in cervical cancer survival in Europe, 1983-1994: a population-based study. *Gynecol Oncol.* 2007;105(3):609-619.
54. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. *Int J Cancer.* 2005;117(1):123-131.
55. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology and prognostic factors. *Semin Surg Oncol.* 2000;19(1):3-10.
56. Janssen-Heijnen MLG, Louwman MW, van de Poll-Franse LV, et al. *Van meten naar weten. 50 jaar kankerregistratie*. Eindhoven: Comprehensive Cancer Centre South; 2005.
57. Elit L, Bondy SJ, Chen Z, Paszat L. A tale of two time periods: ovarian cancer trends in Ontario. *Curr Oncol.* 2007;14(2):57-60.
58. Engelen MJ, Kos HE, Willemse PH, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer.* 2006;106(3):589-598.
59. Jacobsen R, Moller H, Thoresen SO, Pukkala E, Kjaer SK, Johansen C. Trends in testicular cancer incidence in the Nordic countries, focusing on the recent decrease in Denmark. *Int J Androl.* 2006;29(1):199-204.

60. Bray F, Ferlay J, Devesa SS, McGlynn KA, Moller H. Interpreting the international trends in testicular seminoma and nonseminoma incidence. *Nat Clin Pract Urol.* 2006;3(10):532-543.

61. Verhoeven R, Houterman S, Kiemeney B, Koldewijn E, Coebergh JW. Testicular cancer: Marked birth cohort effects on incidence and a decline in mortality in southern Netherlands since 1970. *Int J Cancer.* 2008;122(3):639-42.

62. Moller H, Skakkebaek NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. *Cancer Causes Control.* 1997;8(6):904-912.

63. Richiardi L, Pettersson A, Akre O. Genetic and environmental risk factors for testicular cancer. *Int J Androl.* 2007;30(4):230-241.

64. Richiardi L, Akre O, Lambe M, Granath F, Montgomery SM, Ekbom A. Birth order, sibship size, and risk for germ-cell testicular cancer. *Epidemiology.* 2004;15(3):323-329.

65. Einhorn LH. Curing metastatic testicular cancer. *Proc Natl Acad Sci U S A.* 2002;99(7):4592-4595.

66. Sant M, Aareleid T, Artioli ME, et al. Ten-year survival and risk of relapse for testicular cancer: a EUROCARE high resolution study. *Eur J Cancer.* 2007;43(3):585-592.

67. Ferlay J, Randi G, Bosetti C, et al. Declining mortality from bladder cancer in Europe. *BJU Int.* 2008;101(1):11-19.

68. Malmstrom PU. Why Has the Survival of Patients with Bladder Cancer Not Improved? *BJU Int.* 2008;101(3):267-269.

69. Adamson P, Bray F, Costantini AS, Tao MH, Weiderpass E, Roman E. Time trends in the registration of Hodgkin and non-Hodgkin lymphomas in Europe. *Eur J Cancer.* 2007;43(2):391-401.

70. Brenner H, Coebergh J, Parkin D, et al. Up-to-date monitoring of childhood cancer long-term survival in Europe: leukaemias and lymphomas. *Ann Oncol.* 2007;18(9):1569-1577.

71. Maucort-Boulch D, Djeridane M, Roy P, Riche B, Colonna P, Andrieu JM. Predictive and discriminating three-risk-group prognostic scoring system for staging Hodgkin lymphomas. *Cancer.* 2007;109(2):256-264.

72. Soerjomataram I, de Vries E, Pukkala E, Coebergh JW. Excess of cancers in Europe: a study of eleven major cancers amenable to lifestyle change. *Int J Cancer.* 2007;120(6):1336-1343.

73. Gondos A, Holleczek B, Arndt V, Stegmaier C, Ziegler H, Brenner H. Trends in population-based cancer survival in Germany: to what extent does progress reach older patients? *Ann Oncol.* 2007;18(7):1253-1259.

74. Boyle P, Autier P, Bartelink H, et al. European Code Against Cancer and scientific justification: third version (2003). *Ann Oncol.* 2003;14(7):973-1005.

75. European Network of Cancer Registries. *Eurocim version 4.0. European incidence database V2.3, ICD-10 dictionary (2001) and European mortality database V2.3 (2001)* Lyon 2001.

76. Engholm G, Storm HH, Ferlay J, et al. *http://www-dep.iarc.fr/nordcan.htm* "The NORDCAN database". Association of the Nordic Cancer Registries. (accessed October 2007).

77. Finnish Cancer Registry. *http://www.cancerregistry.fi/eng/statistics/9-37.html "Newest survival rates".* (accessed October 2007).

78. Cancer Registry of Norway. *Cancer in Norway 2005: Cancer incidence, mortality, survival and prevalence in Norway.* Oslo: Cancer registry of Norway;2006.

79. Statistics - Health and Diseases. *Cancer incidence in Sweden 2005.* Stockholm: The National Board of Health and Welfare, Centre for Epidemiology;2007.

80. National Cancer Registry Ireland. *http://www.ncri.ie/data.cgi/index.shtml.* (accessed September 2007).

81. Walsh PM, Comber H. *Patterns of care and survival of cancer patients in Ireland 1994 to 2001: time-trends and regional variation for breast, colorectal, lung and prostate cancer.* Cork: National Cancer Registry;2006.

82. Central Statistics Office Ireland. *Report on Vital Statistics 2004.* Cork: Central Statistics Office;2006.

83. Central Statistics Office Ireland. *Report on Vital Statistics 2003.* Cork: Central Statistics Office;2005.

84. Office for National Statistics. *http://www.statistics.gov.uk/statbase/Product.asp?vlnk=8843 "Cancer Statistics: Registration Series MB1".* (accessed July 2007).

85. WHO Health Organization Statistical Information System. *WHO mortality database.* Geneva: World Health Organization, 2006.

86. Cancer Research UK. *http://info.cancerresearchuk.org/cancerstats/survival/siteandsex/ "Cancer survival statistics by cancer site".* (accessed October 2007).

87. Office for National Statistics. *http://www.statistics.gov.uk/statbase/Product.asp?vlnk=618 "Mortality Statistics: Cause (Series DH2)".* (accessed August 2007).

88. Northern Ireland Cancer Registry. *http://www.qub.ac.uk/research-centres/nicr/Data/ OnlineStatistics/ "Online Statistics".* (accessed October 2007).

89. Northern Ireland Cancer Registry. *Survival of cancer patients in Northern Ireland:1993-2004.* Belfast: Northern Ireland Cancer Registry;2007.

90. Information Services Directorate. *http://www.isdscotland.org/isd/cancer-statistics. jsp?pContentID=183&p_applic=CCC&p_service=Content.show& "Cancer Statistics".* (accessed October 2007).

91. Institut für klinische Epidemiologie der TILAK *http://www.iet.at/index.php?id=3085 „Publikationen".* (accessed July 2007).

92. French Institute for Public Health Surveillance. *http://www.invs.sante.fr/estimations_cancer/ index.htm "Estimation of cancer incidence and mortality in France 1978-2000".* (accessed October 2007).

93. FRANCIM. *Survie des patients atteints de cancer en France*. Paris: FRANCIM; 2007.

94. Epidemiologisches Krebsregister Saarland. *http://www.krebsregister.saarland.de/datenbank/ datenbank.html.* (accessed October 2007).

95. Netherlands Cancer Registry. *<http://www.ikcnet.nl/cijfers/index.php?taal=en "NCR data".* Accessed September 2007.

96. Comprehensive Cancer Centre Amsterdam. *http://www.ikcnet.nl/page.php?nav_id=160&regio_ id=117&id=1735 "Overlevingscijfers IKA-regio".* (accessed October 2007).

97. Comprehensive Cancer Centre South. *http://ikz.maatoplossing.nl/ "Data of the Eindhoven Cancer Registry".* (accessed October 2007).

98. Swiss Association of Cancer Registries. *Cancer in Switzerland: Volume 1 - Statistics of Incidence 1985-2003.* Geneva2006.

99. Registre Genevois des Tumeurs. *http://asrt.ch/RGT/ "La publication en bref".* (accessed October 2007).

100. Modena Cancer Registry. *http://www.rtm.unimo.it/eng/pubblicazioni.html "Publications".* (accessed July 2007).

101. Federico M. *Cancer in Modena 1988-2005.* Modena: Modena Cancer Registry;2007.

102. AIRTUM Working Group. Italian cancer figure, report 2007: Survival. *Epidemiologia & Prevenzione.* 2007;31 (suppl 1)(1):1-96.

103. Malta National Cancer Registry, Department of Health and Information. *http://www.sahha. gov.mt/pages.aspx?page=44 "Information and Statistics".* (accessed August 2007).

104. *Cancer incidence in Slovenia 2001.* Ljubljana: Institute of Oncology, Cancer Registry of Slovenia;2004.

105. *Cancer incidence in Slovenia 2002.* Ljubljana Institute of Oncology, Cancer Registry of Slovenia;2005.

106. *Cancer incidence in Slovenia 2003.* Ljubljana: Institute of Oncology, Cancer Registry of Slovenia;2006.

107. Dušek L, Mužík J, Kubásek M, Koptíková J, Žaloudík J, Vyzula R. *http://www.svod.cz/?sec=analyzy&lang=en «Epidemiology of malignant tumors - analyses»*. (accessed October 2007).

108. *Cancer incidence 2004 in the Czech Republic.* Prague: National Oncologic Registry;2007.

109. Lithuanian Cancer Registry. *http://www.is.lt/cancer_reg/* (accessed October 2007).

110. National Cancer Registry Poland. *http://85.128.14.124/krn/english/index.asp "Reports based on data of National Cancer Registry". (*accessed October 2007).

111. Oberaigner W, Mühlböck H, Harrasser L. *Mammakarzinome in Tirol.* Innsbruck: Institut für klinische epidemiologie der TILAK GmbH;2003.

112. Oberaigner W, Mühlböck H, Harrasser L. *Magenkarzinome in Tirol.* Innsbruck: Institut für klinische epidemiologie der TILAK GmbH;2004.

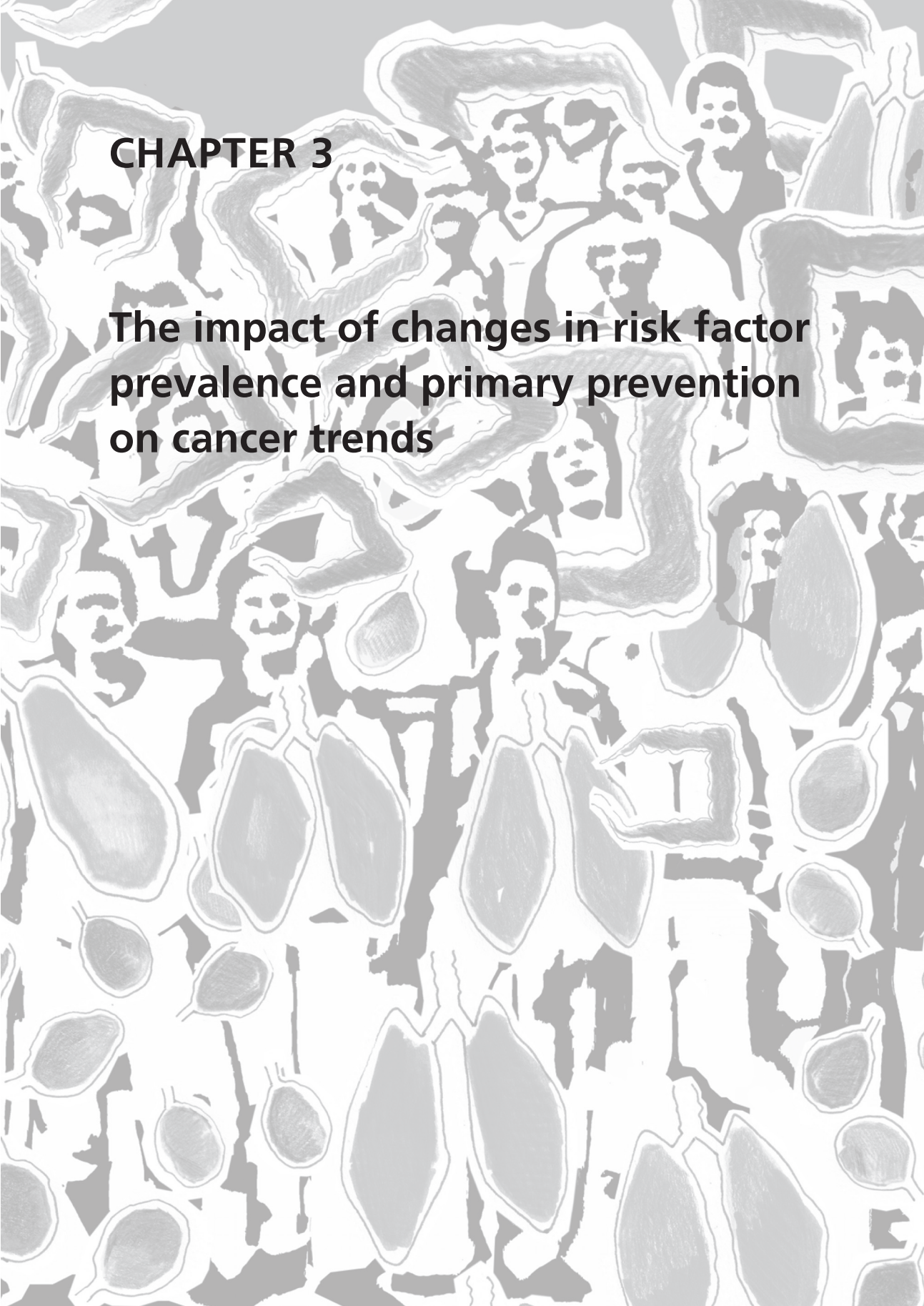
113. Oberaigner W, Mühlböck H, Harrasser L. *Kolorektalen karzinome in Tirol.* Innsbruck: Institut für klinische epidemiologie der TILAK GmbH;2003.

114. Oberaigner W, Mühlböck H, Harrasser L. *Lungenkarzinome in Tirol.* Innsbruck: Institut für klinische epidemiologie der TILAK GmbH;2003.

115. Oberaigner W, Mühlböck H, Harrasser L. *Prostatakarzinome in Tirol.* Innsbruck: Institut für klinische epidemiologie der TILAK GmbH;2003.

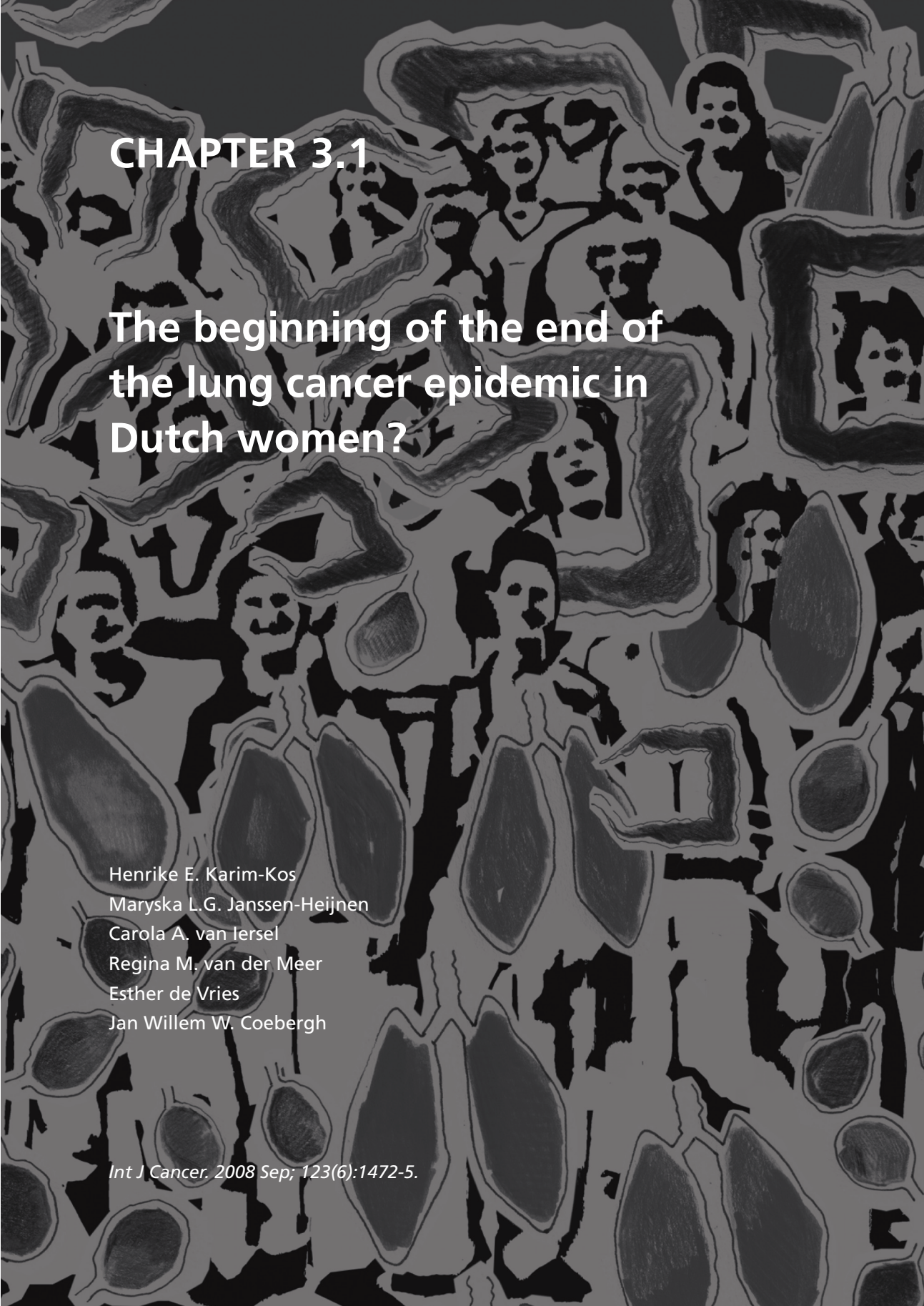
116. Swiss Association of Cancer Registries. *Cancer in Switzerland: Volume 2 - Statistics of Mortality 1985-2003.* Geneva 2006.

117. *http://www.eurocare.it/CDEu3/Index.htm*. Survival of cancer patients in Europe: The EUROCARE-3 study. (accessed August 2007).



CHAPTER 3

The impact of changes in risk factor prevalence and primary prevention on cancer trends



CHAPTER 3.1

The beginning of the end of the lung cancer epidemic in Dutch women?

Henrike E. Karim-Kos
Maryska L.G. Janssen-Heijnen
Carola A. van Iersel
Regina M. van der Meer
Esther de Vries
Jan Willem W. Coebergh

Int J Cancer. 2008 Sep; 123(6):1472-5.

ABSTRACT

In some European countries, female lung cancer mortality and incidence have started to decrease or flatten out, whereas they are still rising in the Netherlands. We present recent mortality and incidence trends of lung cancer and smoking trends in the Netherlands to show the end of the lung cancer epidemic in Dutch women. Lung cancer mortality and incidence rates by gender were analyzed for 4 age groups (20-44, 45-49, 50-54, 55-59) and smoking prevalence rates were examined for women using joinpoint regression and birth cohort analysis. Data on mortality were collected for the period 1960-2006, incidence for the period 1989-2003, and smoking prevalence for the period 1988-2007. Because of decreasing lung cancer mortality and incidence rates among males and dramatically increasing rates among females, rates of young males were surpassed by those of females after the mid-1990s. However, although in young women (20-49) mortality increased with 4-5% per year, it flattened out (no significant in- or decreases) since 1999. Among older women, mortality rates were still increasing markedly. Mortality rates and smoking prevalence tended to decrease in women born after the 1950s. This is the first report suggesting that the lung cancer epidemic in Dutch women is coming to an end. Although the increase in lung cancer incidence and mortality among Dutch women has been one of the most dramatic in Europe, the recent decrease in young women is expected to be followed by a future leveling off or a slight decrease in overall female lung cancer rates.

INTRODUCTION

In the Netherlands, the increase in female lung cancer mortality has been one of the most dramatic in Europe[1] and lung cancer has become the second cause of death from cancer among women since 2000. Lung cancer was responsible for 17% of all female cancer deaths in 2006 and it is likely to become the first within five years.[2] In 2006, 3172 women died from lung cancer, almost nine deaths per day. In contrast to males, with declining rates since the 1980s, the age-standardised (European standard) mortality rate of lung cancer in women has increased dramatically between 1970 and 2006 from 5 to 30 per 100,000 in the Netherlands.[2] Dutch female lung cancer incidence and mortality rates are among the highest in Europe.[3] As smoking prevalence decreased among Dutch women from 40% in the 1970s to 25% in 2007 (**Figure 3.1.1**), the rising incidence and mortality rates are expected to flatten out or decrease, as already observed in Iceland, Ireland, the UK[1] and the USA.[4]

In this short report we present recent age-specific incidence and mortality trends of lung cancer and smoking trends at young and middle age in the Netherlands and suggest the beginning of the end of the lung cancer epidemic in Dutch women.

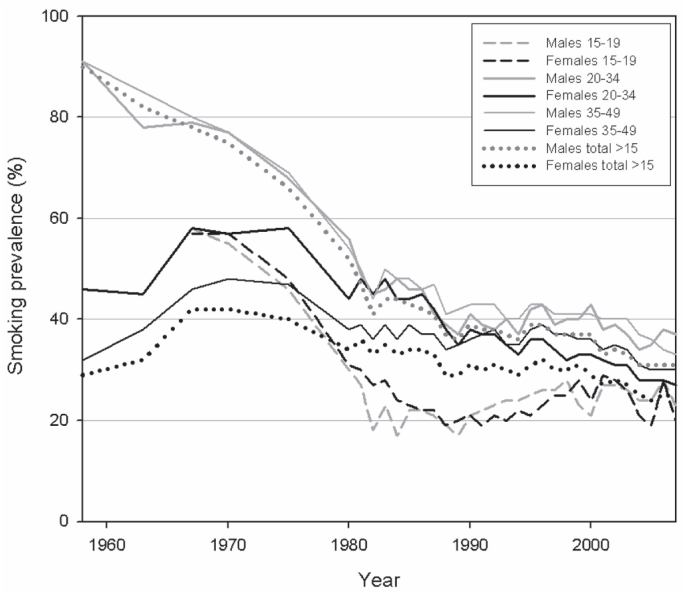


Figure 3.1.1 | Age-specific trends in smoking prevalence for ages>15 by gender in The Netherlands, 1958–2006 (Source: STIVORO[5]).

MATERIAL AND METHODS

Mortality from malignant neoplasms of the trachea, bronchus and lung for the period 1960-2006 were derived from Statistics Netherlands.[2] Four revisions of the International Classification of Diseases (ICD) were used during this period: the seventh (1958-68), eighth (1969-78), ninth (1979-95) and tenth revision since 1996. For the whole period, cancer deaths were recoded according to ICD-codes C33/C34 of the tenth revision of ICD.[6]

Data on lung cancer incidence for the period 1989-2003 were obtained from the nation-wide Netherlands Cancer Registry (www.ikcnet.nl), which consists of 9 regional cancer registries since 1989. The cancer registries receive lists of newly diagnosed cases on a regular basis from the pathology departments, all participating in a nation-wide pathology network (PALGA). In addition, the medical records departments of hospitals provide lists of diagnoses of outpatients and hospitalized patients with a suspected cancer diagnosis. Following this notification, the necessary information of newly diagnosed tumors is abstracted from the medical records by trained tumor registration clerks. Topography is coded according to the International Classification of Diseases of Oncology.[7]

Annual age-specific mortality and incidence rates were calculated for 4 age groups: 20-44, 45-49, 50-54 and 55-59. Rates at ages 20-44 were standardized to the European standard population using the direct method.

Joinpoint regression analysis was used to identify years where a significant change in the mortality trend occurred.[8] The estimated annual percent change (EAPC) and the corresponding 95% confidence interval was calculated for each of those trends by fitting a regression line to the natural logarithm of the rates, using calendar year as regressor variable (i.e., $y = mx + b$ where $y = \ln(\text{rate})$ and x = calendar year, then EAPC = $100 \times (e^m - 1)$). The joinpoint regression models were performed using the Joinpoint Regression Program (version 3.0) from the Surveillance Research Program of the US National Cancer Institute (http://srab.cancer.gov/joinpoint/).

To estimate the effect of birth cohort on trends in mortality of female lung cancer, mortality rates for ages 20-59 were calculated for birth cohorts of 10 years. These 'synthetic' birth cohorts were created based on the year and age of death, using 5-year age and 5-year calendar period analysis.

The effect of birth cohort on smoking trends in women was examined by calculating the smoking prevalence rates for ages 15-64 years by 10-year birth

cohorts. Smoking prevalence data were available for the period 1988-2007 and were collected by STIVORO, the Dutch national expert centre on tobacco prevention.

RESULTS

Figure 3.1.2 shows the dramatic increase of lung cancer mortality among women aged 20-59 in the Netherlands since the 1960s. The same increase was observed in female lung cancer incidence (national incidence data only available since 1989) (**Figure 3.1.3**). As a result of the decreasing male rates and the increasing female rates, male mortality and incidence rates were even surpassed by female rates since the mid-1990s, except for those over age 50. The male-to-female (M:F) mortality rate ratio decreased from 5.0 in 1970 to 0.7 in 2006 for ages 20-44 and from 11 to 0.9 at ages 45-49. Incidence M:F rate ratios were 0.8 for ages 20-44 and 45-49 in 2003.

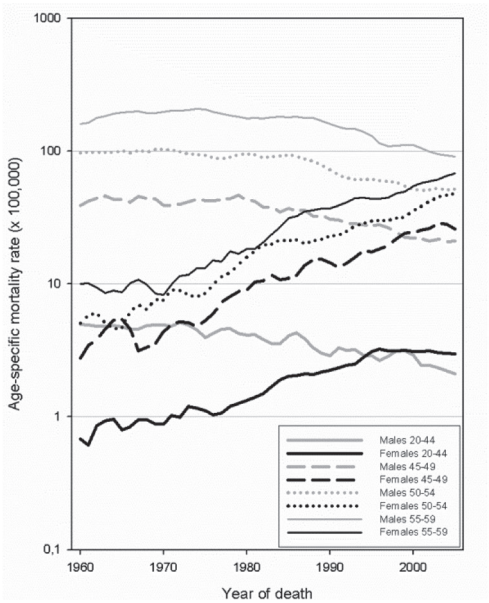


Figure 3.1.2 | Age-specific trends in mortality of lung cancer (3-year moving averages) for ages 20–59 by gender in The Netherlands,1960-2006 (Source: Statistics Netherlands[2])

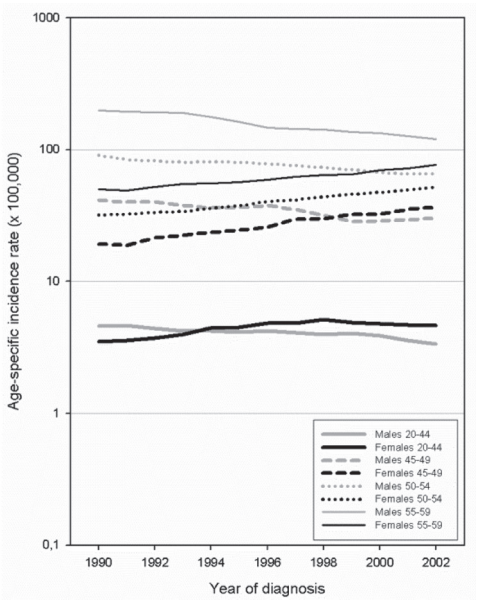


Figure 3.1.3 | Age-specific trends in incidence of lung cancer (3-year moving averages) for ages 20-59 by gender in the Netherlands, 1989-2003 (Source: Netherlands Cancer Registry)

Table 3.1.1 | Results of joinpoint regression analysis of female lung cancer mortality (ages 20-59) in the Netherlands, 1960-2006

	Age-specific mortality rate per 100,000		Joinpoint analysis			
			Trend 1		Trend 2	
Age	1960	2006	Period	EAPC[1] (95% CI)	Period	EAPC[1] (95% CI)
20-44	0.5	3.0	1960-1999	4.3 (3.8, 4.9)	1999-2006	-1.5 (-8.4, 5.8)
45-49	1.5	22.5	1960-2004	5.2 (4.7, 5.7)	2004-2006	-14.1 (-35.4, 14.3)
50-54	5.6	49.6	1960-2006	5.0 (4.7, 5.3)		
55-59	6.1	67.1	1960-1990	5.8 (5.0, 6.7)	1990-2006	4.0 (3.0, 5.0)

[1] EAPC: estimated annual percentage change, calculated based on the rates during the indicated period

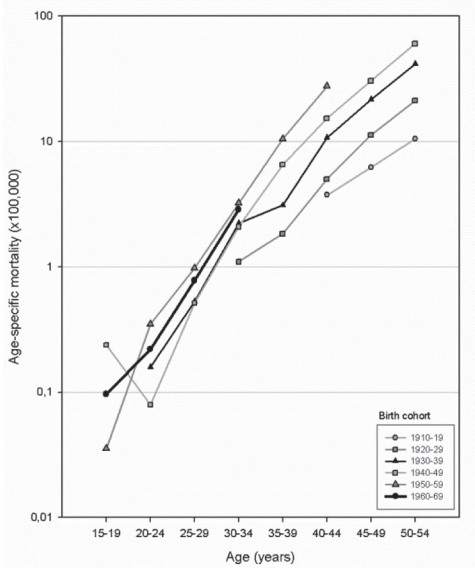


Figure 3.1.4 | Age-specific mortality rates of lung cancer for female birth cohorts in the Netherlands (Source: Statistics Netherlands[2])

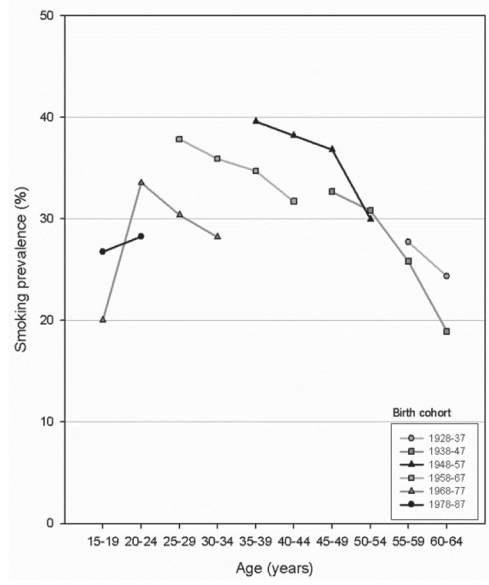


Figure 3.1.5 | Age-specific smoking prevalence for female birth cohorts in the Netherlands (Source: STIVORO)

In young women (ages 20-44), lung cancer mortality increased by 4.3% annually, from 0.5 per 100,000 in 1960 to 3.5 in 1999. After 1999 however, rates dropped to 3.0 per 100,000 in 2006. The same reversal of the increasing mortality trend started in 2004 in women aged 45-49 (from 31 per 100,000 in 2004 to 23 in 2006). Among women aged 50-54 and 55-59 rates kept rising by 4-6% annually (**Table 3.1.1**).

Figure 3.1.4 gives age-specific mortality rates of female lung cancer by birth cohort and showed that mortality tended to decrease in women born after the 1950s. The same pattern was observed for smoking prevalence among women by birth cohort (**Figure 3.1.5**). Women born after the 1950s started smoking less.

DISCUSSION

We demonstrated the beginning of the end of the lung cancer epidemic among Dutch women. Although overall female lung cancer mortality and incidence rates continued to rise markedly in the Netherlands, reaching levels exceeding those of males, we observed a decline in the mortality and incidence trend among young women, particularly for the generation born after the 1950s. These findings are in line with the decreasing smoking prevalence in women born after the 1950s.

Although lung cancer is uncommon among young age groups, these lung cancer trends are important, particularly since they give information on recent changes in risk-factor prevalence (e.g. smoking) and thereby information on the likely future trends in middle and elderly age.[9,10] The end of the lung cancer epidemic among Dutch men was also first observed among young men in the early 1980s.[11]

The decrease in smoking prevalence among women occurred mostly between 1970 and 1989 (-10%). From the 1990s the smoking prevalence became more or less stable and between 2000 and 2007 it decreased with another 5%. Based on this information we expect first a slight decrease in the overall female lung cancer mortality and incidence followed by a leveling off.

In this study, we focused mainly on lung cancer mortality, because mortality data was available for a longer time period than incidence data. As the case-fatality of lung cancer is high and therefore mortality trends closely follow incidence trends, this main focus on mortality is justified. Furthermore, impressive changes in lung cancer survival did not take place in the Netherlands,[12,13] which implies that mortality is mainly influenced by incidence and therefore by changes in risk-factor

prevalence. This is also confirmed by our findings that lung cancer mortality and smoking prevalence among women started to decrease in the same generation.

At the beginning of the 21st century, in Europe there was a general tendency for M:F rate ratios for lung cancer mortality to converge towards 1.0.[14] Convergence of male and female lung cancer rates can be caused by declining male rates and rising female rates as observed in this study and in other European countries like Finland. In countries like Denmark, Sweden and Ireland convergence of the M:F rate ratios were only due to decreasing male rates.[14] Jemal et al.[15] showed that in the USA smoking prevalence converged to 1.0 among young men and women born after 1960, resulting in converging male and female lung cancer rates. From the available recent data on smoking prevalence by birth cohort in the Netherlands we found only an M:F rate ratio of smoking prevalence smaller than 1.0 among young adults aged 20-24 and born in the 1960s, which increased up to 1.2 for those born in the 1980s (data not shown). This finding is confirmed by the data presented in **Figure 3.1.1**; in the 1980s the smoking prevalence rates among men were surpassed by those of women aged 20-34. This is a plausible explanation for the observation that male lung cancer rates were surpassed by female rates in the Netherlands. However, from the 1990s, again men started smoking more than women in this age group, which might result in an increasing M:F ratio for lung cancer trends among young adults in the future.

Despite the fact that smoking prevalence became equal among young men and women in the past, this is not the only explanation for the female lung cancer incidence and mortality rates exceeding those of men. Possible other explanations include a higher female susceptibility to tobacco smoke,[16] a different smoking pattern[17] or more passive smoking[18] among women.

On average 57% of lung cancer is avoidable by reducing smoking in Europe,[19] underlining the importance of anti-smoking interventions to attain lower lung cancer incidence and mortality among men and women. Such interventions should focus on adolescents and young adults to prevent that they start smoking, particularly since there was a slight increase of the smoking prevalence among both boys and girls aged 15-19 between 1990 and 2000 (**Figures 3.1.1** and **3.1.5**). This increase was not observed among women aged 20-34, their smoking prevalence even continued to decrease during this period. This means that many of the 15-19 year old girls who started smoking, stopped before reaching the age of 20. From the annual smoking monitor among youth in the Netherlands it is known that about 45% of smoking

girls aged 15-19 quitted.[20] The slight increase of smoking prevalence among girls aged 15-19 between 1990 and 2000 is therefore not expected to have a major influence on overall female lung cancer mortality and incidence in the future.

In the light of the recently increased smoking prevalence among adolescents, preventing smoking uptake must remain a main public health issue. Besides the importance of anti-smoking interventions (i.e. quit smoking campaigns, smoke free public places and increasing tax on cigarettes) we should also focus on further research to early detection (e.g. screening), better diagnostics and the role of estrogens[21] and genetics[22] in lung cancer to optimize lung cancer treatment and thereby reducing lung cancer mortality.

Acknowledgements

The work on this article was conducted within the project 'Progress against cancer in the Netherlands since 1970's? Epidemiological interpretation of changes in survival, incidence and mortality' funded by the Dutch Cancer Society.

CHAPTER 3.2

Progress against ovarian cancer in the Netherlands: decreased incidence and mortality due to previous changes in risk factors, coinciding with improved survival

Henrike E. Karim-Kos
Anne M. van Altena
Leon F.H.G. Massuger
Marian J.E. Mourits
Jan Willem W. Coebergh
Esther de Vries

Submitted.

ABSTRACT

Objective. Marked changes in reproductive behaviour and disease management make it interesting to assess progress against ovarian cancer.

Design. A population-based study on trends in ovarian cancer incidence, relative survival and mortality derived from the Netherlands Cancer Registry and Statistics Netherlands.

Setting. The Netherlands.

Population. All patients newly diagnosed with ovarian cancer between 1989 and 2009 (N=25,278).

Methods. Trends were evaluated by the estimated annual percentage of change (EAPC) or corresponding p-values. Follow-up was complete until January 2010.

Main outcome measures. Ovarian cancer incidence, 5-year relative survival and mortality.

Results. The age-standarised incidence rate decreased markedly from 15 per 100,000 in 1989 to 11 in 2009 (EAPC -2.1%, 95% CI -2.4, -1.8). The mortality rate decreased from 13 per 100,000 in 1970 to 11 in 1982 (EAPC -1.6%, 95% CI -2.2, -1.0). After 1994, the decrease continued to 8.8 in 2000 (EAPC -3.9%, 95% CI -6.2, -1.6) and rates have remained stable since then. These decreasing trends were most pronounced among young and middle-aged women, starting among women born after the 1920s. Five-year relative survival improved from 36% in 1989-1993 to 42% in 2004-2009 ($p<0.001$), coinciding with a histological subtype shift from 'adenocarcinomas, not other specified' to 'serous carcinomas' with a better prognosis.

Conclusions. Ovarian cancer incidence and mortality markedly decreased since 1989, probably as a result of changes in reproductive behaviour. Five-year relative survival increased with 6-percent points, partly as a result of improved diagnostics coinciding with a histological shift and stage migration, and treatment, which also partly explains the mortality decrease.

INTRODUCTION

In developed areas of the world, ovarian cancer is a common malignancy, ranking 7th most frequent for female cancer incidence and mortality not taking non-melanoma skin cancer into account. The highest incidence areas are in Europe and North America.[23,24] In the beginning of the 2000s, incidence rates were relatively low in the Netherlands compared to other European countries.[3]

Use of oral contraceptives is shown to confer long-term protection against ovarian cancer.[25] In the Netherlands women increasingly used oral contraceptives since their introduction in the mid 1960s, reaching levels up to 40-45% (www.cbs.nl) being one of the highest prevalence rates of use worldwide. During the same period, risk factors for ovarian cancer such as low parity and obesity increased among the Dutch female population.[26]

The prognosis of ovarian cancer is largely determined by FIGO stage. Only a minority of cases are detected at early stages because of non-specific symptoms resulting in an overall poor prognosis for ovarian cancer patients. In Europe, the average 5-year survival improved only modestly during the 1990s until 2002 from 37% to 42%[3] despite substantial advances in surgical and systemic treatment, i.e. more attention for complete debulking and adequate staging, incorporation of taxanes into standard platinum based primary chemotherapy and of several other active non-platinum cytotoxic agents.[27]

Taking into account the changes in population prevalence of the aforementioned protective and risk factors, improved staging and treatment, we studied mortality, incidence and survival trends of ovarian cancer in the Netherlands by age, stage and histological subtype during 1989-2009.

MATERIAL AND METHODS

Data collection

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres, were used.[28] The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge, haematology

departments and regional radiotherapy institutions. Information on patient characteristics like gender, date of birth, and tumour characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3),[7] histology, stage (Tumour Lymph Node Metastasis (TNM) classification),[29] grade, and primary treatment, are obtained routinely from the medical records. The quality of the data is high, due to thorough training of the administrators and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[30] Follow-up of vital status of all patients was calculated as the time from diagnosis to death or to 1st January 2010. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all deceased Dutch citizens.

For the present study, all patients with invasive primary ovarian cancer (ICD-O code C56) diagnosed in the period 1989-2009 in the Netherlands were included (n=25,278). Patients were divided in four age-groups (20-44, 45-59, 60-74, ≥75 years). The study period was divided in four periods: 1989-1993, 1994-1998, 1999-2003, and 2004-2009. Tumour stage was defined according the FIGO staging system,[31] based on postoperative histological information. If post-operative information was unknown, clinical information was used. Histology subtypes were divided into five groups: serous (ICD-0 morphology codes 8441, 8460-61), mucinous (8430, 8470-82), endometrioid (8380-83), adenocarcinomas not otherwise specified (NOS) (8010, 8140, 8260, 8440, 8450) and other (all other ICD-O morphology codes in C56). Women younger than 20 years and older than 95 years at diagnosis were excluded from the survival analysis, as well as cases diagnosed by autopsy.

Mortality data on ovarian cancer for the period 1970-2009 was obtained from Statistics Netherlands.

Statistical analyses

Annual incidence rates for the period 1989-2009 and annual mortality rates for the period 1970-2009 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to the European standard population (European Standardised Rates (ESR)). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval. 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 * (e^a – 1)). Joinpoint regression analysis was used to identify years where a significant change in the incidence and mortality trend occurred.[8] The models were developed using the Joinpoint Regression Program (version 3.3.1) from the Surveillance Research Program of the US National Cancer Institute (http://srab.cancer.gov/joinpoint/).

To estimate the effect of birth cohort on trends in mortality since the 1970s, rates for ages 20-84 were calculated for birth cohorts of 10 years. These 'synthetic' birth cohorts were created based on the year and age of death, using 5-year age and 5-year calendar periods.

Traditional cohort-based relative survival analysis was used for the period 1989-2009 which represents the actual survival of patients diagnosed during 1989-2009. Follow-up was available until January 1, 2010. Therefore, 5-year relative survival of patients diagnosed in the period 2004-2009 could not be calculated with the cohort-based method. To estimate the most up-to-date 5-year relative survival of patients diagnosed in this time period, we used period-based relative survival analyses.[32] Survival trends were evaluated by a linear regression model of annual survival rates and $p<0.05$ was considered as statistically significant.

Multivariable relative survival analyses, using Poisson regression modeling,[33] were performed to estimate relative excess risk (RER) of dying for the periods of diagnosis. The variables period, age and stage were included in the model. The histology variable was added to investigate the effect of histology on the RER of period of diagnosis. Analyses were performed using SAS software (SAS system 9.2, SAS Institute, Cary, NC).

RESULTS

Trends in mortality

The age-standardised mortality rate (ESR) (**Figure 3.2.1**) decreased from 13 per 100,000 in 1970 to 11 in 1982 (EAPC -1.6%, 95% CI -2.2, -1.0) and remained stable during 1982-1994. After 1994, it continued to decrease to 8.8 per 100,000 in 2000 (EAPC -3.9%, 95% CI -6.2, -1.6) remained stable since then. During the study period mortality decreased markedly among young and middle aged women (20-44 yr: 3.4 per 100,000 in 1970 to 0.9 in 2009; 45-59 yr: 21 per 100,000 in 1970 to 8.7 in 2009). For women aged between 60 and 74, mortality started to decrease from 47

per 100,000 in 1991 to 32 in 2009. Mortality increased for women aged above 75 until 1995 and then decreased from 71 per 100,000 to 60 in 2009 (**Figure 3.2.2A**). Age-specific mortality rates of ovarian cancer by birth cohort tended to decrease in women born after the 1920s (**Figure 3.2.3**).

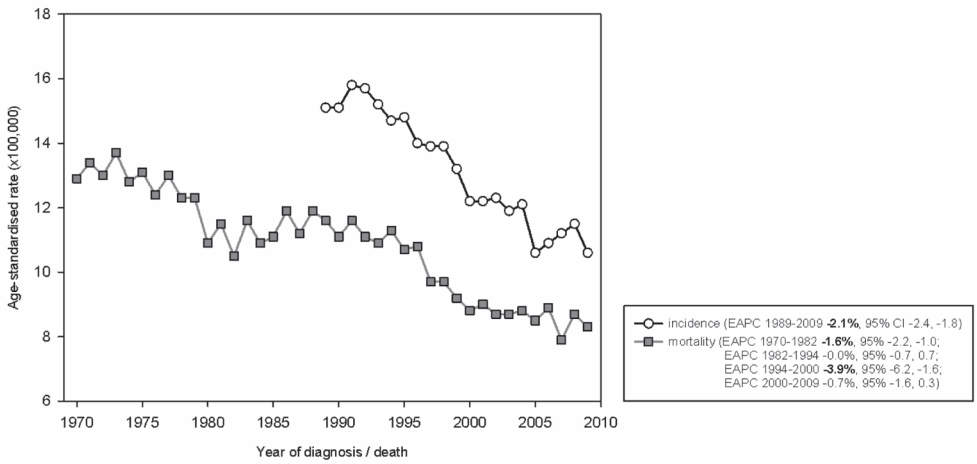
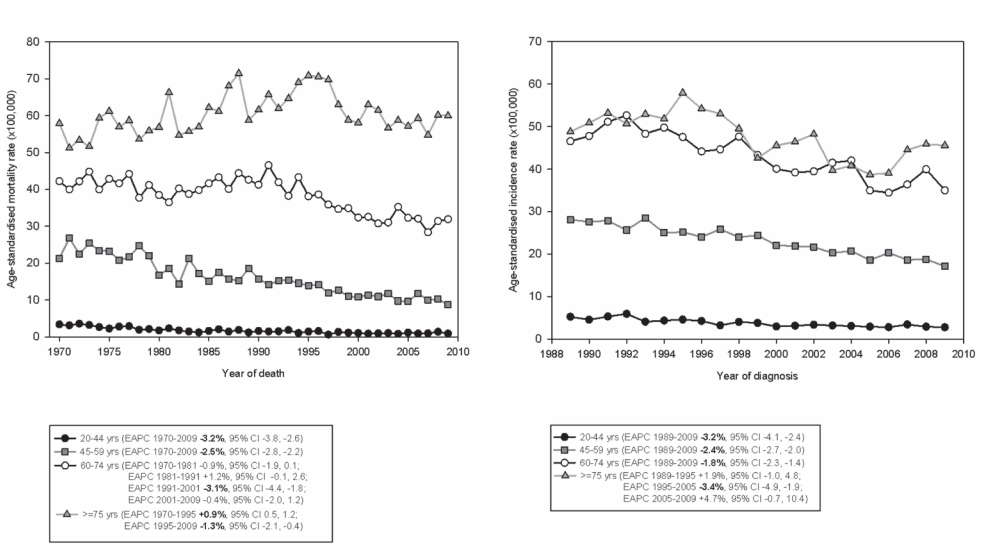


Figure 3.2.1 | Age-standardised incidence and mortality rates (European Standardised Rate (ESR)) of ovarian cancer in the Netherlands, 1989-2009

Trends in incidence

The age-standardised incidence rate (ESR) of all ovarian cancers decreased markedly from 15 per 100,000 in 1989 to 11 in 2009. The estimated annual percentage change (EAPC) in the period 1989-2009 was -2.1% (95% CI -2.4, -1.8; **Figure 3.2.1**). The decreasing incidence trend was most pronounced among young and middle aged women (20-44 yr: 5.2 per 100,000 in 1989 to 2.8 in 2009; 45-59 yr: 28 per 100,000 in 1989 to 17 in 2009). For women aged between 60 and 74 the incidence decreased from 47 per 100,000 in 1989 to 35 in 2009. The incidence trend remained stable for women aged 75 and over until 1995 and then decreased from 58 per 100,000 to 39 in 2005. Thereafter, incidence seemed to increase slightly, though not statistically significantly (**Figure 3.2.2B**). Difference in incidence trends between ages resulted in a lowering of proportion of young women (20-44 yr) from 12% in 1989-1993 to 8% in 2004-2009.



A B

Figure 3.2.2 | Age-standardised mortality(A) and incidence(B) rates (European Standardised Rate) of ovarian cancer by age in the Netherlands

Among all age groups the declines in incidence were most pronounced for FIGO stage I and III. FIGO stage IV decreased among women aged 60 and over, but started to increase from early 2000. For women aged 60-74 incidence of FIGO stage IV decreased from 8.4 per 100,000 in 1989 to 5.6 in 2000 and increased again to 8.7 per 100,000 in 2009, for the elderly (≥75 years) the incidence decreased from 10.5 per 100,000 in 1989 to 7.0 in 2003 and increased again to 13.5 per 100,000 in 2009 (**Figure 3.2.4**). Recently, fewer young women (20-44 years) were diagnosed with an early stage (FIGO stage I and IIA), the proportion decreased from 57% in 1994-1998 to 49% in 2004-2009. At the same time the proportion of advanced stages (FIGO stage IIB/C, III, and IV) increased from 39% to 48%. This shift towards advanced stages was also observed for women aged 75 and over (from 15% and 66% in 1994-1998 to 12% and 74% in 2004-2009, respectively), although this shift was partly due to the decrease in patients with unknown stages. For other age groups we observed increased proportions of advanced stages (45-59 yrs: from 60% in 1994-1998 to 64% in 2004-2009; 60-74 yrs: from 71% to 75%) and no change in the proportion of early stages.

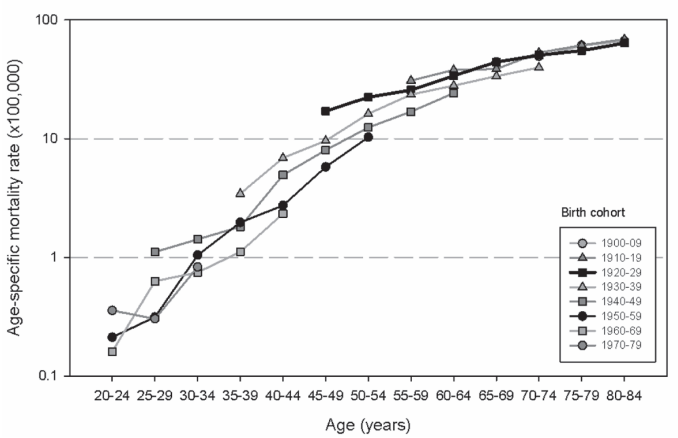


Figure 3.2.3 | Age-specific mortality rates of ovarian cancer by birth cohort (1900-1979) in the Netherlands

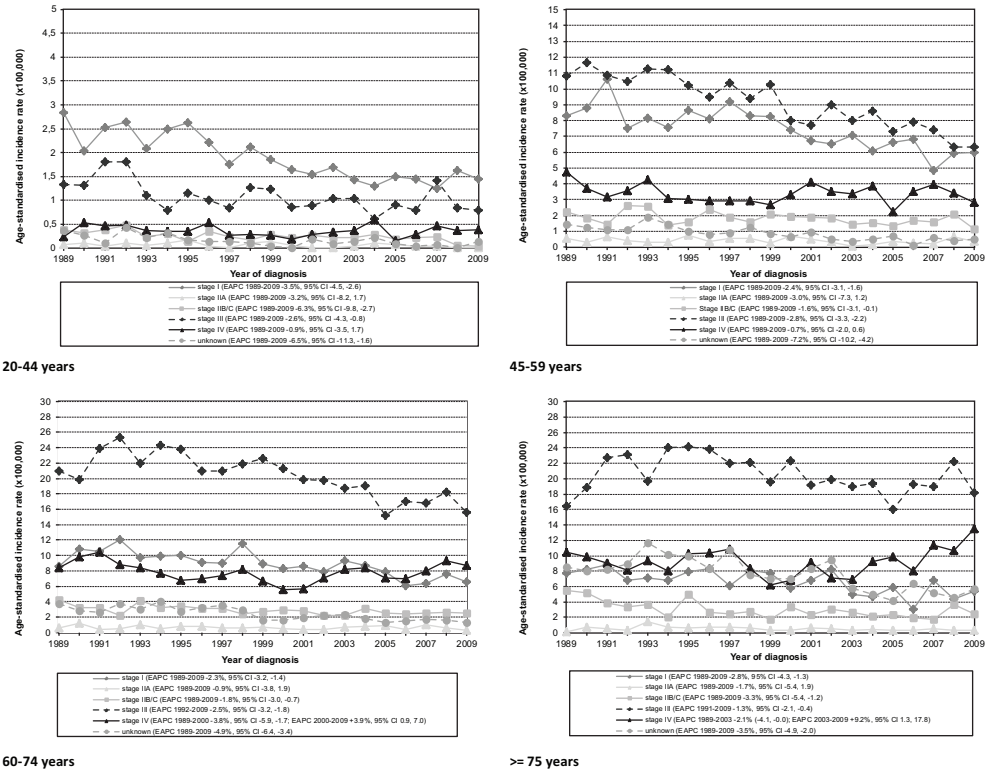


Figure 3.2.4 | Age-standardised incidence rates (European Standardised Rate) of ovarian cancer by age and FIGO stage in the Netherlands, 1989-2009

The decreasing trend in incidence was most striking for adenocarcinomas NOS and mucinous carcinomas which constitute up to 30% and 11% of all ovarian cancers, respectively. An increasing incidence was observed for serous carcinomas among women aged 45 and older since the mid-1990s while incidence of this type declined among young women (20-44 yrs) (**Figure 3.2.5**). These changes in incidence by histological subtype resulted in a marked proportional decrease of adenocarcinomas NOS among all age groups (20-44 yrs: from 21% in 1989-1993 to 8.6% in 2004-2009; 45-59 yrs: from 32% to 13%; 60-74 yrs: from 42% to 20%; ≥75 yrs: from 49% to 38%). This coincided with a marked increase of serous carcinomas (20-44 yrs: from 26% in 1989-1993 to 32% in 2004-2009; 45-59 yrs: from 26% to 45%; 60-74 yrs: from 27% to 52%; ≥75 yrs: from 19% to 34%).

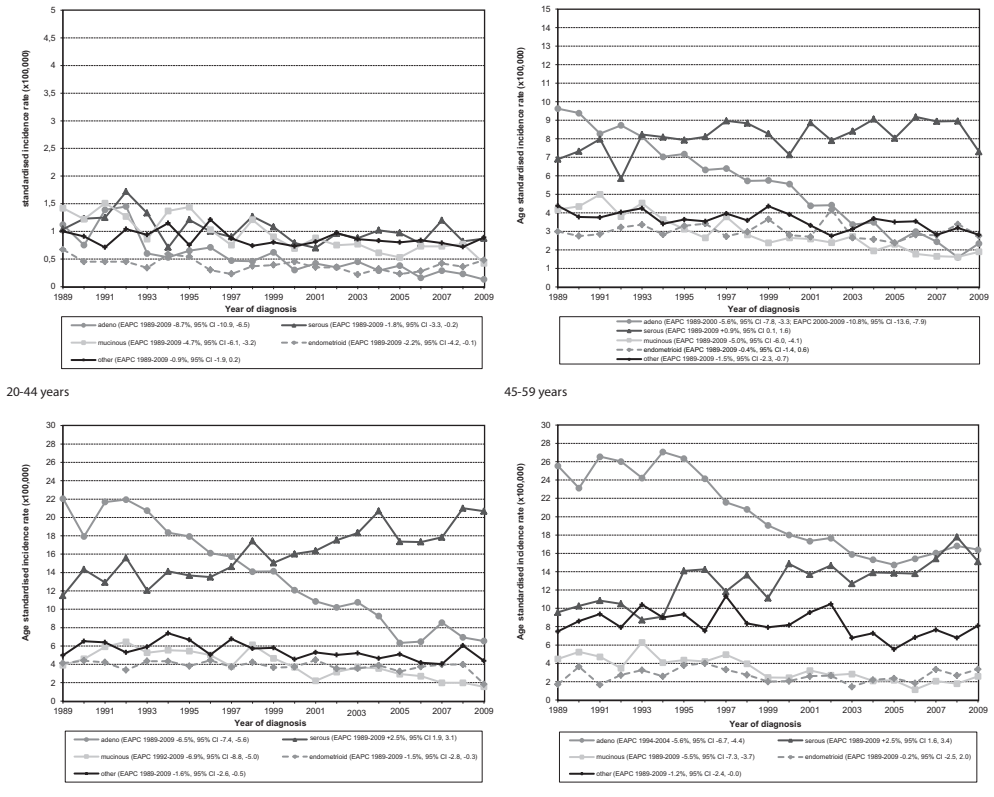


Figure 3.2.5 | Age-standardised incidence rates (European Standardised Rate) of ovarian cancer by age and histological subtypes in the Netherlands, 1989-2009

Within the histological subtypes the stage distribution shifted to late stages for adenocarcinomas NOS (from 80% in 1989-1993 to 87% in 2004-2009) and serous carcinomas (from 75% to 84%) due to a decrease in low and unknown stages. For endometrioids and mucinous carcinomas the proportion of low stages increased (from 43% and 56% to 53% and 64%, respectively).

Trends in survival

Marked improvements were seen for 5-year relative survival which improved from 36% in 1989-1993 to 42% in 2004-2009 (**Table 3.2.1**). This survival improvement was only present among women aged between 45 and 59 (from 46% to 54%), and between 60 and 74 (from 28% to 39%). Five-year relative survival improved only for advanced FIGO stages (from 18% to 28%). When stratifying according to histological subtype, 5-year relative survival improved for women with endometrioid (from 53% to 70%) and mucinous carcinomas (from 58% to 64%). Five-year relative survival for women with serous carcinoma was 38%, but only 21% for women with adenocarcinoma NOS.

Table 3.2.1 | Five-year relative survival (Standard Error) from ovarian cancer (>=20 years) in the Netherlands, 1989-2009

	Period of diagnosis					
	1989-2009	**1989-1993**	**1994-1998**	**1999-2003**	**2004-2009[a]**	***P* trend**
All	*39.0 (0.4)*	35.6 (0.6)	37.5 (0.7)	41.2 (0.7)	42.1 (0.6)	**<0.001**
Age (years)						
20-44	*67.8 (1.0)*	66.5 (1.8)	70.5 (1.9)	67.9 (2.1)	67.4 (2.0)	0.29
45-59	*50.7 (0.6)*	45.8 (1.2)	49.2 (1.2)	53.1 (1.2)	54.2 (1.1)	**<0.001**
60-74	*34.2 (0.6)*	28.1 (1.0)	33.2 (1.0)	37.2 (1.1)	39.3 (1.0)	**<0.001**
>= 75	*18.9 (0.7)*	18.2 (1.3)	15.6 (1.2)	20.5 (1.4)	21.1 (1.2)	0.18
FIGO stage						
I - IIA	*82.7 (0.6)*	81.8 (1.1)	82.3 (1.1)	82.9 (1.1)	83.7 (1.1)	0.59
IIB - IV	*22.9 (0.4)*	17.9 (0.6)	20.1 (0.7)	26.5 (0.8)	27.9 (0.7)	**<0.001**
unknown	*17.7 (1.0)*	18.8 (1.9)	17.7 (1.8)	15.4 (2.0)	18.8 (2.2)	0.58
Histological subtype						
adenocarcinoma	*21.1 (0.5)*	19.4 (0.9)	20.8 (1.0)	24.6 (1.2)	21.3 (1.1)	0.10
endometrioid	*62.5 (1.2)*	52.8 (2.4)	59.7 (2.2)	67.7 (2.2)	69.9 (2.0)	**<0.001**
mucineus	*59.3 (1.0)*	58.0 (1.8)	56.6 (1.9)	62.3 (2.2)	64.1 (2.1)	**0.02**
serous	*38.1 (0.6)*	37.4 (1.3)	36.8 (1.2)	37.6 (1.1)	38.5 (1.0)	0.39
other	*46.4 (0.9)*	44.7 (1.8)	44.9 (1.7)	47.4 (1.8)	48.8 (1.6)	0.72

[a] 5-year relative survival calculated by period-analyses

In the multivariable relative survival model the improvement over time remained significant after adjusting for age and stage. After adding histology to the model survival improvement became smaller, which means that part of the survival improvement during 1989-2009 was explained by the histology shift from adenocarcinomas NOS to serous carcinomas (**Table 3.2.2**).

Table 3.2.2 | Multivariate relative 5-year survival analysis of ovarian cancer (>=20 years) in the Netherlands, 1989-2009

	Multivariate 1 (adjusted for age and stage)		Multivariate 2 (adjusted for age, stage and histology)	
	RER	**(95% CI)**	**RER**	**95% CI**
Period of diagnosis				
1989-1993	1		1	
1994-1998	0.94	(0.90-0.98)	0.97	(0.93-1.02)
1999-2003	0.76	(0.73-0.80)	0.82	(0.78-0.86)
2004-2009	0.69	(0.66-0.72)	0.78	(0.74-0.82)

Abbreviations: RER, Relative Excess Risk of dying; 95% CI, 95% Confidence Interval

DISCUSSION

Mortality from ovarian cancer markedly decreased since the 1970s in the Netherlands. This decrease was most pronounced among young and middle aged women (<60 years) and since 1992 this decrease was also visible among the elderly (>= 60 years), particularly among women born after the 1920s. This means that about one third of ovarian cancer deaths were prevented in 2009 compared to the situation in the early 1970s. The decreasing incidence of ovarian cancer was most likely the main cause of the observed decline in ovarian cancer mortality since the mid-1990s because the strength (EAPCs) of the decreasing incidence trends was almost equal to the strength of the decreasing mortality trends. Beside ageing of the patient population and increase of advanced stages, 5-year relative survival improved by 6 percent-points which should also have contributed to the mortality decrease. This survival improvement coincided with the histological shift from adenocarcinomas NOS to serous carcinomas which have a better prognosis.

Trends in incidence and mortality

The mortality decrease prior to 1982 seems to be largely caused by changes in treatment, like the introduction of cisplatin-containing combination chemotherapy in the late 1970s. These changes resulted in an improvement of the 5-year relative survival from 28% in 1975-1980 to 42% in 1981-1985, while the incidence remained stable.[34]

Since 2000, total ovarian cancer mortality remained stable despite decreases in incidence. This stable mortality was also observed among the elderly (≥60 years), although only significantly stable for women aged 60-74. Possibly, this is caused by the observed increase in FIGO stage IV among the elderly since the early 2000s. The incidence of FIGO stage IV was higher in 2009 than in 1989, partly explained by improved staging but probably partly also being real. Besides, among the elderly the increasing incidence of serous carcinomas is not only explained by a decline in adenocarcinomas NOS, but also by a decline in mucinous carcinomas (proportional decrease from 10% in 1989-1993 to 6% in 2004-2009). Women with a serous carcinoma had a worse prognosis than women with a mucinous carcinoma (5-year relative survival 1989-2009: 38% and 59%, respectively).

The birth cohort analysis performed in this study, suggests that the mortality trend is also influenced by a birth cohort effect; mortality decreased for those born after the 1920s which explains why we observed that mortality started to decrease later among the elderly (>= 60 years). This pattern was also observed among other northern European women.[35] In England and Wales the fall in risk of getting ovarian cancer for women born after the 1920s coincided with the rapidly increasing use of oral contraceptives (OC).[36] In a collaborative reanalysis of data from 45 epidemiological studies, every five years of oral contraceptive use resulted in a 21% risk reduction. This risk reduction persisted for more than 30 years after ceasing oral contraceptive use, although it attenuated somewhat over time. It was estimated that due to the increased number of ever-OC users in high income countries, about 13% of ovarian cancers among women aged under 75 are being prevented in the 2000s.[25] In the Netherlands, OCs became available at the end of 1961, but initially was used only by women late in their reproductive life, mainly for birth control. Since the late 1960s, OCs became a popular method of contraception at young ages. The prevalence of OC use among women aged between 16 and 50 years increased from less than 5% in the mid-60s to 45% in the mid-1990s and 39% in 2010. Among young women (18-24 years) 66% is using OCs.[26,37]

Other protective factors for ovarian cancer are multiparity, late age at first childbirth and breastfeeding. Different cohort studies showed that each birth gives a 10-20% reduction in risk of getting ovarian cancers.[38-40] In the Netherlands, the average number of children per woman declined from 3.2 in the early 60s to 1.5 in the early 80s and afterwards slightly increased to 1.8 in 2010.[41] This decrease is most likely associated with use of OCs and therefore it is not expected to result in an increased risk of ovarian cancer. Increasing age at first childbirth may be also associated with use of OCs. However, after taking OCs use into account Adami et al.[39] found an 11% risk reduction for each 5-year increment in age at first childbirth. This risk reduction is probably only valid for uniparous and not for multiparous women,[42] but there are only Dutch data for uniparous and multiparous women together. In the Netherlands, between the early 1970s and 2010 the average age at first childbirth increased with 5 years (from 24.3 to 29.4 years) which had a possible downward effect on the incidence trend.[41] Another protective factor is breastfeeding and the percentage of babies breastfed at birth has increased from 67% in 1989-1991 to 75% in 2007-2009 and at the age of 6 months this percentage increased from 26% to 35% in the Netherlands, respectively.[43] A recent case-control study showed a strong inverse association between breastfeeding and epithelial ovarian cancer of about 1.4% reduction per month of lactation up to a maximum of 12 months, particularly for mucinous ovarian cancers, and independent of parity.[44] However, not all studies found a significant inverse association.[45]

Recently, it was proposed that serous ovarian cancers originate in the distal fallopian tube or uterus,[46,47] explaining why hysterectomies and tubal ligations are protective against ovarian cancer. The number of hysterectomies in the Netherlands increased during the 1960s and 1970s and started to decrease from the early 1980s from about 28,000 to 11,908 in 2009.[48-50] Unfortunately, no information is available about the frequency of tubal ligation, but we expect that this intervention decreased over time, because a variety of alternative anticonceptive methods became available such as Mirena and OC use. As a result, it is expected that the incidence of serous carcinomas will increase in the future. Among the elderly (≥60 years) we observed an increase in serous carcinomas which could not only be explained by the shift from adenocarcinomas NOS to serous carcinomas and even the total ovarian cancer incidence seems to increase since 2005-2006, possibly due to the decrease in hysterectomies since the 1980s, despite the introduction of OC use.

A positive family history of epithelial ovarian cancers is another well-established risk factor. Carriers of *BRCA1* or *BRCA2* mutations have the highest cumulative life time risk of 30-60% and 5-20%, respectively.[51-53] Both mutations are associated with serous carcinomas. For women with a *BRCA1* or *BRCA2* mutation prophylactic bilateral salpingo-oophorectomy is advised around the age of 40.[54,55] While first the oophorectomy rates declined from 130 per 100,000 woman-years in the early 1980s to less than 85 in 1990[26] we expect this rate only to increase among *BRCA*-carriers. Since only about 5% of ovarian cancers are explained by family history we do not expect that this increase in oophorectomies will notably affect the ovarian cancer incidence trend. However, the decrease since the 1980s could be also one of the reasons of the possible incidence increase among the elderly.

Trends in survival

The overall 5-year survival rate of 39% during 1989-2009 found in this study is comparable with survival rates of other European countries, but lower than in the US.[3, 56, 57] The higher survival rate in the US might be a result of difference in completeness of follow-up between the cancer registries. A high completeness of follow-up as in this study, affects survival outcome negatively.[58]

During the study period we found an improvement in 5-year survival from 36% in 1989-93 to 42% in 2004-09 which is probably due to improved diagnostics and treatment. In this study, we found that the survival improvement was partly explained by the histological shift from adenocarcinomas NOS to serous carcinomas. Serous carcinomas had 18% higher 5-year relative survival than adenocarcinomas NOS in 2004-2009. This histological shift is probably not a real shift, but a result of improved diagnostics and more surgical procedures. Women with an adenocarcinoma NOS are often not diagnosed and treated optimally because of the high age and/or advanced stage of these women. In this study, we found that women with adenocarcinoma NOS were significantly older than other ovarian cancer patients and this age gap increased over time. In 2004-09, women with adenocarcinoma NOS were 71 years compared to other women who were 62 years. Women with adenocarcinoma NOS had also more often an advanced stage than other patients (81% vs 59%).

Another result of improved diagnostics is the stage migration, which also played a role in the improving survival. In this study, we observed a relative increase in advanced stage disease, but also a 2% increase of positive lymph nodes among women with a T1 or T2 tumour, whereas the percentage of women with a T3 tumour

increased with 3% during 1989-2009. However, if stage migration was the only cause for survival improvement we would not have observed any survival improvement for the total patient population.

Survival improvement can be also explained by improved primary treatment (e.g. more often (neo)adjuvant chemotherapy and optimal debulking surgery)[59] and improved treatment strategies after relapsed disease. Another possible factor influencing the outcome of ovarian cancer is whether surgery is provided by a gynaecologic oncologist or a general gynaecologist.[60] Furthermore, it has been shown that women treated in specialized and semispecialized hospitals survive longer than women treated in general hospitals.[61,62] The North Netherlands was one of the first regions that systematically provided assistance in treatment of ovarian cancer patients by sending gynaecologic oncologist to general hospitals since the 1980s. During recent years much debate took place on centralisation of ovarian cancer treatment in the Netherlands, which led to the introduction of Managed Clinical Networks in most areas, centred around University Hospitals.

CONCLUSION

In conclusion, ovarian cancer incidence and mortality markedly decreased since the last decades, most pronounced among young and middle aged women (<60 years) and particularly among women born after the 1920s. The incidence decrease is probably a result of the introduction of OC use and increased age of first childbirth. Five-year relative survival increased with 6-percent points between 1989 and 2009 as a result of improved diagnostics causing a histological shift and stage migration, and treatment, which also partly explains the mortality decrease.

Acknowledgements

The work on this study is funded by the Dutch Cancer Society (grant number EMCR 2006-3489). The funders had no role in the collection of the data, the writing of the manuscript or the decision to submit for publication.

REFERENCES

1. Bosetti C, Levi F, Lucchini F, Negri E, La Vecchia C. Lung cancer mortality in European women: recent trends and perspectives. *Ann Oncol.* 2005;16(10):1597-1604.
2. Statistics Netherlands. *<http://statline.cbs.nl/statweb/>. (*accessed September 2007).
3. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer.* 2008;44(10):1345-1389.
4. Jemal A, Ward E, Thun MJ. Contemporary lung cancer trends among U.S. women. *Cancer Epidemiol Biomarkers Prev.* 2005;14(3):582-585.
5. STIVORO. *Annual report 2006.* The Hague: STIVORO;2007.
6. World Health Organization. *International statistical classification of disease and related health problems*. 10th revision ed. Geneva: World Health Organization; 1992.
7. Fritz A, Percy C, Jack A, et al. *Classification of Diseases for Oncology, ed. 3rd* Geneva: World Health Organization; 2000.
8. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med.* 2000;19(3):335-351.
9. Doll R. Progress against cancer: an epidemiologic assessment. The 1991 John C. Cassel Memorial Lecture. *Am J Epidemiol.* 1991;134(7):675-688.
10. Jemal A, Cokkinides VE, Shafey O, Thun MJ. Lung cancer trends in young adults: an early indicator of progress in tobacco control (United States). *Cancer Causes Control.* 2003;14(6):579-585.
11. Verbeek AL, Peeters PH, Sturmans F. [Has the lung cancer epidemic in the Netherlands reached its peak?]. *Ned Tijdschr Geneeskd.* 1985;129(49):2365-2369.
12. Janssen-Heijnen ML, Schipper RM, Klinkhamer PJ, Crommelin MA, Coebergh JW. Improvement and plateau in survival of small-cell lung cancer since 1975: a population-based study. *Ann Oncol.* 1998;9(5):543-547.
13. Janssen-Heijnen ML, Schipper RM, Klinkhamer PJ, Crommelin MA, Mooi WJ, Coebergh JW. Divergent changes in survival for histological types of non-small-cell lung cancer in the southeastern area of The Netherlands since 1975. *Br J Cancer.* 1998;77(11):2053-2057.
14. Zatonski WA, Manczuk M, Powles J, Negri E. Convergence of male and female lung cancer mortality at younger ages in the European Union and Russia. *Eur J Public Health.* 2007;17(5):450-454.
15. Jemal A, Travis WD, Tarone RE, Travis L, Devesa SS. Lung cancer rates convergence in young men and women in the United States: analysis by birth cohort and histologic type. *Int J Cancer.* 2003;105(1):101-107.
16. Wei Q, Cheng L, Amos CI, et al. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. *J Natl Cancer Inst.* 2000;92(21):1764-1772.
17. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. *Lung Cancer.* 2001;31(2-3):123-137.
18. Gorlova OY, Zhang Y, Schabath MB, et al. Never smokers and lung cancer risk: a case-control study of epidemiological factors. *Int J Cancer.* 2006;118(7):1798-1804.
19. Soerjomataram I, de Vries E, Pukkala E, Coebergh JW. Excess of cancers in Europe: a study of eleven major cancers amenable to lifestyle change. *Int J Cancer.* 2007;120(6):1336-1343.
20. Hoogeveen E. *[Smoking habits of young people 2007].* Amsterdam: TNS NIPO;2007.

21. Hede K. Lung cancer may be different for men and women, but researchers ponder what to do? *J Natl Cancer Inst.* 2007;99(24):1830-1832.

22. Landi S, Gemignani F, Canzian F, et al. DNA repair and cell cycle control genes and the risk of young-onset lung cancer. *Cancer Res.* 2006;66(22):11062-11069.

23. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127(12):2893-2917.

24. GLOBOCAN 2008. Cancer incidence, mortality and prevalence worldwide in 2008. *<http://globocan.iarc.fr/>.* (accessed December 2011).

25. Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet.* 2008;371(9609):303-314.

26. Koper NP, Kiemeney LA, Massuger LF, Thomas CM, Schijf CP, Verbeek AL. Ovarian cancer incidence (1989-1991) and mortality (1954-1993) in The Netherlands. *Obstet Gynecol.* 1996;88(3):387-393.

27. Cannistra SA. Cancer of the ovary. *N Engl J Med.* 2004;351(24):2519-2529.

28. Netherlands Cancer Registry. *<http://cijfersoverkanker.nl/>. (*accessed December 2011).

29. Wittekind C, Green FL, Hutten RPV, Klimpfinger M, Sobin LH. *TNM Atlas*. 5th ed. Berlin: Springer-Verlag; 2005.

30. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol.* 1993;22(3):369-376.

31. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet.* 2006;95 Suppl 1:S161-192.

32. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer.* 1996;78(9):2004-2010.

33. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med.* 2004;23(1):51-64.

34. Balvert-Locht HR, Coebergh JW, Hop WC, et al. Improved prognosis of ovarian cancer in The Netherlands during the period 1975-1985: a registry-based study. *Gynecol Oncol.* 1991;42(1):3-8.

35. Gonzalez-Diego P, Lopez-Abente G, Pollan M, Ruiz M. Time trends in ovarian cancer mortality in Europe (1955-1993): effect of age, birth cohort and period of death. *Eur J Cancer.* 2000;36(14):1816-1824.

36. dos Santos Silva I, Swerdlow AJ. Recent trends in incidence of and mortality from breast, ovarian and endometrial cancers in England and Wales and their relation to changing fertility and oral contraceptive use. *Br J Cancer.* 1995;72(2):485-492.

37. Statistics Netherlands. Historical data: Health and welfare - lifestyle. *<http://statline.cbs.nl/statweb/>. (*accessed December 2011).

38. Hankinson SE, Colditz GA, Hunter DJ, et al. A prospective study of reproductive factors and risk of epithelial ovarian cancer. *Cancer.* 1995;76(2):284-290.

39. Adami HO, Hsieh CC, Lambe M, et al. Parity, age at first childbirth, and risk of ovarian cancer. *Lancet.* 1994;344(8932):1250-1254.

40. Braem MG, Onland-Moret NC, van den Brandt PA, et al. Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. *Am J Epidemiol.* 2010;172(10):1181-1189.

41. Statistics Netherlands. Population - birth. *<http://statline.cbs.nl/statweb/>. (*accessed May 2012).
42. Albrektsen G, Heuch I, Kvale G. Reproductive factors and incidence of epithelial ovarian cancer: a Norwegian prospective study. *Cancer Causes Control.* 1996;7(4):421-427.
43. Statistics Netherlands. Health and welfare - birth and mortality. *<http://statline.cbs.nl/statweb/>. (*accessed May 2012).
44. Jordan SJ, Siskind V, A CG, Whiteman DC, Webb PM. Breastfeeding and risk of epithelial ovarian cancer. *Cancer Causes Control.* 2010;21(1):109-116.
45. World Cancer Research Fund / American Institute for Cancer Research. *Food, nutrition, physical activity and the prevention of cancer: a global perspective.* Washington DC: AICR;2007.
46. Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol.* 2007;19(1):3-9.
47. Massuger L, Roelofsen T, Ham M, Bulten J. The origin of serous ovarian cancer may be found in the uterus: a novel hypothesis. *Med Hypotheses.* 2010;74(5):859-861.
48. Bosman JM, Lako CJ, Sturmans F, Willems JH. [The increasing number of hysterectomies in the Netherlands: the influence on incidence of and mortality due to cervix carcinoma]. *Ned Tijdschr Geneeskd.* 1983;127(21):900-905.
49. Hoogendoorn D. [The odds on hysterectomy and estimation of the number of cancer deaths prevented by hysterectomies in their current incidence]. *Ned Tijdschr Geneeskd.* 1984;128(41):1937-1940.
50. National Medical Registration - Diagnoses. *<http://cognosserver.prismant.nl/cognos7/cgi-bin/ppdscgi.cgi?DC=Q&E=/Prisma-Landelijke-LMR/Landelijke+LMR-informatie+-+Diagnosen>. (*accessed December 2011).
51. Pharoah PD, Ponder BA. The genetics of ovarian cancer. *Best Pract Res Clin Obstet Gynaecol.* 2002;16(4):449-468.
52. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003;72(5):1117-1130.
53. van der Kolk DM, de Bock GH, Leegte BK, et al. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. *Breast Cancer Res Treat.* 2010;124(3):643-651.
54. Hermsen BB, Olivier RI, Verheijen RH, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. *Br J Cancer.* 2007;96(9):1335-1342.
55. van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? *Int J Cancer.* 2009;124(4):919-923.
56. Chan JK, Cheung MK, Husain A, et al. Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol.* 2006;108(3 Pt 1):521-528.
57. Verdecchia A, Guzzinati S, Francisci S, et al. Survival trends in European cancer patients diagnosed from 1988 to 1999. *Eur J Cancer.* 2009;45(6):1042-1066.
58. de Vries E, Karim-Kos HE, Janssen-Heijnen ML, Soerjomataram I, Kiemeney LA, Coebergh JW. Explanations for worsening cancer survival. *Nature reviews.* 2010;7(1):60-63.
59. van Altena AM, Karim-Kos HE, de Vries E, Kruitwagen RF, Massuger LF, Kiemeney LA. Trends in therapy and survival of advanced stage epithelial ovarian cancer patients in the Netherlands. *Gynecol Oncol.* 2012;125(3):649-654.
60. Engelen MJ, Kos HE, Willemse PH, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer.* 2006;106(3):589-598.

61. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecol Oncol.* 2007;105(3):801-812.

62. Vernooij F, Heintz AP, Witteveen PO, van der Heiden-van der Loo M, Coebergh JW, van der Graaf Y. Specialized care and survival of ovarian cancer patients in The Netherlands: nationwide cohort study. *J Natl Cancer Inst.* 2008;100(6):399-406.

CHAPTER 4

The impact of changes in cancer management on cancer trends

CHAPTER 4.1

Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006

Ruben G.H.M. Cremers
Henrike E. Karim-Kos
Saskia Houterman
Rob H.A. Verhoeven
Fritz H. Schröder
Theodorus H. van der Kwast
Paul J.M. Kil
Jan Willem W. Coebergh
Lambertus A.L.M. Kiemeney

Eur J Cancer. 2010 Jul; 46(11):2077-87

ABSTRACT

Background. Prostate cancer occurrence and stage distribution changed dramatically during the end of the 20th century. This study aimed to quantify and explain trends in incidence, stage distribution, survival and mortality in the Netherlands between 1989 and 2006.

Methods. Population-based data from the nationwide Netherlands Cancer Registry and Causes of Death Registry were used. Annual incidence and mortality rates were calculated and age-adjusted to the European Standard Population. Trends in rates were evaluated by age, clinical stage and differentiation grade.

Results. 120,965 men were newly diagnosed with prostate cancer between 1989 and 2006. Age-adjusted incidence rates increased from 63 to 104 per 100,000 person-years in this period. Two periods of increasing incidence rates could be distinguished with increases of predominantly in cT2-tumours between 1989 and 1995 and predominantly in cT1c-tumours since 2001. cT4/N+/M+-tumour incidence rates decreased from 23 in 1993 to 18 in 2006. The trend towards earlier detection was accompanied by a lower mean age at diagnosis (from 74 in 1989 to 70 in 2006), increased frequency of treatment with curative intent and improved 5-year relative survival. Mortality rates decreased from 34 in 1996 to 26 in 2007.

Conclusions. The increase of prostate cancer incidence in the early 1990s was probably caused by increased prostate cancer awareness combined with diagnostic improvements (transrectal ultrasound, (thin) needle biopsies), but not PSA testing. The subsequent peak since 2001 is probably attributable to PSA testing. The decline in prostate cancer mortality from 1996 onwards may be the consequence of increased detection of cT2-tumors between 1989 and 1995. Unfortunately, data on the use of PSA tests and other prostate cancer diagnostics to support these conclusions are lacking.

INTRODUCTION

In the last decades of the 20th century, prostate cancer incidence increased in most high-income countries. It is generally accepted that a large part of this increase can be accounted for by earlier (and increased) detection due to more frequent digital rectal examination as a consequence of greater prostate cancer awareness, incidental diagnosis due to the increasing use of transurethral resection of the prostate (TURP) and developments in diagnostic techniques such as transrectal ultrasound (TRUS) imaging and thin needle biopsies.[1-4]

The late 1980s, PSA testing became available.[5] Particularly in the United States of America (USA), but also in other high-income countries, a further steep increase in prostate cancer incidence was observed after the introduction of PSA testing.[6] Welch et al. calculated that from 1986 to 2005 an excess of at least one million men were diagnosed with and treated for prostate cancer in the USA due to PSA testing.[7] Recently, the European Randomised study of Screening for Prostate Cancer (ERSPC) showed a 20% decrease in prostate cancer related mortality in study participants as an effect of programmed population-based PSA testing.[8] However, PSA testing is not routine practice yet in the Netherlands.[9] Consequently, whether PSA testing is responsible for the observed decrease in the incidence of metastasized tumours and mortality in the Netherlands over the past 16 years is questionable.

New therapies or improvements in existing therapies can also cause trends or trend changes in prognosis. Radical surgery and radiotherapy (external-beam radiotherapy and brachytherapy) are available for the treatment of localised prostate cancer and, for advanced disease, these treatments are sometimes combined with hormonal therapy.[10] It is not known whether changes in the application of these therapies have had an effect on trends in the prognosis of patients with prostate cancer in the Netherlands.

Insight in incidence, disease stage and mortality patterns in the Netherlands may reveal a need for policy changes. Prostate cancer represents a large burden for society and with the ageing population the number of newly diagnosed patients in the Netherlands is expected to rise from 9500 patients in 2006 to an estimated 15,000 in 2015.[11] The number of prevalent patients for whom periodical check-ups will be necessary is expected to increase even more dramatically. The aim of this population-based study was to identify and explain temporal trends in prostate

cancer incidence, disease stage, survival and mortality in the Netherlands from 1989 to 2006.

MATERIAL AND METHODS

The Association of Comprehensive Cancer Centres (CCCs) has registered data of all newly diagnosed neoplasms in the Netherlands since 1989. The resulting nationwide Netherlands Cancer Registry (NCR; www.ikcnet.nl) is considered to be of very high quality due to the standardised identification of new cases of cancer through the national automated pathology archive (PALGA), the national registry of hospital discharges (LMR), haematology departments and radiotherapy institutions, and because of the thorough training and testing of the registrars. After identification of new cases, these registrars abstract data from the medical files in all Dutch hospitals. Computerised consistency checks and re-abstraction and re-entry of data further improve the quality of the data. Completeness is estimated to be at least 95%.[12] Population-based data concerning prostate cancer diagnoses between 1989 and 2006 were analysed for the purpose of this study.[11] One of the eight CCCs (CCC South) began with cancer registration in the 1950s. Therefore, we were also able to make use of data from CCC South for the period 1970-1988 in order to investigate longer term trends in overall incidence.[13] The data from the CCC South were used only for the long-term evaluation of overall incidence and mortality. For the calculation of survival, the NCR links its database with the population-based demography registry that keeps data on vital status of all Dutch citizens. This nationwide demography database was started in 1995. Four of the eight CCCs contributing data to the NCR have retrospectively collected vital status data of all patients diagnosed before 1995. Mortality data, obtained from Statistics Netherlands, were available from 1970 to 2007.[14]

Histology was coded according to the International Classification of Diseases for Oncology (ICD-O).[15] Differentiation was graded using the World Health Organisation (WHO) grading system until 2003, after which it was replaced by the Gleason score.[16] Histological grading was categorised as well differentiated (WHO grade 1 or Gleason score 2-6), moderately differentiated (WHO grade 2 or Gleason score 7) or poorly differentiated (WHO grade 3 or Gleason score 8-10). Patients with

undifferentiated (grade 4) tumours (<1%) were included in the category 'poorly differentiated tumours'.

Clinical stage was recorded strictly according to the formal TNM classification in use at the time of diagnosis and grouped into cT1a/b, cT1c (existing since 1993), cT2, cT3, cT4/N+/M+ or 'unknown' (cTx) if insufficient information was available for accurate staging.[17] For patients who had undergone a radical prostatectomy, the clinical and post-surgical T-stage were crosstabulated to evaluate trends in clinical overstaging and understaging by period of diagnosis.

The first-line treatment (or treatment combination) was recorded. Patients who were incidentally diagnosed with prostate cancer in TURP specimens and who received no further treatment, were categorized into the 'no therapy'-group.

The study period was divided into three 5-year episodes and one 3-year period: 1989-1993, 1994-1998, 1999-2003, and 2004-2006. Patients were grouped into three age categories in order to identify age-specific trends in stage distribution and treatment (<65, 65-74 and ≥75 years) and into five age categories for incidence and mortality rates (45-54, 55-64, 65-74, 75-84 and ≥85 years).

Statistical analysis

Annual incidence and mortality rates for the period 1989-2006 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to the European standard population (European Standardised Rates (ESR)). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the 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 * (e^a – 1)). [18] Incidence rates were also calculated per age group, differentiation grade and clinical stage. Treatment administration was described as percentage per age group and calendar period.

Follow-up of all patients was calculated as the time from diagnosis to death or to January 1st 2008. Five-year relative survival was used to estimate disease-specific survival. Relative survival was calculated as the absolute survival among cancer patients divided by the expected survival for the general male population with the same age.[19] For the stage-stratified survival analysis, the pTNM classification was used. If pTNM was not available, cTNM was used. Traditional cohort-based relative

survival analysis was used for the period 1989-2003 which represents the survival of patients diagnosed during 1989-2003. Period-based relative survival analysis was used for the most recent period 2004-2006, in order to obtain a more up-to-date estimate for this period.[20] Survival trends were quantified as the mean annual percentage change (MAPC) from 1989 to 2006 as estimated by a linear regression model. This calculation assumes that the rates increased or decreased at a constant rate over the entire period. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

RESULTS

Age-specific incidence

A total of 120,965 patients were diagnosed with prostate cancer between 1989 and 2006. The annual number of diagnoses more than doubled from 4201 in 1989 to 9516 in 2006. The mean age at diagnosis decreased from 74 years in 1989 to 70 in 2006.

Prostate cancer incidence rates gradually increased in the CCC South catchment area between 1970 and 1989, with an EAPC of 1.9% (95% CI 1.1-2.7%). Thereafter, the incidence in the whole country increased steeply from 63 per 100,000 person-years in 1989 to 90 in 1995, with an EAPC of 7.1% (95% CI 4.5-9.8%) (**Figure 4.1.1**). Incidence rates remained stable between 1995 and 2000 (EAPC -0.9%; 95% CI -5.9 to 3.8%), but rose from 88 in 2000 to 104 in 2006 (EAPC 3.6%; 95% CI 1.1-6.1%). The CCC South data in the period 1989-2006 showed the same pattern as the nation-wide data.

Stage-specific incidence

Since the introduction of the cT1c-category in the TNM classification for PSA-detected prostate cancer in 1993, cT1c-tumor incidence rose to 35 per 100,000 person-years in 2006 (EAPC: 18.2%; 95% CI 16.0-20.5%) (**Figure 4.1.3**). The largest increase was observed from 2001 onwards. The incidence rate for cT1a/b-tumours dropped from 1992 to 1993 and decreased further until 2001. The incidence rate of cT2-tumours increased from 19 in 1989 to 37 in 1995 (EAPC 16.7%; 95% CI 13.5-20.0%) and then decreased to 30 in 2006 (EAPC -1.6%; 95% CI -2.7 to -0.5%). After increasing from 1989 to 1994 (EAPC 12.4%; 95% CI 6.0-19.3%), the incidence rate of

cT3-tumours remained stable until the end of the study period (EAPC 1.4%; 95%CI -0.2 to 3.0). The incidence rate of cT4/N+/M+-tumours decreased from 1993 to 1999 (EAPC -4.5%; 95%CI -6.6 to -2.2%), after which it remained stable. In absolute numbers, the annual number of diagnosed cT4/N+/M+-tumours increased gradually from 1,345 cases nationwide in 1989 to 1,614 in 2006.

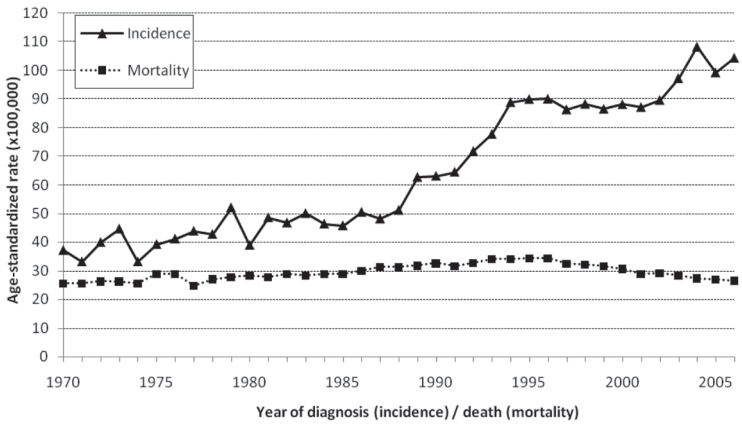


Figure 4.1.1 | Age-standardised rates (European Standard Population) for incidence and mortality of prostate cancer in the Netherlands 1970-2006 (incidence rates 1970-1988: data Comprehensive Cancer Centre South; incidence rates 1989-2006: data Netherlands Cancer Registry - no differences between CCCS and NCR data in period 1989-2006 -; mortality rates 1970-2006: Statistics Netherlands)

Age-stratified incidence rates increased over time for men under the age of 75 years (**Figure 4.1.2**). Incidence rates for men aged 65-74 years rose from 1989 until 1995 (EAPC 8.9%; 95% CI 5.9-12.7%), were stable until 2000 (EAPC 0.7%; 95% CI -2.9 to 4.4%) and then rose again until 2006 (EAPC 4.5%; 95% CI 0.8-8.4%). For men aged 55-64 incidence rates increased throughout the study period: EAPC 17.7% (95% CI 0.8-37.3%) from 1991 to 1994 and 5.8% (95% CI 4.9-6.8%) from 1994 to 2006.

For men over 75, incidence rates increased until 1994, but then decreased until 2006 with EAPCs of -1.8% (95% CI -2.7 to -0.9%) for men aged 75-84 and -7.4% (95% CI -12.1 to -2.7%) for men over 85.

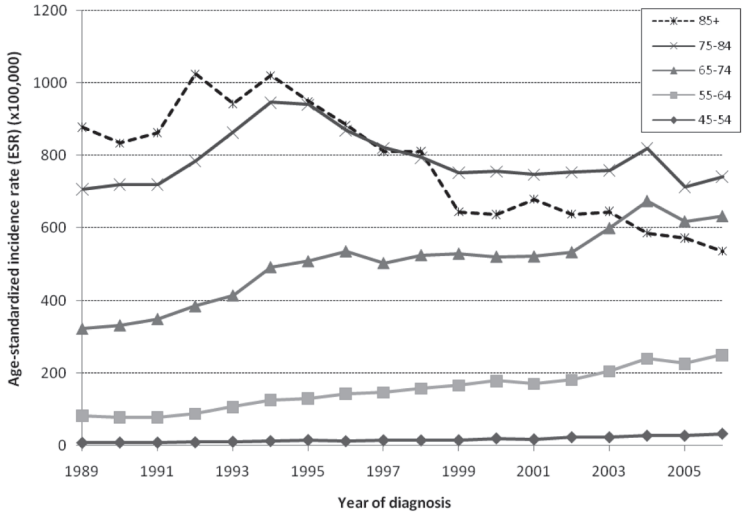


Figure 4.1.2 | Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1989-2006, stratified by age category

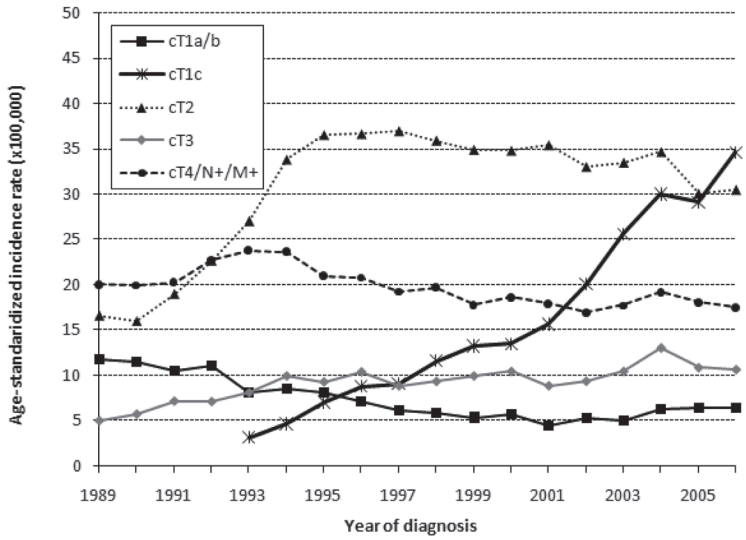


Figure 4.1.3 | Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1989-2006, stratified by clinical stage

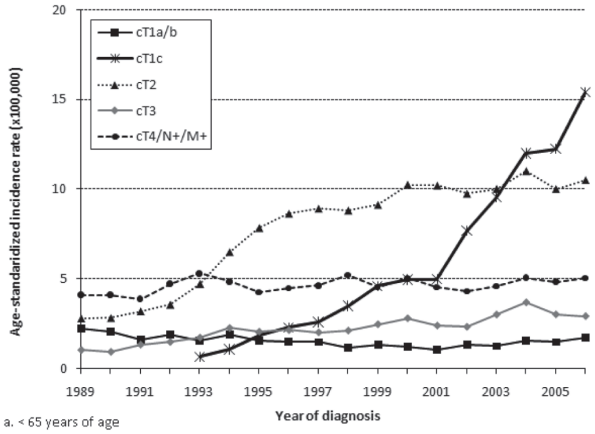


Figure 4.1.4 | Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1989-2006, stratified by clinical stage in three age categories: (a) < 65 years of age (b) 65-74 years of age and (c) > 74 years of age

Age-stratified analysis of these data shows that the increase in cT1c-tumours was most markedly present in men under 75 years of age and that increase seemed to accelerate from 2001 onwards (**Figure 4.1.4a-c**). The incidence rate of cT2-tumours rose quickly until the mid-1990s for all age categories, after which it remained stable for men under 75 and decreased for men over 75. The incidence rate of cT3-tumours gradually increased for men under 75 and remained nearly constant for men over 75. The decrease in cT4/N+/M+-tumour incidence from 1993 to 1999 was most clearly present for men over 75.

The incidence rate of well-differentiated tumours increased from 1991 to 1995 (EAPC 8.3%; 95% CI 5.5-11.2%) and then decreased until 2003 (EAPC -6.1%; 95% CI -9.2% to -2.9%) (**Figure 4.1.5**). For moderately differentiated tumours, the EAPC was 5.5% (95% CI 4.2-6.9%) from 1989 to 2003. Since 2003, the incidence of well-differentiated tumours increased, while moderately differentiated tumours decreased.

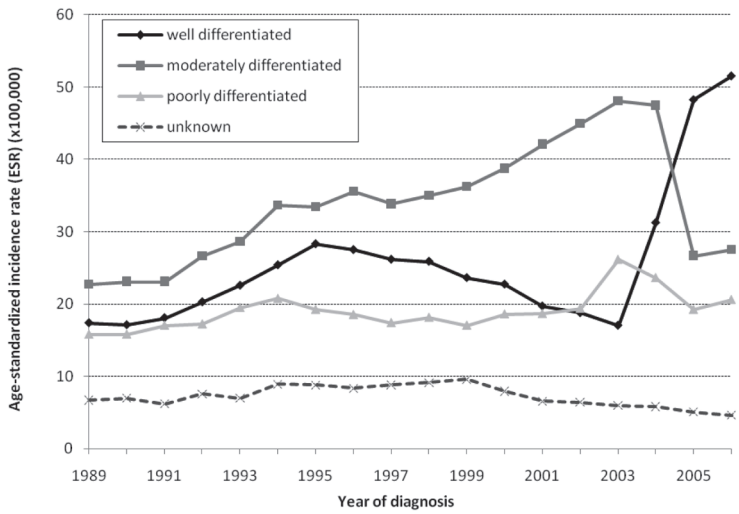


Figure 4.1.5 | Age-standardised incidence rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands, stratified by grade of differentiation (until 2003 the WHO grading system was used to determine differentiation; from 2004 onwards the Gleason scoring system was used: Gleason score 2-6 = well differentiated, Gleason score 7 = moderately differentiated, Gleason score 8-10 = poorly differentiated)

Clinical understaging

17,117 patients underwent a radical prostatectomy. For these patients, both cTNM and pTNM were known. Approximately one third of these patients who were considered cT2 (n=8,868) were clinically understaged and had pT3 (n=2,675) or pT4 (n=246). Patients classified as cT3 were overstaged in 27% of the cases with a known pT-classification (n=136/499). The amount of understaging of cT2- and cT3-tumors remained relatively constant during the last three periods of diagnosis. Clinical overstaging of cT3-tumors occurred more frequently over time, rising from 18% in 1989-1993 to 37% in 2004-2006.

Treatment

For 1,333 patients (1.1%) the primary treatment was not registered. These patients were excluded from this analysis. Over time, patients under 75 with cT1- and cT2-tumours more frequently underwent radical prostatectomy. Patients aged 65-74 with localised tumours underwent surgery less frequently than their younger counterparts. Still, the percentage of men undergoing radical prostatectomy almost doubled to 20% between 2004 and 2006. Radiotherapy as sole therapy increased mainly through increased application of brachytherapy. Active surveillance was chosen less often (from 38% of all cT1-tumours in 1989 to 9% in 2006). The latter group included patients with incidental prostate cancer found during TURP.

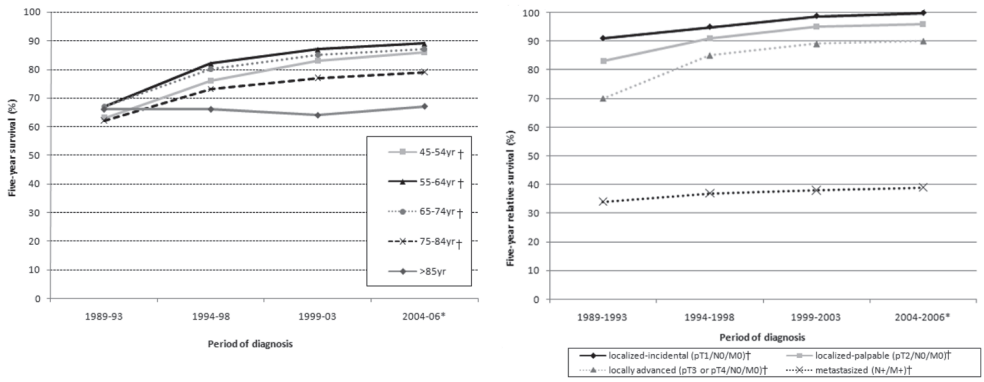
Patients under 75 with cT3-tumours received concurrent radiotherapy and hormonal therapy in more than 70% of cases since the late 1990s. Patients over 75 with localised disease most often received either no therapy (60%, 30% and 20% of the patients with cT1-, cT2- and cT3-tumour, respectively) or hormonal therapy.

For cT4/N+/M+ prostate cancer the only available therapy is hormonal therapy. This was given to 80% to 90% of the patients in all age categories. The combination of radiotherapy and hormonal therapy was chosen for approximately 10% of patients under 75 years of age (data not shown).

Survival

Five-year survival significantly increased in all age categories under 85 and all stages (**Figure 4.1.6**). The age-stratified analysis showed that men aged 45-54 had the highest MAPC with 1.8% annual increase (95% CI 1.2-2.3%). This increase declined gradually with every higher age category to 1.3% (95% CI 1.0-1.6%) for men aged 75-84 and no change for men over 85 years of age. The stage-specific increase in

survival was strongest for men with pT3/pT4-tumours with a MAPC of 1.6% (95% CI 1.2-2.0%). Locally extended or metastatic cancer had the lowest MAPC with 0.4% annual increase in survival (95% CI 0.2-0.7%).



A B

Figure 4.1.6 | (a) Five-year relative survival from prostate cancer by period of diagnosis, stratified by age category (*calculation by period analysis for period of diagnosis 2004-06); (b) 5-year relative survival from prostate cancer by period of diagnosis, stratified by pathological stage (*calculation by period analysis for period of diagnosis 2004-06); † significant change ($p < 0,05$) in 5-year relative survival

Mortality

Disease-specific mortality rates increased slightly from 1970 to 1995 (from 26 to 34 per 100,000 person-years) (EAPC = 1.2; 95% CI 1.0-1.3%) and then decreased to 26 in 2007 (EAPC = -2.5%; 95% CI -3.0 to -2.0%) (**Figure 4.1.1**). This pattern was observed for all men over 65 years of age (**Figure 4.1.7**) and was most evident in men over 85 years of age, with an EAPC from 1996 to 2007 of -3.4% (95% CI -4.0 to -2.8%).

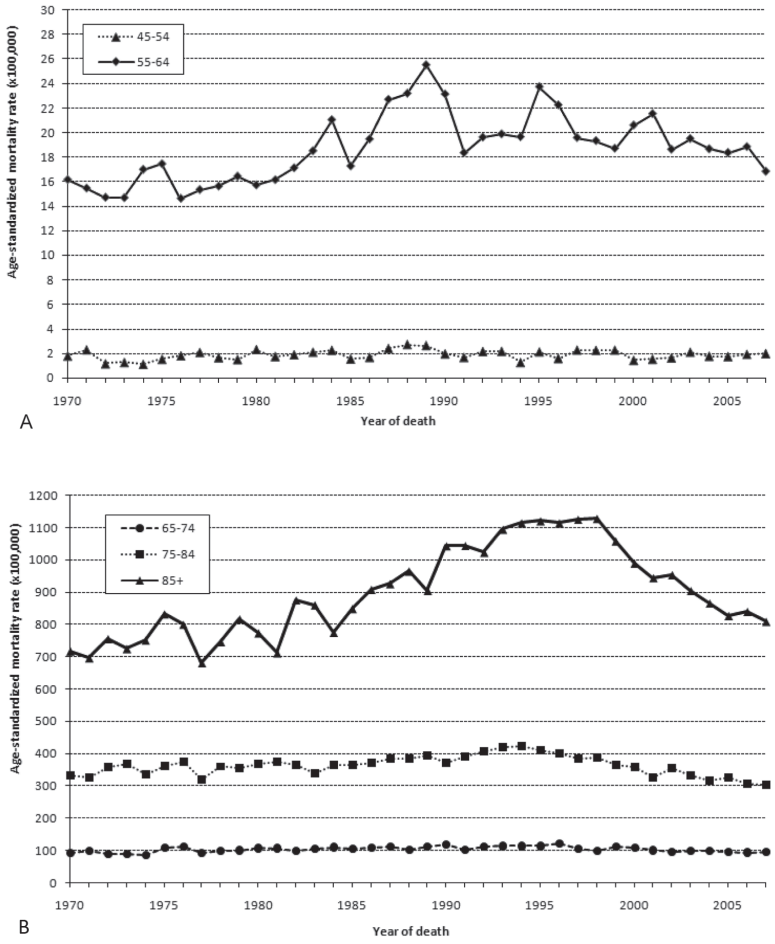


Figure 4.1.7 | Age-standardised mortality rates per 100,000 person-years (European Standard Population) for prostate cancer in the Netherlands 1970-2006, stratified by age category: (a) 45-54 years, 55-64 years and (b) 65-74 years, 75-84 years, 85+ years

DISCUSSION

Age-specific incidence

Between 1989 and 2006, two periods with significant increases in prostate cancer incidence were observed. The increase in the first period, from 1989 to 1995, is

often explained as an effect of PSA testing.[13,21,22] However, arguments exist against this explanation. In the Netherlands, PSA testing was introduced relatively slowly, although valid population-based data about the use of PSA tests throughout the study period are not available. An interim analysis of the Rotterdam section of the ERSPC found 8% effective contamination in the control arm between 1997 and 2000.[23] Also, according to a Statistics Netherlands survey, in 2001 only 14% of men over 45 years of age had a PSA measurement in the previous five years.[9] Moreover, the increase in incidence from 1989 to 1995 was present in all age categories, while PSA testing in asymptomatic men would be expected to be used less frequently among elderly (over 75 years of age) because of reservations towards treatment for men with a relatively short life expectancy (less than 10 years). Although the percentage of men over 75 years of age who had a PSA test in the previous 5 years (40%) is approximately equal to the percentage of men between 55 and 75 years of age, 43% of all the men over the age of 70 who reported having had a PSA test, was between 70 and 74 years of age (Dr. Bruggink, Statistics Netherlands, personal communication). A difficulty with the interpretation of these percentages, though, is that with these numbers on cannot distinguish whether these PSA tests were the first to be undergone by the interviewed men. This is unfortunate as the first PSA test is the most important one when testing for prostate cancer. Very likely, men who have had PSA tests before, will remain to be tested at a later age by their GP or urologist.

Stage-specific incidence

Unfortunately, there is no detailed information available about PSA-detected tumours before 1993, as the cT1c-category was only introduced in the cTNM classification (and the NCR registry protocol) in 1993. Therefore, the cT1a/b-category is heterogeneous until 1992, comprising both TURP-detected and PSA-detected prostate cancer. The stage-specific analyses from 1993 onwards reveal that cT1c-tumour incidence continuously increased and was accompanied by a decrease in the incidence of cT1a/b-tumours until 2001. This increase, together with the increase in cT2-tumour incidence until 1995 and the decrease in cT4/N+/M+-tumour incidence from 1993 to 1999, results in the biphasic increase observed in the overall incidence.

From these data, it can be deduced that the rise of prostate cancer incidence in the early 1990s was mainly caused by an increase in cT2-tumours, probably due to more frequent digital rectal examinations (DRE) and technical improvements in

diagnostics, such as TRUS imaging and the use of (thin) needle biopsies. Because cT1c-tumour incidence continued to rise while the incidence of all other stages stabilized since 2000, PSA testing must have caused the subsequent peak from 2000 to 2006. This is further supported by the fact that incidence rates increased only for patients under 75 years of age and by the results of the Statistics Netherlands survey, which showed that the percentage of men over 45 years of age who had their serum PSA measured in the previous five years rose from 14% in 2001 to 26% in 2008.[9] Direct population-based data to support this are not available, however.

Incidence rates of locally extensive and metastatic (cT4/N+/M+) disease evidently decreased from 1993 to 1999, particularly in men over 65. As interventions directed at detection of cancer in an earlier stage need time to show their beneficial effect on metastasized disease or mortality, a delay between the rise in localized tumors and decrease in metastasized tumors is to be expected. Also, one might expect to see a rise of localised prostate cancer in a younger age category, followed by a decrease in more advanced disease in an older age category. This study found a difference in onset of the increase in localised prostate cancer (1989/1990) and decrease of metastasized cancer (1993) of approximately 4 years. This corresponds reasonably well to the effect of early detection of prostate cancer on mortality as observed in the ERSPC, which only became apparent after 7 to 8 years.[8] Thus, some change must have occurred around 1990, most probably an increased use of DRE, TRUS imaging and (thin) needle biopsies, but not yet PSA testing. However, this conclusion is somewhat speculative. Other factors might also have contributed to a rise in localised prostate cancer and the subsequent decrease in metastasized disease.

From 1995 to 2003, more moderately differentiated tumours were detected, whereas the incidence of well-differentiated tumours decreased. Knowing that the incidence of cT1c-tumours increased in the same period, this could indicate that PSA testing was effective in detecting moderately differentiated tumours. The trend continued until the registration protocol was changed from the WHO grading system to the Gleason scoring system in 2004. Unfortunately, these systems are not easily interchangeable, as the WHO grading system is based on cellular and nuclear characteristics and the Gleason scoring system on growth patterns. The sudden changes in well-differentiated and moderately differentiated tumours around 2004 were most probably caused by this change in protocol.

Other western countries have shown similar increases in prostate cancer incidence in the study period. The situation in the United Kingdom (UK) might resemble the Dutch situation. In the UK, similar trends were seen with regard to prostate cancer incidence and mortality.[24] In the UK, as in the Netherlands, PSA uptake was considerably lower than in the USA, as illustrated by an overall annual rate of 6.0% for PSA testing in men aged 45-84 with no previous diagnosis of prostate cancer between 1999 and 2002.[25] Consequently, it is possible that the rise in prostate cancer incidence in the UK in the early 1990s and the decrease in mortality since the mid-1990s was also caused by an increased prostate cancer awareness. Without analyses of stage-specific data from the UK, however, this will remain unclear.

The overall prostate cancer incidence in the Netherlands is still considerably lower than in, e.g. Sweden and North America.[26,27] Interestingly, however, prostate cancer incidence has been decreasing in the USA since 2001.[28] This might indicate that the "prevalent pool" of prostate cancer cases in the USA is being exhausted. The following years will learn whether a similar trend will occur in the Netherlands and other western countries.

Treatment

Over time, patients under 65 with localised (cT1- and cT2-) tumours more often underwent surgery (radical prostatectomy). At the same time, the proportion of patients who received no therapy/TUR- only decreased. This might again be explained by PSA testing. Since PSA became available, patients who were otherwise eligible for TURP may now have had a PSA test with, if indicated, subsequent random prostate biopsies prior to the resection. This would result in an increasingly smaller proportion of prostate cancers detected at TURP.[29]

Patients under 75 with cT3-tumors received radiotherapy in 50% of the cases in the early 1990s. Since 1999, the combination of radiotherapy and hormonal therapy was chosen for over 70% of cT3-patients. This reflects that this combination is considered the gold standard for cT3 prostate cancer, as proposed by Bolla and colleagues in 1997.[30] In addition to this indication, our data showed that, with time, this combination was also given more often to patients under 75 with cT1- and cT2-tumors.

Men over 75 years have a life expectancy shorter than 10 years.[31] As a result, according ot the guidelines, the majority of patients over 75 with a cT1-tumour did not receive therapy. Those who received treatment were most often treated

with hormonal therapy. As for the younger patients, combined radiotherapy and hormonal therapy for cT3-tumors were applied more frequently with time.

Treatment options for cT4/N+/M+ prostate cancer are still very limited. Hormonal treatment remained the cornerstone of treating extensive disease, reflected by the fact that over 90% of these patients in all age categories received hormonal treatment. A small minority received radiotherapy in addition to the hormonal treatment.

Survival

Survival from prostate cancer improved for all stages and age categories, except for patients over 85. Tumour stage and grade changes may have played a role in this. With the development of new imaging techniques, tumour staging became more precise. This could result in upstaging , for example, of what previously would have been recorded a large cT2-tumour to a minimal cT3-tumor, consequently increasing survival in both strata. Also, a grade shift could have been caused by the insight that Gleason scores lower than 6 should not be given on needle biopsy material, an advice stated by Epstein in 2000 and adopted by the ISUP in 2005.[32-34] However, as a decrease in prostate cancer mortality was also observed, this suggests that a genuine improvement of prostate cancer specific survival is also present.

Mortality

Prostate cancer mortality rates in the Netherlands have decreased since the mid-1990s. In most western European countries, a levelling-off of prostate cancer mortality rate has also been observed since the mid-1990s.[35] Another study comparing 1985-1989 with 1995-1998 found that prostate cancer mortality for males between 65 and 84 years declined by 4% in the EU and 6% in the USA.[36]

The decrease in prostate cancer mortality in the Netherlands might again be attributed to PSA testing. However, we have argued that PSA testing probably did not cause the decrease in incidence of metastasized cancer from 1993 to 1999. A similar argument can be put forward for the mortality rates although, again, we cannot support this with hard data. As the decrease in mortality started in 1996, the change most probably took place around 1990 (assuming approximately 7 years lag-time before an intervention shows an effect on mortality rates)[8] and was therefore most probably due to an increased use of DRE, TRUS and needle biopsy rather than to PSA testing. In addition to this, more precise staging and, subsequently, better

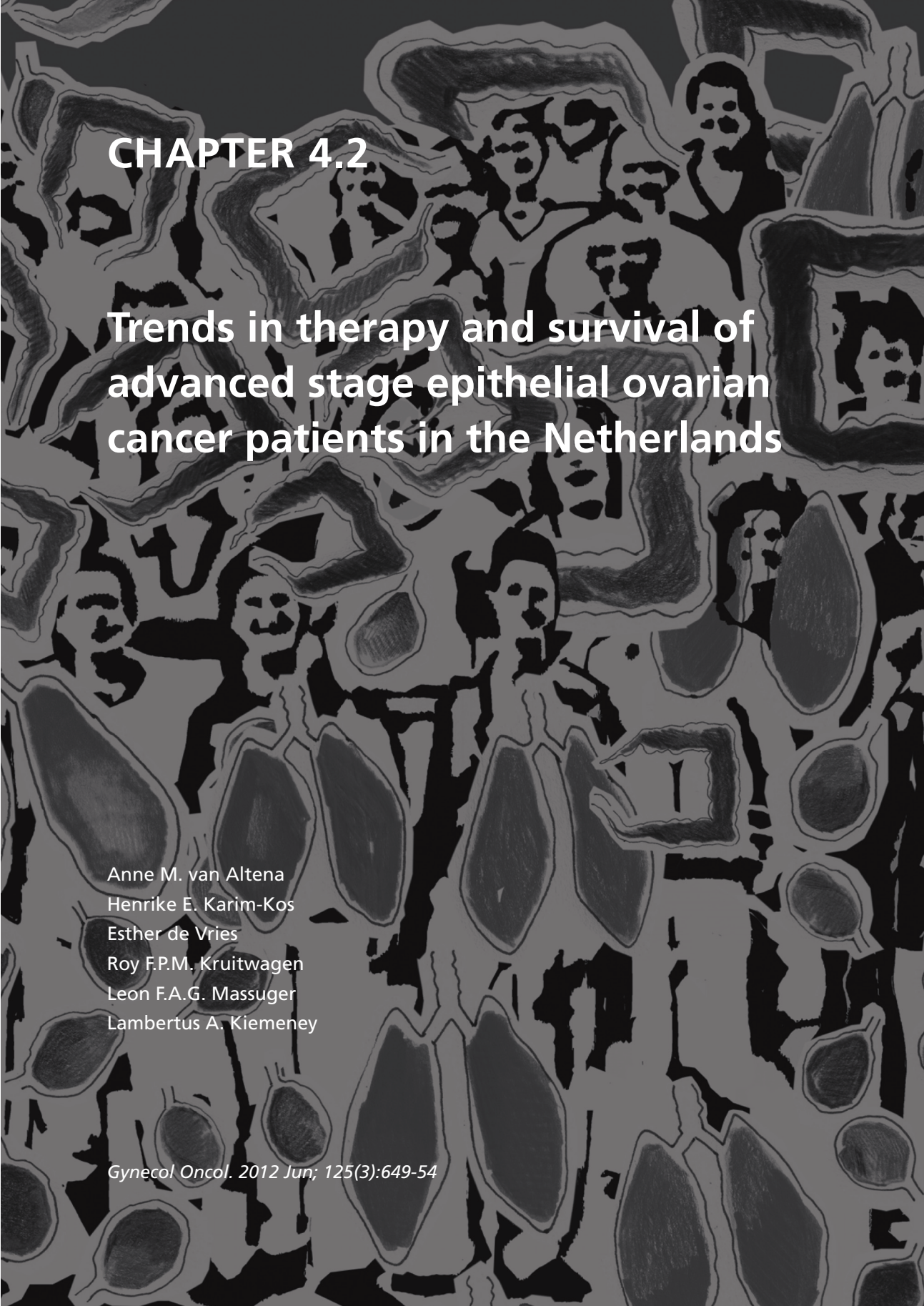
treatment might also have contributed to the decrease in prostate cancer mortality. Unfortunately, it is not possible to disentangle the extent to which these factors have played a role in the observed trends.

CONCLUSION

The NCR data presented here have shown that prostate cancer incidence increased between 1989 and 2006. This increase was most likely caused by an increased application of DRE in combination with technical improvements in diagnostics (TRUS, (thin) needle biopsies), whereas the subsequent peak in prostate cancer incidence from 2000 to 2006 can be attributed to PSA testing. The decline in prostate cancer mortality from 1996 onwards may be the consequence of the increased detection of cT2 prostate cancer from 1989 to 1995. Other unobserved factors may also have played a role in causing these trends.
Prostate cancer was more often detected in an early stage and treated with a curative intent, leading to a decreased incidence of metastatic prostate cancer, a lower mortality rate and increased survival. Thus, it can be said that significant progress has been made against prostate cancer in the Netherlands. However, this progress has come at the expense of considerable overdiagnosis. With the rising burden of prostate cancer due to the aging population, major improvements are still needed in the areas of biomarkers and detection, imaging and staging in order to avoid overdiagnosis.

Acknowledgements
This research was performed within the framework of the project "Progress against cancer in the Netherlands since the 1970?" (Dutch Cancer Society (EMCR 2006-3489)). Dr. Cremers was supported by Contract Number 202059 (ProMark) from the Seventh Framework Program from the European Union.

We thank the working group Output (K. Aben, R. Damhuis, J. Flobbe, M. Van der Heiden, P. Krijnen, L. Van de Poll, S. Siesling, J. Verloop) of the NCR for providing data from the cancer registry and the registration clerks for their dedicated data collection. Dr. J.W. Bruggink of Statistics Netherlands is acknowledged for his information about PSA testing data from the POLS survey.



CHAPTER 4.2

Trends in therapy and survival of advanced stage epithelial ovarian cancer patients in the Netherlands

Anne M. van Altena
Henrike E. Karim-Kos
Esther de Vries
Roy F.P.M. Kruitwagen
Leon F.A.G. Massuger
Lambertus A. Kiemeney

Gynecol Oncol. 2012 Jun; 125(3):649-54

ABSTRACT

Background. The aim of this study was to describe trends in survival and therapy in advanced stage epithelial ovarian cancer (EOC) in the Netherlands and to determine if changes in therapy affected survival.

Methods. All EOC patients diagnosed in the Netherlands during 1989-2009 were selected from the Netherlands Cancer Registry. Differences in treatment over time were tested by the Cochran-Armitage trend test. Multivariable relative survival analyses were performed to test whether changes in treatment are associated with survival.

Results. 23,399 patients were diagnosed with EOC, of whom 15,892 (67.9%) in advanced stage (stage ≥2b). In advanced stage patients, the proportion receiving (neo-)adjuvant chemotherapy and optimal debulking (residuals <1cm) increased over time in all age groups. In elderly patients (≥75 years) a stable proportion (approximately 28%) did not receive any treatment. Five-year relative survival in advanced stage patients increased from 18% in 1989-1993 to 28% in 2004-2009. In the multivariable model survival improved over time (relative excess risk (RER) of 2004-2009 was 0.71, 95% CI 0.67-0.75 compared to 1989-1993). This RER attenuated to 0.85 (95% CI 0.80-0.90) and 0.91 (95% CI 0.83-0.99) with inclusion of treatment variables in the model (surgery with chemotherapy or optimal surgery with chemotherapy, respectively). This suggests that the improvement was mainly, although not entirely, caused by changes in treatment.

Conclusions. Treatment in advanced stage EOC patients in the Netherlands improved over the last two decades; more patients received (neo)adjuvant chemotherapy and underwent an optimal debulking surgery. Changes in treatment led to partial improvement of survival in EOC patients.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the most lethal gynaecological malignancy in the Western World. In the Netherlands, approximately 1200 new patients are diagnosed with ovarian cancer each year, with approximately 900 deaths annually.[37] Due to the non-specific symptoms of this malignancy the majority of patients are diagnosed in an advanced stage of disease, i.e., stage 2b or higher. Since survival proportions drop significantly with increasing stage of disease patients with epithelial ovarian cancer in general face a very poor prognosis.

Management of epithelial ovarian cancer has changed during the last decades. Cisplatin was introduced in the USA in the mid 1970s and was later adopted as part of first line chemotherapy treatment. The use of paclitaxel-containing chemotherapy started in the early 1990s. In the late 1960s and early 1970s the concept of cytoreductive surgery (debulking) was introduced. A meta-analysis by Bristow showed that maximum cytoreduction is associated with an increase in survival.[38] The last decade, achieving an optimal debulking has become an important goal in therapy. Recently, the organization of EOC care has become an important issue. Both the surgeon performing the debulking surgery as well as the number of this type of surgeries performed per year and the type of hospital seem to affect survival of patients with EOC.[39,40] In the Netherlands, where traditionally patients were staged and treated in the hospital of diagnosis, this knowledge has led to the introduction of so-called regionalized care for EOC patients. Although at present a gynaecologic oncologist nearly always assists in surgery of patients with EOC in general and semi-specialized hospitals, still a minority of patients with EOC are indeed operated in referral hospitals.

The main goal of all these therapeutical changes is of course improvement of survival. A previous population-based study in the Netherlands showed an improved prognosis in the period 1975 until 1985.[41] International studies show an increased survival over the past decades. Generally this information is based on data obtained from trials and therefore not easily generalizable to the general population. In many studies details on therapy are lacking so the effect of changes in therapy on survival are unknown and often the population consists of ovarian cancer patients without respect for the subtypes of ovarian cancer which show very different survival rates. The aims of this nation-wide population-based study were to describe the trends in treatment and survival of advanced stage EOC patients during the period 1989 till

2009 and to study the possible effect of changes in therapy on the survival of EOC patients.

MATERIAL AND METHODS

Data collection

Population-based data were used from the Netherlands Cancer Registry (NCR). The NCR, which reached full national coverage in 1989, is based on notification of all newly diagnosed malignancies in the Netherlands by the automated nationwide pathology archive (PALGA). An additional source is the national registry of hospital discharge diagnoses, which accounts for up to 8% of all cases. Information on patient characteristics like date of birth, and tumour characteristics such as date of diagnosis, topography (International Classification of Diseases for Oncology (ICD-O-3)[42]), histology, TNM stage (Tumour Lymph Node Metastasis classification[43]) and FIGO stage,[44] grade, and primary treatment, are obtained from the medical records. The quality of the data is high, due to thorough training of the dedicated registrars and computerized consistency checks. Completeness is estimated to be at least 95%.[45] The information on vital status and date of death before January 1, 2010 was obtained from the municipal demography registries and from 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all Dutch citizens.

For the present study, all cases with epithelial ovarian cancer (C56, morphology code 8000, 8010-8013, 8020-8033, 8041-8231, 8255-8574 and 9000) diagnosed in the period 1989-2009 in the Netherlands were selected (n=23,399). This covers common histological types like serous, mucinous and endometrioid carcinoma, as well as adenocarcinoma not otherwise specified (NOS), mixed types, rare carcinomas (including clear cell carcinoma). All advanced stage patients, defined by FIGO stage 2b or higher were included in the analyses of treatment and survival (n=15,892). The tumour stage was based on postoperative findings, except when no operation had been performed, in which case clinical stage was used. Patients were divided in two age groups for treatment analysis (<75 and ≥75 years) and in four age groups for survival analyses (<44, 45-59, 60-74, and ≥75 years). The study period was divided into four categories: 1989-1993, 1994-1998, 1999-2003, and 2004-2009. Debulking data were available from 1995 till 2009 for four of the eight regional cancer registries

contributing to the NCR which are representative for the whole of the Netherlands. Optimal surgery was defined as a debulking surgery with residual tumour lesions smaller than 1 cm in maximum diameter. Patients younger than 15 years of age (n=4) and older than 95 years of age (n=28) were excluded from survival analyses, as well as all cases diagnosed by autopsy only (n=76).

Statistical analyses

Treatment was described as percentages per age group and calendar period. Differences in treatment over time were tested by the Cochran-Armitage trend test. Follow-up of vital status of all patients was calculated as the time from diagnosis to death or to the censuring date of January 1, 2010. Relative survival was calculated as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same structure for age and gender. Relative survival is calculated as the ratio of the observed survival among cancer patients to the expected survival of the general population.[19] For the period 1989-2003 cohort-based survival analysis was used. For the period 2004-2009 period-based survival analysis was conducted, in order to better capture recent survival experience.[20] Survival trends were quantified as the mean annual percentage change within 1989-2009 estimated by a linear regression model. Survival trends were evaluated by a linear regression model and $p<0.05$ was considered as statistically significant.

Multivariable relative survival analyses, using Poisson regression modeling,[46] were performed to estimate relative excess risk (RER) of dying for the periods of diagnosis. The variables period, age, stage and histology were included in the model. The two treatment variables were added to investigate the effect of therapy on the RER of period of diagnosis. The first variable was *Surgery with chemotherapy* (yes versus no) which was registered in all cancer registries. The second treatment variable, registered in four registries was *(Optimal) Surgery with Chemotherapy* and it was categorized in four groups: No surgery with chemotherapy, Yes but no optimal surgery, Yes but optimal surgery unknown and Yes and optimal surgery. Analyses were performed using SAS (SAS system 9.2, SAS Institute, Cary, NC).

RESULTS

A total of 23,399 patients were diagnosed with epithelial ovarian cancer in the Netherlands during the period 1989-2009. Median age at diagnosis of the patients was stable at 65 years during this period. The majority (68%) of the patients were diagnosed in an advanced stage (n=15,892) while 5,893 patients were diagnosed in early stages of disease (**Table 4.2.1**). An increasing number of serous carcinomas was found with a simultaneously decreasing number of adenocarcinomas NOS.

Table 4.2.1 | Characteristics of all epithelial ovarian cancer patients diagnosed between 1989 and 2009 in the Netherlands by period of diagnosis (n=23,399)

	Period of diagnosis n (%)				
	1989-1993	**1994-1998**	**1999-2003**	**2004-2009**	**Total period**
Age (years)					
<44	653 (11.4)	514 (8.8)	425 (7.9)	451 (7.1)	2,043 (8.7)
45-59	1,567 (27.3)	1,626 (27.8)	1,642 (30.4)	1,870 (29.2)	6,706 (28.7)
60-74	2,287 (39.8)	2,248 (38.4)	2,004 (37.1)	2,419 (37.8)	8,958 (38.3)
≥75	1,243 (21.6)	1,463 (25.0)	1,332 (24.6)	1,656 (25.9)	5,692 (24.3)
FIGO stage					
I	1,415 (24.6)	1,430 (24.4)	1,302 (24.1)	1,403 (21.9)	5,550 (23.7)
II A	84 (1.5)	96 (1.6)	68 (1.3)	95 (1.5)	343 (1.5)
IIB/IIC	433 (7.5)	360 (6.2)	365 (6.8)	433 (6.8)	1,591 (6.8)
III	2,470 (43.0)	2,591 (44.3)	2,431(45.0)	2,735 (42.8)	10,227 (43.7)
IV	976 (17.0)	876 (15.0)	862 (16.0)	1,360 (21.3)	4,074 (17.4)
unknown	372 (6.5)	498 (8.5)	374 (6.9)	370 (5.8)	1,614 (6.9)
Histology					
Serous	1,565 (27.2)	1844 (31.5)	2,061 (38.2)	2,966 (46.4)	8,436 (36.1)
Mucinous	848 (14.7)	794 (13.6)	592 (11.0)	552 (8.6)	2,786 (11.9)
Endometrioid	525 (9.1)	576 (9.8)	570 (10.6)	693 (10.8)	2,364 (10.1)
Adeno NOS§	2,415 (42.0)	2,078 (35.5)	1,609 (29.8)	1,478 (23.1)	7.580 (32.4)
Other	397 (6.9)	559 (9.6)	570 (10.6)	707 (11.1)	2,233 (9.5)
Total	5,750	5,851	5,402	6,396	23,399

§ Adenocarcinoma not otherwise specified

Trends in treatment in advanced stage disease

For patients with advanced stage disease the optimal management consists of a combination of debulking surgery and chemotherapy. An increasing number of patients received this combination, both in the younger (<75 years) and in elderly group (>75 years), with percentages rising from 63% in 1989-1993 to 82% in 2004-2009 and 23% to 34%, respectively (**Table 4.2.2**). This increase in the proportion of patients receiving a combination of therapy occurred simultaneously with a decreasing proportion of patients receiving chemotherapy alone, from 22% to 10% in the group under the age of 75 and from 30% to 21% in the elderly group. Also the percentage of patients receiving only surgery (though occasionally combined with hormonal therapy) showed a small decrease in both age groups. The proportion of patients receiving radiotherapy was negligible. In the younger patient group the proportion of patients receiving no therapy decreased. The only group that showed no change over time was the group of elderly not receiving any treatment. Nearly one third of the patients of 75 years or over received no therapy. A change was seen towards more optimal debulking procedures. This was true for the group of patients under 75 where the proportion of optimal debulking surgeries increased from 43% to 66% as well as for the elderly patients where the proportion increased from 17% to 24%.

Trends in survival

Overall survival rates of EOC patients increased during the period 1989 and 2009 but figures differ between early stage (**Figure 4.21A**) and advanced stage disease (**Figure 4.2.1B**). Women with stage I or IIa disease showed a stable 5-, and 10-year survival rate (**Table 4.2.3**). In advanced stage disease 1-, 3-, 5- and 10-year relative survival showed a significant increase. The 5-year survival increased between the period 1989-1993 and 2004-2009 from 19% to 28% (**Figure 4.2.1B**). As for the age of the patients, 5-year survival increased in the age groups 45-59 and 60-74, while in the age group above 74 years survival remained stable (**Table 4.2.3**).

Multivariable relative excess risk

The multivariable model for patients with an advanced stage of ovarian cancer without treatment included in the model showed improvements in survival over time, a lower survival for patients with more advanced stage of disease and a lower survival with increasing age (**Table 4.2.4**).

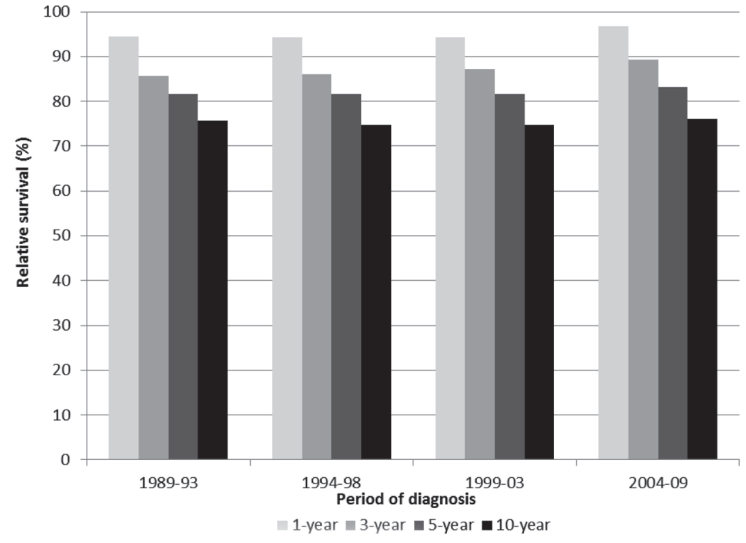
Table 4.2.2 | Treatment of advanced stage EOC patients by period of diagnosis and age at diagnosis (n=15,892)

Treatment Age	**1989-1993** n	(%)	**1994-1998** n	(%)	**1999-2003 n**	(%)	**2004-2009** n	(%)	**p-value**[a]
Surgery and chemotherapy									
<75	1881	(62.8)	1999	(70.4)	2162	(78.5)	2680	(81.7)	<.001
≥75	203	(22.9)	239	(24.2)	284	(31.3)	429	(34.4)	<.001
Surgery alone									
<75	220	(7.3)	208	(7.3)	149	(5.4)	127	(3.9)	<.001
≥75	116	(13.1)	186	(18.8)	146	(16.1)	116	(9.3)	<.001
Chemotherapy alone									
<75	660	(22.0)	431	(15.2)	286	(10.4)	317	(9.7)	<.001
≥75	268	(30.3)	224	(22.7)	192	(21.2)	256	(20.5)	<.001
Radiotherapy									
<75	42	(1.4)	13	(0.5)	12	(0.4)	12	(0.4)	<.001
≥75	12	(1.4)	3	(0.3)	3	(0.3)	2	(0.3)	.01
No therapy									
<75	165	(5.5)	159	(5.6)	121	(4.4)	122	(3.7)	<.001
≥75	244	(27.6)	273	(27.7)	224	(24.7)	374	(30.0)	.15
Optimal Debulking[b]									
<75	-	-	*417*	*(43.0)*	*558*	*(57.2)*	*779*	*(66.2)*	*<.001*
≥75	-	-	*51*	*(16.7)*	*94*	*(25.6)*	*118*	*(23.7)*	*.02*

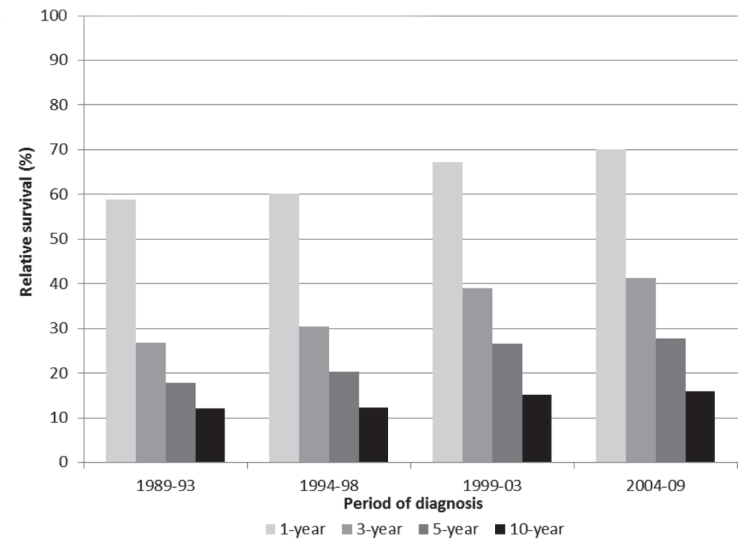
[a] Cochrane-Armitage trend test; [b] Definition of optimal debulking: tumour residuals after surgery smaller than 1 cm. Data on optimal debulking are available from 1995 from four regional cancer registries

Addition of the treatment variable S*urgery with chemotherapy* (yes versus no) to the model attenuated the relative excess risk during the study period, e.g. for 2004-2009 the relative excess risks changed from 0.71 (95% CI 0.67-0.75) to 0.85 (95% CI 0.80-0.90). This suggests that improvements in survival probabilities over time were partially due to changes in therapy. Patients who did receive surgery combined with chemotherapy had a better survival compared to patients who did not (RER 0.36; 95% CI 0.34-0.37).

The multivariable model for advanced stage patients in four regional cancer registry areas which had information on debulking, including the variable *(Optimal) Surgery with chemotherapy* is shown in the last two columns of **Table 4.2.4**. Addition of the variable showed a change in the RER for calendar period 2004-2009 from 0.78 (95% CI 0.71- 0.85) to 0.91 (95% CI 0.83 - 0.99). Patients who underwent surgery and chemotherapy but with a non-optimal result had a better survival compared with patients who did not undergo surgery (RER 0.35; 95% CI 0.31-0.39) while patients with an optimal result of their debulking surgery had the best survival (RER 0.26; 95% 0.23-0.28).



A



B

Figure 4.2.1 | Relative survival (1, 3, 5 and 10 years) for EOC patients in early stage of disease (A) and advanced stage of disease (B) by period of diagnosis. For the period 1989-2003 cohort analysis was used and for the period 2004-2009 period analysis was conducted. Survival trends were evaluated by a linear regression model.

Table 4.2.3 | The 5-year relative survival (SE) in EOC patients by period of diagnosis, age and stage of disease

	1989-1993	1994-1998	1999-2003	2004-2009[a]	*p* Annual trend
Stage					
I	82.9 (1.2)	82.6 (1.2)	82.6 (1.3)	84.1 (1.1)	.89
IIA	60.7 (5.9)	67.2 (5.6)	64.9 (6.4)	69.0 (5.8)	.07
IIB/C	43.4 (2.6)	51.0 (2.9)	56.7 (2.8)	63.3 (2.6)	<.001
III	17.9 (0.8)	20.7 (0.8)	26.8 (1.0)	28.6 (0.9)	<.001
IV	6.1 (0.8)	6.6 (0.9)	13.2 (1.2)	14.1 (1.1)	<.001
Age at diagnosis					
<45 years	64.4 (1.9)	67.4 (2.1)	64.4 (2.3)	63.6 (2.3)	.06
45-59	44.4 (1.3)	48.0 (1.3)	52.3 (1.3)	53.6 (1.2)	<.001
60-74	27.7 (1.0)	32.4 (1.1)	37.0 (1.1)	39.1 (1.1)	<.001
≥ 75	18.0 (1.4)	14.8 (1.2)	19.1 (1.3)	20.5 (1.3)	.20
Histology					
Serous	37.3 (1.3)	36.8 (1.2)	37.6 (1.1)	38.5 (1.0)	.70
Mucinous	58.1 (1.8)	56.7 (1.9)	62.4 (2.2)	64.1 (2.1)	.02
Endometrioid	52.8 (2.4)	59.7 (2.2)	67.7 (2.2)	69.9 (2.0)	<.001
Adeno NOS	19.3 (0.9)	20.8 (1.0)	24.6 (1.2)	21.4 (1.1)	.09
Other	43.0 (2.7)	34.8 (2.2)	39.4 (2.2)	42.2 (2.1)	.84
Total	34.7 (0.7)	36.0 (0.7)	40.0 (0.7)	41.1 (0.7)	<.001

[a] The survival rates of this period were based on period analysis.

Table 4.2.4 | Relative excess risk (RER) of dying for advanced stage EOC patients in the Netherlands including the treatment variable *Surgery with chemotherapy* and for patients in four cancer registry regions including the treatment variable (*Optimal) Surgery with chemotherapy*[a]

	Multivariate model for the Netherlands without treatment / with treatment variable				Multivariate model for four regions without treatment / with treatment variable			
	RER	**95%CI**	**RER**	**95%CI**	**RER**	**95%CI**	**RER**	**95%CI**
Period								
1989-1993	1.00	Reference	1.00	Reference				
1994-1998	0.94	0.89-0.99	1.01	0.96-1.06	1.00	Reference	1.00	Reference
1999-2003	0.75	0.71-0.80	0.88	0.83-0.92	0.77	0.71-0.84	0.89	0.82 – 0.98
2004-2009	0.71	0.67-0.75	0.85	0.80-0.90	0.78	0.71-0.85	0.91	0.83 – 0.99
Age								
<44	0.63	0.58-0.69	0.69	0.63-0.75	0.65	0.54-0.78	0.64	0.53 – 0.77
45-59	0.71	0.67-0.74	0.80	0.76-0.84	0.69	0.63-0.76	0.81	0.74 – 0.89
60-74	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
≥75	2.11	2.01-2.11	1.60	1.52-1.68	2.25	2.06-2.46	1.53	1.39 – 1.68

Table 4.2.4 | *Continued*

	Multivariate model for the Netherlands without treatment / with treatment variable				Multivariate model for four regions without treatment / with treatment variable			
	RER	**95%CI**	**RER**	**95%CI**	**RER**	**95%CI**	**RER**	**95%CI**
Stage								
IIB-C	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
III	2.39	2.19-2.60	2.37	2.18-2.58	2.41	2.03-2.86	2.46	2.07 – 2.91
IV	3.97	3.62-4.34	3.37	3.08-3.69	3.94	3.29-4.72	3.46	2.89 – 4.14
Histology								
Serous	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Mucinous	1.76	1.63-1.90	1.54	1.49-1.60	1.86	1.61-2.15	1.54	1.33 – 1.78
Endometrioid	0.93	0.85-1.01	0.92	0.88-0.96	0.90	0.76-1.06	0.91	0.77 – 1.07
Adenocarcinoma NOS[b]	1.62	1.55-1.69	1.32	1.27-1.37	1.74	1.61-1.90	1.40	1.29 – 1.53
Other	1.76	1.61-1.93	1.58	1.51-1.66	1.94	1.63-2.31	1.62	1.36 – 1.93
Surgery with chemotherapy								
No			1.00	Reference				
Yes			0.36	0.34-0.37				
(Optimal) Surgery with Chemotherapy								
No							1.00	Reference
Yes, suboptimal surgery							0.35	0.31-0.39
Yes, optimal unknown							0.30	0.25-0.35
Yes, optimal surgery							0.26	0.23-0.28

[a] Optimal surgery is defined as a debulking surgery with residual tumour lesions smaller than one cm in maximum diameter. [b] Adenocarcinoma not otherwise specified

DISCUSSION

This nationwide study of therapy and survival in advanced stage epithelial ovarian cancer supports the notion that the cornerstone of treatment consists of surgery combined with (neo) adjuvant chemotherapy. This combination has been applied in an increasing proportion of the Dutch EOC patients. Treatment options other than surgery and/or chemotherapy are rarely applied in EOC patients. Also elderly patients are more often treated in accordance with the (internationally) advised regimen, though still about 30% of the older patients with advanced stage of disease receive no treatment at all. The multivariable analyses demonstrate that changes in treatment partially led to improvement of survival. However, 10-year

survival figures for all stages show a small increase only from 29 to 31% despite all the efforts made with respect to therapeutic improvements.

All published studies on survival of ovarian cancer patients show an improvement over time. In the Supplemental Table S1 an overview is provided of population-based studies presenting series diagnosed since 1990 in high incidence countries.[26,47-58] Within Europe survival figures are fairly similar.[26] Differences in survival may be the result of different data sources used, e.g., in the study by Engel et al.[51] a hospital-based instead of population-based series was presented. Also the inclusion (as in most studies) or exclusion of non-epithelial ovarian cancer patients will influence survival. One Dutch population-based study on the prognosis of ovarian cancer patients was published before but it included non-epithelial cancer patients also.[41] Accordingly, survival data cannot be compared with our data. Both studies however show an improvement in 5-year survival figures.

Changes in chemotherapeutics over the years have improved survival. As early as the 1980s cisplatin-based combination therapy was found to be more effective than alkylating agents only.[59,60] Later on cisplatin was replaced by carboplatin because of less toxicity and better quality of life in EOC patients.[61] The introduction of taxanes again showed an improvement in survival in ovarian cancer patients.[62] The internationally recommended chemotherapy regimen as well as the first choice chemotherapy in the Dutch Guideline for EOC patients is now carboplatin plus paclitaxel.[63] Unfortunately the National Cancer Registry has no detailed data on agents, number of courses, doses or if it was adjuvant or neoadjuvant chemotherapy that was given in order to verify compliance with this guideline.

Since 1995 detailed data on surgical therapy are registered in four regions of the NCR. The data on the debulking result show an increase in the proportion of optimal debulking surgeries with tumour residuals smaller than one cm in largest diameter. The multivariable analysis showed that survival improvement was partially explained by this increase in optimal debulking surgeries. Internationally, the emphasis with respect to debulking surgery is on complete debulking with no visible tumour residuals. Unfortunately, these data were not registered. An increasing number of interval debulkings may result in more optimal surgery results, but data on the type of surgery (primary or interval debulking surgery) were also not available.

In The Netherlands, the care of cancer patients is increasingly organized regionally. Regionalised care for EOC patients was introduced in the late 1990s in

most regions in the Netherlands and at present is adopted nation-wide. By now, most EOC patients are operated by a registrered gynaecologic oncologist, either in a central oncology centre or in the referral hospital. Surgical care provided by gynaecologic oncologists also leads to improvement of survival.[39,64]

Not only direct improvements in treatment such as complete debulking but also improvements in staging procedures can indirectly result in a better prognosis. Staging procedures were not registered in the NCR in the majority of cases but since both the 2004 and 2009 Dutch guideline emphasize the importance of a complete staging procedure this may probably have led to an improvement in staging. Also, in the nation-wide data an increasing number of lymph node and distant metastases were recorded over time in T1 and T2 tumours suggesting more extended application of staging procedures. Stage migration therefore, may play a role in improved survival estimates per stage, known as the Will Rogers phenomenon, but it cannot explain overall improvement of survival.[65]

Besides improvements in therapy, there may be additional factors influencing the improved survival. Earlier diagnosis can lead to improvement of survival, both artificially (lead time bias) and through earlier effective intervention. To date, there is no reliable method of screening that can detect early stage ovarian cancer. So far studies demonstrated that both CA125 measurements[66-68] as well as (a combination with) ultrasonography[68,69] seem ineffective for detecting ovarian cancer at an earlier stage. Even in high risk populations screening appeared ineffective.[70] Only prophylactic bilateral salpingo-oophorectomy (BSO) has shown to be effective in the prevention of ovarian cancer in high risk populations.[71] Prophylactic surgery may have an effect on survival when prevalent (mostly early stage) but so far undiagnosed cases are operated. In the two decades that are covered by our study the number of prophylactic BSOs that were performed may have increased but the expected effect on survival is very small

Changes in the histological pattern of EOC could explain changes in survival. During the study period a shift from adenocarcinomas NOS to serous carcinomas was found. Serous carcinomas had an 17 percent-point better 5-year survival than adenocarcinomas NOS in 2004-09. Patients with adenocarcinoma NOS are older and have more often an advanced stage of disease. This histological shift is probably the result of improved diagnostics and more surgical procedures in the elderly patient with advanced stage of disease. Furthermore, the proportion of endometrioid carcinomas increased and the proportion mucinous carcinomas decreased. Survival

increased in both histology groups and the shifts in these groups have probably not materially influenced overall survival.

Other factors that may have an impact on survival are age, co-morbidity and performance status because these may influence the choice of treatment. Data on age as independent prognostic factor are conflicting.[72,73] A retrospective population-based study in the Netherlands showed that the majority of the EOC stage II and III patients with age above 70 years did not receive the standard treatment.[74] Moreover, both age and co-morbidity were independent predictors of receiving the advised treatment. Age also had a prognostic effect in multivariable analyses unlike co-morbidity. A trend was shown in prescribing the advised treatment more often. We demonstrate the same trend over the last 20 years in both age groups, but survival has mainly improved in the age group of 45-74 years. Unfortunately, information on co-morbidity and performance status is not available. Therefore, we are not able to explain why nearly one third of the patients above 75 years did not receive any treatment or what the relation is between these factors and survival.

The study was limited by the lack of information on chemotherapy schedules, comorbidity and interval debulking surgery. Another limitation of this study is the use of two different methods to calculate 5-year relative survival. Although the results from period-based analysis can differ slightly from cohort-based results, it has been repeatedly shown that the period based results come very close to the later obtained cohort-based results. A difference between two calendar periods based on the two different methods likely points to a change in prognosis.[75]

CONCLUSION

Changes in therapy over the last 20 years in the Netherlands have contributed to the improved 5-year survival of advanced stage epithelial ovarian cancer patients. The poor 5-year survival of 41% in the last calendar period, however, urges further improvements of cancer care in EOC patients.

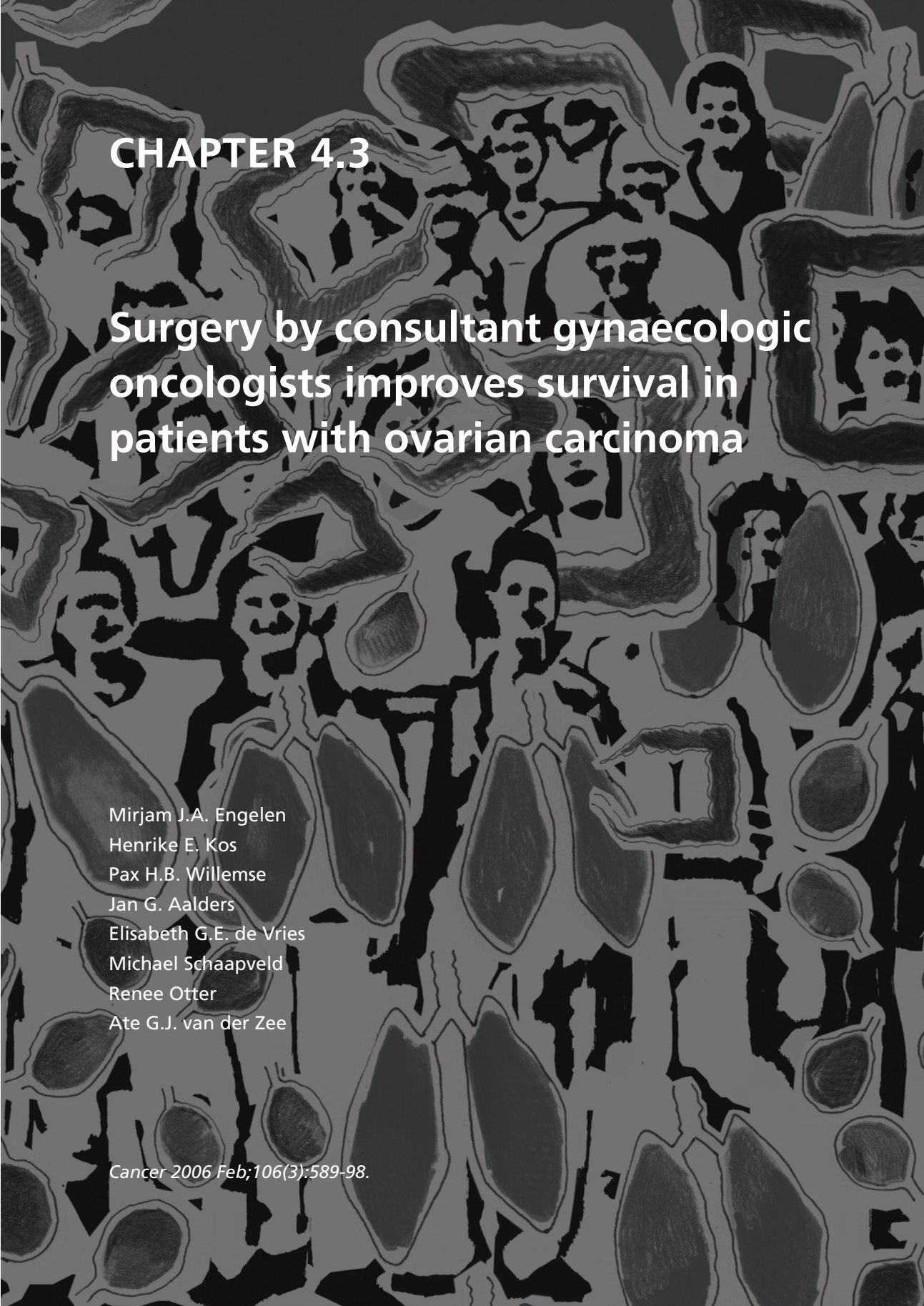
Acknowledgements

This research was performed within the framework of the project 'Progress against cancer in the Netherlands since the 1970s?' (Dutch Cancer Society grant EMCR 2006-3489). The authors thank the NCR for providing the data and the registration clerks for the dedicated data collection.

Table S1. | Published population-based studies on survival in epithelial ovarian cancer (EOC) or ovarian cancer (OC) diagnosed since 1990 in high incidence areas

Reference (Period)	Number of patients	Region	Tumor	Change in 5-year relative survival
Bjorge et al.[47] (1954-1993)	14,160	Norway	EOC	0.30 to 0.35
Klint et al.[48] (1964-2003)	unknown	Denmark	OC	0.20 to 0.33
		Finland		0.25 to 0.44
		Iceland		0.18 to 0.34
		Norway		0.31 to 0.41
		Sweden		0.28 to 0.43
Barnholtz-Sloan et al.[49] (1973-1997)	32,845	SEER USA[a]	EOC	0.37 to 0.43
Brenner et al.[50] (1976-1995)	2,124	Germany (Saarland)	OC	0.29 to 0.39
Engel et al.[51] (1978-1997)	3,750	Germany (Munich area)[b]	OC	0.43 to 0.49
Minelli et al.[52] (1978-1982)	unknown	Italy (Umbria)	OC	0.33 to 0.41
Hannibal et al.[53] (1978-2002)	13,035	Denmark	OC	0.22 to 0.33
Laurvick et al.[54] (1978-2002)	1,336	Western Australia	OC	0.32 to 0.36[c]
Chan et al.[55] (1988-2001)	26,670	SEER USA	EOC[d]	0.42 to 0.46[c]
Karim-Kos et al.[26] (1990-2002)	unknown	Europe (10 countries)	OC	0.37 to 0.42
Akhtar-Danesh et al.[56] (1992-2005)	7,771	Canada	EOC	0.49 to 0.53
Chirlaque et al.[57] (1995-1999)	1,649	Spain (8 regions)	OC	0.43
Coleman et al.[58] (1995-2007)	unknown	Australian registries	OC	0.36 to 0.38
		Canadian registries Norway		0.38 to 0.42
		Denmark		0.37 to 0.40
		UK registries		0.32 to 0.36
				0.33 to 0.36
Van Altena et al. (1989-2009)	23,399	Netherlands	EOC	0.35 to 0.41

[a] SEER Surveillance Epidemiology and End Results; [b] Population gathered via hospital registry system; [c] from Kaplan-Meier survival figure; [d] EOC without clear cell



CHAPTER 4.3

Surgery by consultant gynaecologic oncologists improves survival in patients with ovarian carcinoma

Mirjam J.A. Engelen
Henrike E. Kos
Pax H.B. Willemse
Jan G. Aalders
Elisabeth G.E. de Vries
Michael Schaapveld
Renee Otter
Ate G.J. van der Zee

Cancer 2006 Feb;106(3):589-98.

ABSTRACT

Background. Consultant gynecologic oncologists from the regional Comprehensive Cancer Center assisted community gynecologists in the surgical treatment of patients with ovarian carcinoma when they were invited. For this report, the authors evaluated the effects of primary surgery by a gynecologic oncologist on treatment outcome.

Methods. The hospital files from 680 patients with epithelial ovarian carcinoma who were diagnosed between 1994 and 1997 in the northern part of the Netherlands were abstracted. Treatment results were analyzed according to the operating physician's education by using survival curves and univariate and multivariate Cox regression analyses.

Results. Primary surgery was performed on 184 patients by gynecologic oncologists, and on 328 patients by general gynecologists. Gynecologic oncologists followed surgical guidelines more strictly compared with general gynecologists (patients with International Federation of Gynecology and Obstetrics (FIGO) Stage I–II disease, 55% vs. 33% (P=0.01); patients with FIGO Stage III disease, 60% vs. 40% (P=0.003)) and more often removed all macroscopic tumor in patients with FIGO Stage III disease (24% vs. 12%; P=0.02). When patients were stratified according to FIGO stage, the 5-year overall survival rate was 86% versus 70% (P=0.03) for patients with Stage I-II disease and 21% versus 13% (P=0.02) for patients with Stage III-IV disease who underwent surgery by gynecologic oncologists and general gynecologists, respectively. The hazards ratio for patients who underwent surgery by gynecologic oncologists was 0.79 (95% confidence interval (95%CI), 0.61–1.03; adjusted for patient age, disease stage, type of hospital, and chemotherapy); when patients age 75 years and older were excluded, the hazards ratio fell to 0.71 (95%CI, 0.54–0.94) in multivariate analysis.

Conclusions. The surgical treatment of patients with ovarian carcinoma by gynecologic oncologists occurred more often according to surgical guidelines, tumor removal more often was complete, and survival was improved.

INTRODUCTION

Patients with ovarian carcinoma have the worst prognosis of all patients with gynecologic malignancies. Their overall 5-year survival rate approximates 40%, mainly due to the large proportion of patients who present with advanced disease. The life-time risk of developing ovarian carcinoma is 1 in 75.[76] In the Netherlands, with a population of 17 million, there are 1100 newly diagnosed patients each year, for an average of 1-2 new patients per year for every gynecologist. The treatment of ovarian carcinoma is multidisciplinary in nature. Chemotherapy has had a major impact on survival and, currently, most patients receive platinum-containing combinations.[77] Over a decade ago, when not all patients received platinum-containing chemotherapy, the effect of cytoreductive surgery on survival was considered minor compared with the impact of platinum.[78] Currently, however, with virtually all patients with advanced stage disease receiving platinum, optimal cytoreduction is considered an important tool to improve survival.[38]

Surgery is important to determine the correct disease stage and to remove as much tumor as possible in patients.[79-82] Several studies have shown that patients with ovarian carcinoma who underwent surgery by a gynecologist had better survival compared with patients who underwent surgery by a general surgeon.[83-86] Subsequently, it was suggested that surgery by a gynecologic oncologist would improve survival further.[87,88] However, that hypothesis could not be confirmed in a large population-based study on differences in patterns of care of patients with ovarian carcinoma.[84] In a more recent population-based study on the impact of surgery by a gynecologic oncologist compared with a general gynecologist, a survival benefit was found for patients with International Federation of Gynecology and Obstetrics (FIGO) Stage III disease.[89] The results of that study cannot be generalized because patients with nonepithelial tumors also were included in the study population, and the effect of treatment in teaching hospitals was not addressed. However, because it also was found that gynecologic oncologists attained optimal cytoreduction more often compared with general gynecologists,[90] it is expected that survival will be improved when surgery is performed by gynecologic oncologists.

The Comprehensive Cancer Center North covers the northern part of the Netherlands, a mainly rural area with a population of approximately 2.1 million. Within our region, guidelines regarding the diagnosis and treatment for most malignancies have been developed and revised since the middle 1970s. The Working

Party on Gynecological Tumors, which includes gynecologists, medical oncologists, pathologists, and radiotherapists, believed that, especially in the smaller hospitals, which treated <10 patients with ovarian carcinoma per year, treatment results needed improvement. Since 1980, gynecologic oncologists at our regional university hospital regularly have assisted their fellow gynecologists in the community hospitals when performing surgery on patients with suspected ovarian carcinoma. The difference in patterns of care offered to patients with ovarian carcinoma in our region provides a perfect, natural, population-based experiment for studying the effect of surgery by a gynecologic oncologist on the quality of surgery and the outcome of patients. The results of this natural experiment are presented herein.

MATERIAL AND METHODS

The medical charts of 680 consecutive patients who were diagnosed with epithelial ovarian carcinoma between January 1994 and January 1998 in the northern part of the Netherlands were reviewed. Patients were identified from the Regional Cancer Registry of the Comprehensive Cancer Center North. Data were collected on a specifically designed case-report form by registry clerks of the Cancer Center. The case-report forms were monitored by one of the authors (M.J.A.E.). The data gathered from the inpatient and outpatient hospital files included comorbidity, for which an adapted Charlson score[91] was used, the results from diagnostic tests, the surgery reports, the pathology reports, information on additional treatments (including chemotherapy and radiotherapy), and follow-up. Most attention was paid to the surgical procedures undertaken. Findings at inspection and palpation were noted along with which tissues and organs were removed, whether there was spill, residual tumor (size and location), the amount of blood loss, and complications.

Regional guidelines

Guidelines on the diagnostic work-up, surgical and medical treatment, and follow-up of patients with ovarian carcinoma are made and revised regularly by the regional Working Party on Gynecological Tumors. The surgical guidelines largely resemble FIGO guidelines.[92] For statistical analysis in the current study, treatment according to surgical guidelines was defined as total abdominal hysterectomy and bilateral salpingo-oophorectomy,(partial) omentectomy, at least one lymph node

removed, and at least one peritoneal biopsy taken for patients with early-stage disease; and as total abdominal hysterectomy and bilateral salpingo-oophorectomy and (partial) omentectomy for patients with Stage III disease. When the uterus or one ovary already had been removed before the current procedure, removal of the remaining organs was considered guideline treatment. Patients with FIGO Stage IV disease were left out of the analyses concerning correct surgical staging because uniform surgical guidelines were lacking for Stage IV disease.

The regional guidelines also advise on adjuvant treatment. In the first half of the study period, adjuvant chemotherapy (the first choice was six cycles of cyclophosphamide and carboplatin) was advised for all stages and grades of disease except for Stage IA, IB, and IIA well differentiated tumors in patients without residual tumor. Age older than 70 years and a creatinine clearance <60 mL/minute were regarded as contraindications, and the second choice (melphalan) was advised for those patients. In the second half of the study period, these contraindications were regarded as relative, and chemotherapy was advised for all stages except Stage IA and IB well differentiated tumors in patients without residual tumor. The first choice remained cyclophosphamide with carboplatin, and paclitaxel was introduced as second-line treatment.

Statistical analysis

Differences between patients who underwent surgery by general gynecologists and patients who underwent surgery by gynecologic oncologists were assessed using the Kruskal-Wallis test for continuous variables and the chi-square test for categoric variables. The survival of patients who underwent surgery was calculated as the difference between date of first surgical procedure and either the date of death or the date of last patient contact for patients who did not die during follow-up. Because the exact dates of disease progression or recurrence were not scored in a standard manner, we choose overall survival as the only endpoint. Observed survival rates were estimated by using the Kaplan-Meier method. The log-rank test was used to assess differences in survival between patients who underwent surgery by a gynecologic oncologist and patients who underwent surgery by a general gynecologist, with the patients stratified into a group with early-stage disease (FIGO Stage I-II) and a group with late-stage disease (FIGO Stage III-IV). In multivariate analyses, a Cox proportional hazards model was used to assess the effect of the type of surgeon (gynecologic oncologist or general gynecologist) on survival adjusted

for prognostic variables, hospital of surgery, and chemotherapy. Variables entered the model as a confounder when β estimates of the type of surgeon changed by >10%. The proportional hazards assumption was confirmed by inspection of log (-log[survival]) curves and by examination of time-dependent covariates. *P* values <0.05 were considered significant. All analyses were conducted using SPSS software (version 11.0; SPSS Inc., Chicago. IL).

RESULTS

Patients

Apart from the University Hospital, our region is comprised of 13 general hospitals and 3 teaching hospitals that participate in the training of medical specialists. The annual number of new patients with ovarian carcinoma in the different hospitals varies from 2 patients to 24 patients. The largest numbers (20-24 new patients per hospital annually) were treated in the 3 teaching hospitals. Gynecologists in these hospitals only incidentally will call for the assistance of their academic colleagues (8% of first procedures). The smaller nonteaching hospitals, which treat 2-11 new patients annually, used this service for 42% of first surgical procedures (range, 0-76% of first procedures).

The current study population consisted of all 680 patients who were diagnosed with epithelial ovarian carcinoma between January 1994 and January 1998 in the northern part of the Netherlands. Forty-eight patients were excluded; no data could be retraced in 9 patients, 9 patients were diagnosed at autopsy, 5 patients were treated outside of our region, the original diagnosis of primary ovarian carcinoma had changed in 11 patients (2 patients had borderline ovarian tumors, 2 patients had nonepithelial ovarian tumors, and 7 patients had tumors located in other primary sites), 12 patients were diagnosed concurrently with a second malignancy other than carcinoma of the endometrium or skin, and 2 patients were included twice in the database. Having a prior malignancy was no reason for exclusion from the study. Therefore, the study population was comprised of 632 patients.

Thirty-four patients who had incomplete surgical staging procedures underwent a second surgical staging. In these patients, findings from the first surgery and the restaging procedure were combined and analyzed statistically as a single procedure. Those who underwent surgery by general surgeons (n=25 patients) for the most part

were patients with suspected colon carcinoma. In general, these patients were older and had a higher disease stage (FIGO Stage IV, 32%) compared with patients who underwent surgery by gynecologists. On univariate survival analysis, the patients who underwent surgery by a general surgeon had a hazards ratio of 3.70 (95% confidence interval (95% CI) 2.33-5.89) compared with patients who underwent surgery by a gynecologic oncologist. Because the patients who underwent surgery by a general surgeon were not comparable to the patients who underwent surgery by a gynecologist, and because we were interested in possible (dis)advantages of surgery by gynecologic oncologists compared with surgery by general gynecologists, the patients who underwent surgery by a general surgeon were excluded from further analyses along with two patients for whom the type of operating surgeon was unknown.

Ninety-three of 632 patients (14.7%) did not undergo primary surgery. Six patients underwent intervention surgery after they received primary chemotherapy. The remaining 87 patients, who did not undergo surgery, had a median age of 81 years (range, 42-93 yrs). Thirteen percent of patients were staged clinically with at least FIGO Stage I-II disease, 16% of patients had Stage III disease, 48% of patients had Stage IV disease, and the stage of disease was unknown in 23% of patients. No treatment was instituted in 56 patients. Reasons for withholding treatment were patient wishes, age, comorbidity, or a combination thereof in 39 patients; noneligible performance status in 12 patients; and unknown reasons in 5 patients.

The characteristics of 512 patients who underwent primary surgery by a gynecologist are summarized in **Table 4.3.1**, which shows that patients who underwent surgery by a gynecologic oncologist were younger and more often underwent surgery in a nonteaching hospital (by a visiting gynecologic oncologist) compared with patients who underwent surgery by a general gynecologist. Among the patients who were treated by a gynecologic oncologist, 85% received chemotherapy, when indicated, which contained a platinum compound in 91% of patients. In the patients who were treated by a general gynecologist, 75% of patients received chemotherapy, if indicated, which contained a platinum compound in 81% of patients. The percentages of patients who received chemotherapy if indicated and the percentages of patients who received a platinum compound differed (P=0.01) between gynecologic oncologists and general gynecologists. In only 5% of 512 patients, chemotherapy was not indicated, because those patients were diagnosed with well differentiated Stage IA or IB disease.

Table 4.3.1 | Characteristics of patients with ovarian carcinoma who underwent primary surgical procedures

	General gynecologist		Gynecologic oncologist		
	No. of patients	**%**	**No. of patients**	**%**	***P* value**
Age					
Median (yrs)	65		60		0.002
Range (yrs)	16-92		25-87		
<40	14	4.2	14	7.6	0.01
40-49	53	16.2	33	17.9	
50-59	70	21.3	41	22.3	
60-69	73	22.3	55	29.9	
70-79	85	25.9	36	19.6	
≥ 80	33	10.1	5	2.7	
FIGO stage					
I	97	29.6	48	26.1	0.17
II	38	11.6	17	9.2	
III	142	43.3	98	53.3	
IV	51	15.5	21	11.4	
Tumor grade					
1	53	16.2	31	16.8	0.93
2	81	24.7	44	23.9	
3-4	132	40.2	78	42.2	
Unknown	62	18.9	31	16.8	
Histology					
Serous	179	54.6	84	45.7	0.003
Mucinous	31	9.5	33	17.9	
Endometroid	21	6.4	23	12.5	
Clear cell	20	6.1	13	7.1	
Adenocarcinoma NOS / unclassified	77	23.5	31	16.8	
Preoperative CA 125					
≤35 U/mL	50	15.2	27	14.7	0.02
>35 U/mL	234	71.3	147	79.9	
Unknown	44	13.4	16	5.4	
Comorbidity					
No	228	69.5	135	73.4	0.36
Yes	100	30.5	49	26.6	
Ascites					
Absent	97	29.6	48	26.1	0.21
Present	211	64.3	130	70.7	
Unknown	20	6.1	6	3.3	

Table 4.3.1 *Continued*

	General gynecologist		Gynecologic oncologist		
	No. of patients	**%**	**No. of patients**	**%**	***P* value**
Hospital of surgery					
Teaching	184	56.1	64	34.8	<0.001
Nonteaching	144	43.9	120	65.2	
Chemotherapy					
No	95	29.0	33	17.9	<0.001
Yes, platina	188	57.3	138	75.0	
Yes, no platina	45	13.7	13	7.1	
Total no. patients	**328**		**184**		

FIGO International Federation of Gynecology and Obstetrics; NOS not otherwise specified.

Surgery

In **Table 4.3.2**, the details of the surgical staging and debulking procedures are shown for patients with FIGO Stage I-III ovarian carcinoma. In patients with Stage I/II disease, (partial) omentectomy and lymph node sampling or lymphadenectomy were performed more often by gynecologic oncologists compared with general gynecologists (*P*<0.001 for both). In patients with FIGO Stage III disease, more patients underwent complete debulking surgery by gynecologic oncologists (24% vs. 12%; *P*=0.02). Furthermore, 62% of patients with FIGO Stage III disease who underwent surgery by a gynecologic oncologist were left with residual tumor masses that measured <2 cm in greatest dimension compared with 45% of patients who underwent surgery by general gynecologists (*P*=0.05). The amount of residual tumor in patients with FIGO Stage III disease had a major impact on survival, with 5-year survival rates of 54% for patients with no residual disease, 15% for patients who had residual disease masses that measured < 2cm in greatest dimension, and 6% for patients who had more residual disease (*P*<0.001). In all disease stages, patients more often received surgical treatment according to prevailing surgical guidelines when they underwent surgery by a gynecologic oncologist (patients with FIGO Stage I-II disease, *P*=0.01; patients with FIGO Stage III disease, *P*=0.003; chi-square test). The risk of dying for patients who did not undergo surgery according to surgical guidelines was almost twice the risk for patients who underwent surgery according to the guidelines. For patients with FIGO Stage I-II disease, the 5-year survival rate

was 84% when guidelines were followed and 73% when guidelines were not followed (hazards ratio 1.95; 95% CI 0.82-4.63 (*P*=0.13)); for patients with FIGO Stage III disease, the 5-year survival rates were 32% and 11%, respectively (hazards ratio 1.97; 95% CI 1.45-2.68 (*P*<0.001)). The survival advantage for patients who underwent surgery according to the guidelines remained nearly unchanged in an exploratory multivariate analysis that compared the survival of these patients with the survival of patients in whom surgical guidelines were not followed (adjusted for patient age, disease stage, and chemotherapy; hazards ratio 1.79; 95% CI 1.33-2.41 (*P*<0.001)).

Table 4.3.2 | Surgical procedures undergone by 440 patients with International FIGO Stage I, II, and III ovarian carcinoma

	FIGO stage I-II					FIGO stage III				
	General gynecologist		Gynecologic oncologist			General gynecologist		Gynecologic oncologist		
Surgical procedure	**No.**	**%**	**No.**	**%**	***P value***	**No.**	**%**	**No.**	**%**	***P* value**
Salpingo-oophorectomy										
No	1	0.7	-	-	0.45	32	22.5	13	13.3	0.13
Unilateral	20	14.8	4	6.2		16	11.3	6	6.1	
Bilateral	16	11.9	9	13.8		28	19.7	18	18.4	
Bilateral with hysterectomy	96	71.1	51	78.5		61	43.0	56	57.1	
Unknown	2	1.5	1	1.5						
Omentectomy										
No	46	34.1	5	7.7	<0.001	23	16.2	2	2.0	0.002
Total/partial	89	65.9	58	89.2		116	81.7	93	94.9	
Unknown	-	-	2	3.1		3	2.1	3	3.1	
Biopsy										
None	33	24.4	3	4.6	<0.001					
≥1	59	43.7	48	73.8						
Unknown	43	31.9	14	21.5						
Pelvic and/or paraaortic lymph node sampling/lymphadenectomy										
No	90	66.7	25	38.5	<0.001					
Yes	41	30.4	40	61.5						
Unknown	4	3.0	-	-						

Table 4.3.2 | *Continued*

	FIGO stage I-II					FIGO stage III				
	General gynecologist		Gynecologic oncologist			General gynecologist		Gynecologic oncologist		
Surgical procedure	**No.**	**%**	**No.**	**%**	***P value***	**No.**	**%**	**No.**	**%**	***P* value**
Postoperative residual tumor										
No macroscopic	113	83.7	60	92.3	0.50	15	10.6	22	22.4	0.09[a]
<2 cm	6	4.4	2	3.1		22	15.5	18	18.4	
>2 cm	2	1.5	-	-		45	31.7	25	25.5	
Size unknown	3	2.2	1	1.5		43	30.3	26	26.5	
Unknown	11	8.1	2	3.1		17	12.0	7	7.1	
Postoperative complications										
None	125	92.6	54	83.1	0.04	114	80.3	82	83.7	0.61
≥1	10	7.4	11	16.9		28	19.7	16	16.3	
Peri-operative death										
No	135	100.0	65	100.0	-	137	96.5	97	99.0	0.41
Yes	-	-	-	-		5	3.5	1	1.0	
Surgical guidelines										
Not followed	61	45.2	23	35.4	0.01[b]	81	57.0	36	36.7	0.01[b]
Followed	30	22.2	28	43.1		53	37.3	55	56.1	
Unknown	44	32.6	14	21.5		8	5.6	7	7.1	
Total no. of patients	**135**		**65**			**142**		**98**		

FIGO International Federation of Gynecology and Obstetrics; [a] *P* =0.02, residual tumor mass versus no residual tumor mass (unknown not included); *P* =0.05, residual tumor mass <2 cm versus residual tumor mass >2 cm (unknown size not included); [b] *P*=0.01 for International Federation of Gynecology and Obstetrics (FIGO) Stage I–II ovarian carcinoma and *P*=0.003 for FIGO Stage III ovarian carcinoma (unknown not included).

Survival

Figure 4.3.1 shows that the 5-year survival rate for patients who had FIGO Stage I-II ovarian carcinoma was 86% when surgery was performed by a gynecologic oncologist and 70% when surgery was performed by a general gynecologist (*P*-=0.03). For patients who had FIGO Stage III–IV disease, the 5-year survival rates were 21% (median survival, 23 mos) and 13% (median survival, 15 mos) (*P*=0.02), respectively (**Figure 4.3.2**). In univariate analysis, age, FIGO stage, tumor grade, mucinous or endometrioid histotype, the presence of ascites, an elevated serum CA 125 level, comorbidity, and residual tumor all were found to be significant prognostic factors in the study population, as shown in **Table 4.3.3**.

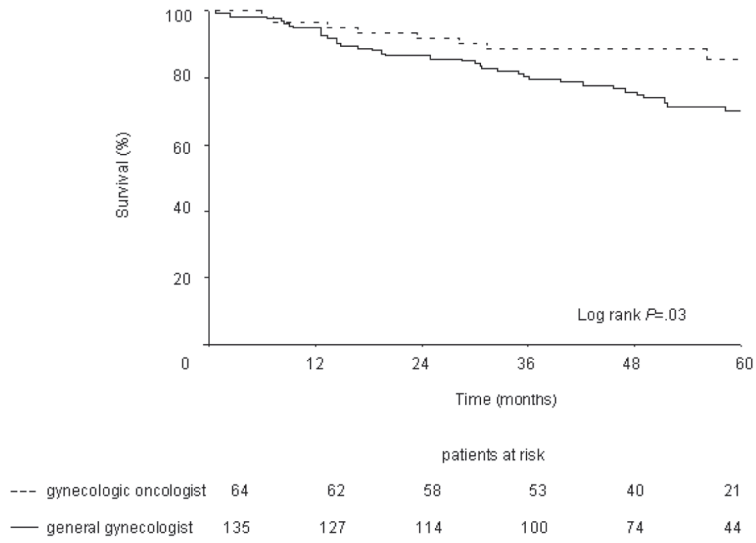


Figure 4.3.1 | Crude overall 5-year survival in patients with International Federation of Gynecology and Obstetrics Stage I-II ovarian carcinoma who underwent surgery performed by gynecologic oncologists and surgery performed by general gynecologists.

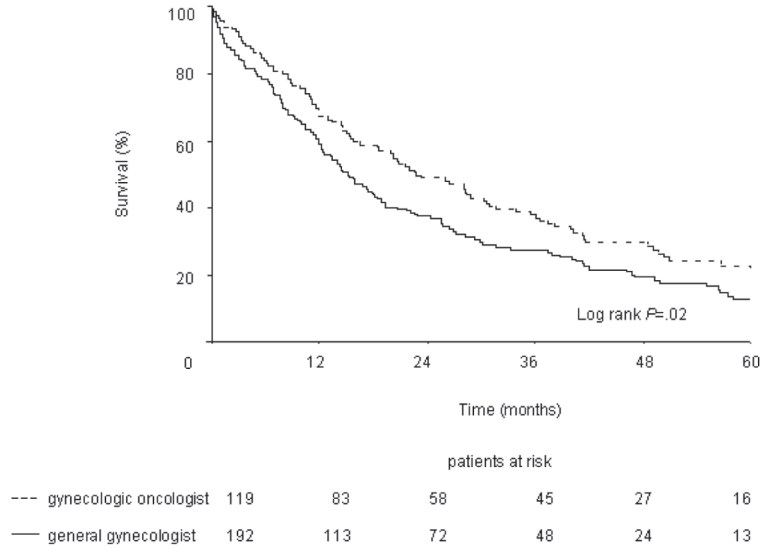


Figure 4.3.2 | Crude overall 5-year survival in patients with International Federation of Gynecology and Obstetrics Stage III-IV ovarian carcinoma who underwent surgery performed by gynecologic oncologists and surgery performed by general gynecologists.

Table 4.3.3 | Univariate Cox Proportional Hazards analysis of patients who underwent a primary surgical procedures

Variable	No. of patients	No. of deaths	HR	95% CI	*P* value
Surgeon					
General gynecologist	183	194	1.00		0.11
Gynecologic oncologist	326	98	0.82	0.64-1.05	
Patient age					
<50	114	39	1.00		<0.001
50-59	109	61	1.81	1.21-2.70	
60-69	128	69	1.86	1.26-2.76	
≥70	158	123	3.87	2.70-5.56	
FIGO stage					
Stage I	144	24	1.00		<0.001
Stage II	55	20	2.46	1.35-4.46	
Stage III	238	183	7.80	5.09-11.96	
Stage IV	72	65	15.98	9.93-25.71	
Tumor grade					
Grade 1	84	26	1.00		<0.001
Grade 2	124	67	2.15	1.37-3.38	
Grade 3-4	209	147	3.34	2.20-5.08	
Unknown	92	52	2.16	1.35-3.46	
Histology					
Serous	262	169	1.00		<0.001
Mucinous	64	23	0.46		
Endometroid	43	12	0.32		
Clear cell	33	16	0.69		
Adenocarcinoma NOS	107	72	1.18		
Preoperative CA 125					
≤35 U/mL	76	20	1.00		<0.001
>35 U/mL	380	241	3.31	2.10-5.22	
Unknown	53	31	2.79	1.59-4.90	
Comorbidity					
No	360	188	1.00		<0.001
Yes	149	104	1.69	1.33-2.15	
Ascites					
Absent	143	50	1.00		<0.001
Present	340	230	2.63	1.98-3.51	
Unknown	26	12	1.53	0.87-2.71	

Table 4.3.3 | *Continued*

Variable	No. of patients	No. of deaths	HR	95% CI	*P* value
Residual tumor					
No macroscopic	217	53	1.00		<0.001
< 2 cm	59	44	4.37	2.93-6.53	
> 2 cm	96	87	8.14	5.76-11.52	
Unknown	137	108	5.52	3.97-7.69	
Hospital of surgery					
Teaching	246	136	1.00		0.29
Nonteaching	263	156	1.13	0.90-1.43	

HR hazards ratio; 95% CI 95% confidence interval; FIGO International Federation of Gynecology and Obstetrics; NOS not otherwise specified.

Multivariate Analysis

In a Cox proportional hazards analysis, the crude hazards ratio (risk of dying) was 0.82 (95% CI 0.64-1.05) for patients who underwent surgery by a gynecologic oncologist versus a general gynecologist. The presence of ascites, preoperative CA 125 level, and comorbidity did not appear to affect the correlation between type of gynecologist and survival. However, patient age, disease stage, and the type of hospital (teaching or nonteaching) were found to affect this relation and therefore required adjustment. When we adjusted for age, stage, and type of hospital, the hazards ratio of surgery by a gynecologic oncologist was 0.77 (95% CI 0.60–1.00) (**Table 4.3.4**). When chemotherapy was included in the model, because platinum-based chemotherapy in particular was prescribed more often to patients who underwent surgery by a gynecologic oncologist, the hazards ratio became 0.79 (95% CI 0.61-1.03). Younger patients especially appeared to benefit from specialized surgical treatment, because, after correcting for age, stage, type of hospital, and chemotherapy, the hazards ratio fell to 0.71 (95% CI 0.54-0.94) when patients older than age 75 years were excluded (leaving 431 patients for analysis).

Table 4.3.4 | Cox Multivariate Model Adjusted for the Impact of Covariates on the Difference in Risk of Dying (HR) for Patients with Ovarian Carcinoma who Underwent Surgery Performed by Gynecologic Oncologists Compared with Patients who Underwent Surgery Performed by General Gynecologists

Crude survival difference, all stages	HR	95% CI	*P* value
Univariate			
General gynecologist	1.00		0.11
Gynecologic oncologist	0.82	0.64-1.05	
Adjusted for age, stage and type of hospital			
General gynecologist	1.00		0.05
Gynecologic oncologist	0.77	0.60-1.00	
Adjusted for age, stage, type of hospital and chemotherapy			
General gynecologist	1.00		0.08
Gynecologic oncologist	0.79	0.61-1.03	
Adjusted for age, stage, type of hospital, chemotherapy and age <76 yrs			
General gynecologist	1.00		0.02
Gynecologic oncologist	0.71	0.54-0.94	

HR hazards ratio; 95% CI 95% confidence interval

DISCUSSION

The phenomenon of traveling gynecologic oncologists assisting general gynecologists in community hospitals in the northern region of the Netherlands gave us the unique opportunity to explore the impact of surgery by gynecologic oncologists on patients with ovarian carcinoma. In the current, population-based study, we were able to correct for all kinds of possible confounding factors, such as patient selection and hospital type, which often was not possible in previously published studies concerning the impact of surgery by gynecologic oncologists on survival in patients with ovarian carcinoma. The results of the current study indicate clearly that surgery by a gynecologic oncologist indeed improves survival, because the multivariate analysis demonstrated a 23% reduction in the risk of dying for patients who underwent surgery by gynecologic oncologists after adjusting for patient age, disease stage, and the type of hospital. After an additional adjustment for chemotherapy, the reduction in the risk of dying became 21% (no longer significant; *P*=0.08), most likely due to the relatively small numbers. However, when patients older than age 75 years were excluded from the analysis, the reduction in

risk of dying became 29% (*P*=0.02), suggesting that younger patients in particular benefit from surgery by gynecologic oncologists.

The overall survival of patients with late-stage ovarian carcinoma, as presented in the current study, may appear to be low on first sight, with 5-year survival rates of 21% and 13% for patients who underwent surgery by gynecologic oncologists and general gynecologists, respectively. However, our rates are comparable to those reported from other population-based studies. A Scottish group (Junor et al.[89]) reported 3-year survival rates of 20% for patients with FIGO Stage III disease and 6% for patients with FIGO Stage IV disease and reported a median survival of 18 months and 13 months for patients with Stage III disease who underwent surgery by gynecologic oncologists and general gynecologists, respectively (in our population, the median survival was 23 mos and 15 mos, respectively). In Utah, a median survival of 26 months versus 16 months was observed for patients with ovarian carcinoma who had late-stage disease treated by gynecologic oncologists versus general gynecologists, respectively.[89] In addition, a Norwegian group (Tingulstad et al.[93]), reporting results from a case-control study regarding the centralization of treatment for ovarian carcinoma, observed 5-year survival rates of 26% and 4% for patients with advanced stage ovarian carcinoma who underwent surgery by gynecologic oncologists and general gynecologists, respectively.[88,89,93]

It has been postulated before that patients with ovarian carcinoma should be treated by gynecologic oncologists, because this may improve their survival.[94,95] In ovarian carcinoma, residual tumor mass after first surgery has a major impact on survival, and the current results showed that complete cytoreduction was attained more often by gynecologic oncologists than by general gynecologists in patients with FIGO Stage III disease. Moreover, 62% of patients with FIGO Stage III disease who underwent surgery by a gynecologic oncologist were left with residual tumor masses that measured <2 cm in greatest dimension compared with 45% of patients who underwent surgery by general gynecologists. In their meta-analysis on cytoreductive surgery for ovarian carcinoma, Bristow et al. reported a weighted mean percentage of optimal debulking (defined as the greatest dimension of residual disease <1-2 cm in 95% of selected studies) of 42% for a mix of operating physicians.[38] Eisenkop and Spirtos published a survey among gynecologic oncologists on optimal debulking rates and reported optimal debulking in 70% of patients with FIGO Stage IIIC disease.[96]

Apart from residual tumor mass, another major issue that may influence patient survival is treatment according to prevailing guidelines. Guidelines for the treatment of ovarian carcinoma have been published by regional, national, and international organizations.[97] We observed greater compliance with surgical guidelines among gynecologic oncologists than among general gynecologists. Furthermore, patients with Stage I-II and Stage III ovarian carcinoma who underwent surgery according to the guidelines had a better survival.

Stage migration, which means that, through adequate staging, patients are assessed correctly with a more advanced stage of disease, cannot be excluded to account in part for the survival benefit of patients who undergo surgery performed by gynecologic oncologists when comparing survival figures in the different stages. However, in the current study, this survival benefit was found consistently in all patient subgroups.

Data that lead to findings comparable to those in the current study have been presented previously in other studies. However, the interpretation of many of those (older) studies is hampered by their association with important flaws. Such flaws also have prevented the gynecologic community as a whole from accepting and implementing the conclusions from those studies in the daily practice for patients with suspected ovarian carcinoma. A first example of a major flaw in many previous population-based studies is that survival analyses of patients who underwent surgery by general gynecologists often were mixed with survival analyses of patients who underwent surgery by general surgeons.[87,88] Our current results show that survival was especially poor for patients with ovarian carcinoma who underwent surgery by general surgeons, which also has been reported in other studies;[83-86] however, our results also showed that patients who underwent surgery by general surgeons differed from patients who underwent surgery by gynecologists. The majority of those patients already had gastrointestinal complaints and underwent surgery because of suspected colon carcinoma. Moreover, those patients were older and had higher FIGO stage disease. Differences in age, stage, or histotype of patients treated by general surgeons compared with gynecologists also have been noted previously; however, previous investigators did not report on the most important characteristic, namely, the presumptive preoperative diagnosis that indicated advanced-stage disease, that we present in the current study.[83,85,86] Because of this clear patient selection bias, patients who undergo surgery by general surgeons should be excluded from comparative analyses between patients who do or do not

undergo surgery by gynecologic oncologists in population-based studies in ovarian carcinoma.

Another important flaw in comparative survival analyses of patients with ovarian carcinoma is the possible beneficial influence of treatment in a teaching hospital.[98] The advantage of undergoing surgery in a teaching hospital, which also was found in our multivariate analysis, is not understood easily. In subgroup analyses, the variables of patient age, disease stage, and type of first-course chemotherapy were excluded as explanations. Surgeon's patient volume also was found to have no significant influence on survival. Possibly, the explanation may be sought in more subtle issues, such as the dose of chemotherapy given, the treatment of recurrent disease, the type and dosage of second-line chemotherapy, etc. Because the teaching hospitals also had much larger caseloads per hospital, hospital volume may be the more correct term for the effect found.[99] The issue of beneficial influence of treatment in a teaching hospital was not addressed in the one population-based study that is most comparable to our current work[89] or in the Norwegian case–control study regarding the centralization of primary surgery in patients with ovarian carcinoma.[93]

Finally, the third major issue that, in many population-based studies, may bias patient survival analyses in favor of gynecologic oncologists, is patient selection. In our multivariate analysis, however, we were able to correct for patient selection by adjusting for disease stage, patient age, teaching hospital, and chemotherapy, thereby excluding patient selection as a possible explanation for the observed better survival of patients who underwent surgery by gynecologic oncologists.

When implementing the conclusion from the current study that patients with ovarian carcinoma optimally should undergo surgery by gynecologic oncologists, two important topics should be addressed. First, the referral of every patient who has a pelvic mass to cancer centers will prove to be hard because of problems with logistics and manpower. In this respect, a triage system may be applied to allow the identification of patients who have a low likelihood of ovarian carcinoma,[100] or the referral guidelines of the Society of Gynecologic Oncologists and the American College of Obstetricians and Gynecologists can be followed.[101] Second, in patients who have a nonsuspected ovarian carcinoma removed suboptimally by a general gynecologist, a relaparotomy should be considered.[102] Disease restaging is worthwhile, especially in patients with apparently early-stage ovarian carcinoma, because adjuvant chemotherapy does not appear to improve survival in optimally

staged patients with early stage disease.[103] In patients with apparently advanced stage disease that was not debulked optimally by a general gynecologist, either direct relaparotomy by a gynecologic oncologist or intervention surgery after response to three cycles of chemotherapy may be considered.[104,105]

The results of the current study demonstrate clearly that surgery by a gynecologic oncologist has a positive effect on survival, reducing the risk of dying by >20% for patients with ovarian carcinoma. Specific surgical training appeared to be important, because a surgeon's patient volume alone had no effect on survival. Receiving treatment in a teaching hospital also improved survival. These results imply that every patient who has suspected ovarian carcinoma deserves to undergo surgery performed by a gynecologic oncologist. For the short term, a traveling gynecologic oncologist may be an acceptable alternative to the referral of all patients with ovarian carcinoma to a center with gynecologic oncologists. However, care should be taken that correct surgical treatment is followed by the right additional chemotherapy, particularly in smaller hospitals, in which the caseload for the medical oncologist is as low as that for the gynecologist. In the future, our objective should be to concentrate the treatment of patients who have ovarian carcinoma in teaching hospitals with gynecologic oncologists.

Acknowledgements

Supported by the Comprehensive Cancer Center North Netherlands. The authors thank all registry clerks of the Comprehensive Cancer Center North for their meticulous data acquisition.

CHAPTER 4.4

Centralisation of oesophageal cancer surgery: does it improve clinical outcome?

Michel W.J.M. Wouters
Henrike E. Karim-Kos
Saskia le Cessie
Bas P.L. Wijnhoven
Leo P.S. Stassen
Willem H. Steup
Hugo W. Tilanus
Rob A.E.M. Tollenaar

Ann Surg Oncol. 2009 Jul; 16(7):1789-98.

ABSTRACT

Background. The volume-outcome relationship for complex surgical procedures has been extensively studied. Most studies are based on administrative data and use in-hospital mortality as the sole outcome measure. It is still unknown if concentration of these procedures leads to improvement of clinical outcome. The aim of our study was to audit the process and effect of centralizing esophageal resections for cancer by using detailed clinical data.

Methods. From January 1990 until December 2004, 555 esophagectomies for cancer were performed in 11 hospitals in the region of the Comprehensive Cancer Center West (CCCW); 342 patients were operated on before and 213 patients after the introduction of a centralization project. In this project patients were referred to the hospitals which showed superior outcomes in a regional audit. In this audit patient, tumor, and operative details as well as clinical outcome were compared between hospitals. The outcome of both cohorts, patients operated on before and after the start of the project, were evaluated.

Results. Despite the more severe comorbidity of the patient group, outcome improved after centralizing esophageal resections. Along with a reduction in postoperative morbidity and length of stay, mortality fell from 12% to 4% and survival improved significantly (P=0.001). The hospitals with the highest procedural volume showed the biggest improvement in outcome.

Conclusions. Volume is an important determinant of quality of care in esophageal cancer surgery. Referral of patients with esophageal cancer to surgical units with adequate experience and superior outcomes (outcome-based referral) improves quality of care.

INTRODUCTION

The number of publications that report on the relationship between the volume of high-risk surgical procedures and patient outcome continues to grow.[106] Most studies show better outcome with increasing number of operations performed by a specialized center or surgeon. However, there is still a debate about the level of evidence of these studies and the appropriateness of minimum volume thresholds for high-risk surgical procedures.[107-109] For example, there are no randomized controlled trials that have compared outcome for complex surgical procedures between high- and low-volume hospitals. Despite this apparent lack of evidence, authors claim that many surgical deaths could be saved by centralizing these high-risk procedures.[110] However, studies that have analyzed the actual effect of centralization (or regionalization) on hospital volumes and outcomes are rare.[111]

It has been widely acknowledged that esophagectomy for cancer is a complex surgical procedure and that concentration in high-volume centers could lead to improved outcome.[112,113] However, translation of the conclusions of observational series to clinical practice is difficult. Cutoff values between high- and low-volume esophageal surgery vary greatly between studies. In The Netherlands, van Lanschot et al. investigated the volume-mortality relationship for esophageal resections, analyzing data from the Dutch National Medical Registry.[114] The results of their study where in favour of patients treated in the high volume hospitals in our country, suggesting that referring patients to hospitals with higher case-volumes could reduce postoperative mortality. The purpose of our study was to analyze whether centralization of esophageal cancer surgery truly improves clinical outcome. Besides mortality, we were also interested in a more extensive set of outcome measures, including overall survival. As case mix has also been shown to be an important predictor for treatment outcomes, we included detailed clinical data of individual patient and tumor characteristics.[115]

MATERIAL AND METHODS

Comprehensive Cancer Center Leiden

Eleven hospitals in the mid-western part of The Netherlands are affiliated to the Comprehensive Cancer Center West (CCCW). In this urbanized area travelling

distances between hospitals are not more than 45 km (30 miles). In 1997, a Professional Network of Surgical Oncologists (PNSO) involving all affiliated hospitals was established, with the objective of improving the effectiveness and efficiency of surgical care for patients with cancer. In the light of the increasing number of reports on a volume-outcome relationship for esophagectomies, the network decided to evaluate surgical care for patients with esophageal cancer treated in the CCCW region since the year 1990.

Retrospective Registration

All surgically treated esophageal carcinomas from 1990 to 1999 were identified through the cancer registry of the CCCW, in which all cancer patients diagnosed and treated in the mid-western part of The Netherlands (1.7 million inhabitants) are registered. All 11 hospitals formally gave their consent to participate in this audit and were subsequently visited by two investigators who retrieved the original patient files. Patient demographics, pathological notes, data on surgical and (neo) adjuvant treatments, comorbidity as well as postoperative morbidity, mortality, length of stay, and survival were extracted from the patients' files. Pathological notes were reviewed in detail by two independent researchers and all cancers were staged according to the tumor-node-metastasis (TNM) staging system of the International Union against Cancer (UICC) 1997. The obtained pTNM stages were then cross-checked with the tumor stages in the cancer registry. Discrepancies in tumor stage were discussed between the researchers and a trained data manager from the CCCW/cancer registry database. If consensus could not be reached, the tumor stage was classified as "unknown."

Intervention

In January 2000 the results of this retrospective analysis were presented at the PNSO meeting.[115] Differences in volume and outcome between hospitals were discussed and all surgeons agreed to participate in a prospective registration. Also, all surgeons agreed upon the scenario of having to refer esophageal cancer patients to centers with a better outcome if their own results proved to be unfavorable (outcome-based referral). These referrals were on a voluntary basis, however, for both the patient and surgeon.

Prospective Registration

From January 2000 until December 2004 the same data were prospectively collected from the original patient files, and again all affiliated hospitals took part in this exercise. Completeness of the data was cross-checked with the independently collected information from the cancer registry. Each year, interim results were presented and discussed within the group of surgeons at the meeting of the PNSO.

Control Group

To put the data of the CCCW in national perspective, we compared the outcome of the CCCW region with the results of the nearest referral center for esophagectomy outside the CCCW region. In this high-volume university hospital, information of patients operated on for an esophageal carcinoma is prospectively collected from original patient files by a data manager.

Statistics

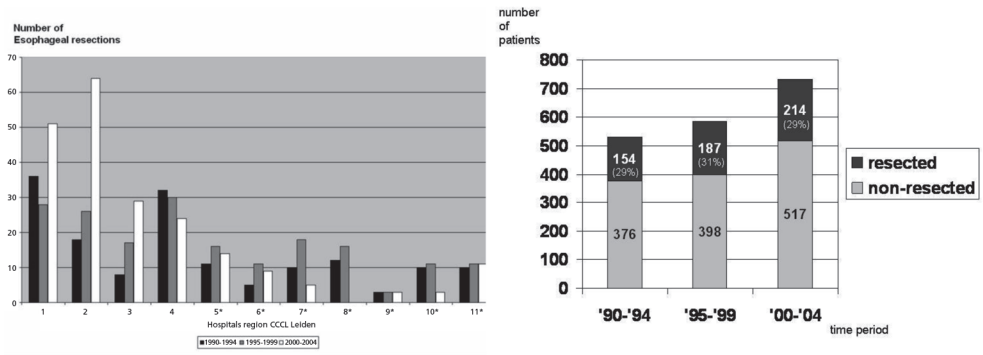
Differences in patient, tumor, and treatment characteristics, as well as in outcome measurements were assessed using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. Patients with an "unknown" status for a given variable were excluded for the analyses. Duration of survival was calculated as the difference between date of surgery and either date of death or date of last patient contact. To prevent the problem of differential follow-up, for all groups follow-up was cut-off at 2 years after surgery. Observed survival rates were estimated by using the Kaplan-Meier method. The logrank test was used to assess differences in survival between patients who were operated in different time periods and in low- versus high-volume hospitals. The Cox proportional hazard model was used to calculate hazard ratios, adjusting for possible confounding variables. All analyses were conducted using SPSS software (version 12.0; SPSS Inc.,Chicago, IL).

RESULTS

Hospital volume

Between 1990 and 2004, evaluation and treatment of patients with esophageal cancer was performed in 11 hospitals in the region of the CCCW (one university hospital, five teaching hospitals, and five general hospitals). In 555 consecutive

patients, an esophageal tumor was resected with curative intent. **Figure 4.4.1a** illustrates the distribution of surgical procedures within the studied time period for the 11 hospitals, and **Figure 4.4.1b** shows the resection rates for esophageal carcinomas diagnosed in the CCCW region in three different time periods.



A B

Figure 4.4.1 | A Number of esophageal resections in hospitals in region of CCCW per 5-year period (1990-1994, 1995-1999, 2000-2004). *Hospitals that abandoned esophageal resections during 2000-2004 period. Hospital 4 abandoned esophageal resections after 1st January 2005. **B** Resection rates of newly diagnosed patients with esophagus carcinoma in hospitals in CCCW region per 5-year period (1990-1994, 1995-1999, 2000-2004).

From 1990 to 1999, none of the hospitals performed more than seven esophageal resections per year (low-volume hospitals; LVH). From the year 2000 onwards, a gradual concentration of esophageal resections occurred, and in two hospitals (I and II) procedural volumes increased to more than ten resections per year (high-volume hospitals; HVH). In the same period of time, a mean annual number of 56 esophageal resections was performed in the nearest high-volume center.

Patient, Tumor, and Treatment Characteristics

Table 4.4.1 shows the patient, tumor, and procedural characteristics of esophageal resections performed in three consecutive time periods. There was no significant difference in age, gender, histological type or location of the tumors. However, the number of patients with comorbidities increased during the study period. Stage I tumors were more frequently seen in the later time periods, and an increasing number of transhiatal resections were performed. The number of nodes evaluated

by the pathologist changed in time, with a mean number of 6.3, 7.5, and 13.5 nodes reported for the different time periods. In the 2000-2004 time period more neoadjuvant chemotherapy was used, especially in patients with a tumor in the lower esophagus, included in a trial on perioperative epirubicin, cisplatin, and fluorouracil (ECF).[116]

Table 4.4.1 | Characteristics of patients who underwent esophageal resection by period of surgery

	1990-1994		1995-1999		2000-2004		
Characteristics	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**P value**
Age (years)							0.19
Median	66		65		64		
Range	37-87		33-85		33-86		
Gender							0.70
Male	109	70.8	139	74.3	159	74.3	
Female	45	29.2	48	25.7	55	25.7	
Co-morbidity							0.25[a,b]
No	68	44.2	74	39.6	83	38.8	
1 organ system	51	33.1	61	32.6	85	39.7	
2 organ systems	19	12.3	30	16.0	41	19.2	
≥ 3 organ systems	4	2.6	7	3.7	4	1.9	
Unknown	12	7.8	15	8.0	1	0.5	
Histology							0.93[a,c]
Adenocarc.	107	69.5	130	69.5	144	67.3	
Squamous carc.	45	29.2	51	27.3	52	24.5	
Barrett's dysplasia	1	0.6	3	1.6	6	2.8	
Other	-	-	2	1.1	5	2.3	
Unknown	1	0.6	1	0.5	7	3.3	
Tumour localisation							0.97[a,d]
Cervical esoph.	4	2.6	3	1.6	4	1.9	
Mid esoph.	23	14.9	30	16.0	32	15.0	
Distal esoph. / GE junction	127	82.5	152	81.3	177	82.7	
Unknown	-	-	2	1.1	1	0.5	

Table 4.4.1 | *Continued*

	1990-1994		1995-1999		2000-2004		
Characteristics	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**P value**
Stage (pTNM)							0.65[a]
0	2	1.3	5	2.7	6	2.8	
I	10	6.5	26	13.9	31	14.5	
II	80	51.9	80	42.8	82	38.3	
III	52	33.8	60	32.1	74	34.6	
IV	9	5.8	12	6.4	15	7.0	
Unknown	1	0.6	4	2.1	6	2.8	
Neo-adjuvant treatment							<0.001[a,e]
No	150	97.4	165	88.2	160	74.8	
Chemo ± radiotherapy	2	1.3	19	10.1	54	25.2	
Unknown	2	1.3	3	1.6	-	-	
Surgical approach							<0.001[a,f]
Abdomino-cervical	53	34.4	97	51.9	156	72.9	
Thoraco-abdominal	62	40.3	34	18.2	11	5.1	
Abd-thor-cervical	16	10.4	27	14.4	27	12.6	
Abdominal	23	14.9	29	15.5	15	7.0	
Unknown	-	-	-	-	5	2.3	
Anastomoses							<0.001[g]
Cervical	69	44.8	126	67.4	187	87.4	
Thoracic	60	39.0	30	16.0	12	5.6	
Abdominal	25	16.2	31	16.6	15	7.0	
Total no. of patients	154		187		214		

GE gastro-esophageal; [a] "Unknown" category was excluded; [b] Linear trend analysis; [c] Squamous versus adenocarcinoma plus Barrett's dysplasia; [d] Distal esophagus/GE-junction versus others; [e] No neoadjuvant therapy versus others; [f] Abdomino-cervical versus others; [g] Cervical versus thoracic plus.

Outcome

The outcome of esophagectomies in the CCCW region improved with time (**Table 4.4.2**). The percentage of patients with a microscopic radical resection (R0) improved from 69% to 73%. The number of patients who left the hospital without adverse events was highest in the 2000-2004 period. Hospital stay was shortened significantly and inhospital mortality was reduced almost threefold. As shown in **Figure 4.4.2**, significantly better 2-year survival is seen for the last time period (P=0.001). After exclusion of in-hospital mortality, this difference is still significant (P=0.045).

Table 4.4.3 shows the results of a multivariate analysis for the risk of dying after surgery in the three time periods with adjustments for the impact of the covariates: stage, comorbidity, surgical approach, and neoadjuvant treatments. Somewhat higher stages of the disease and more patients with multiple comorbidities were operated in the last time period. Although there are significant differences in surgical approach and the use of neoadjuvant chemotherapy between time periods, the survival benefit in the 2000-2004 period remains significant in multivariate analysis (hazard ratio (HR) 0.61). An analysis of the data after exclusion of patients who received (neo)adjuvant treatment showed similar improvements in mortality rates and survival after 2000. Also, a multivariate analysis was performed after exclusion of the patients who died during hospital stay (**Table 4.4.4**). Improvements in survival stayed (borderline) significant after adjustments for differences in stage, age, gender, and comorbidities (P=0.05), but after introducing surgical approach in the model, significance was lost (P=0.25).

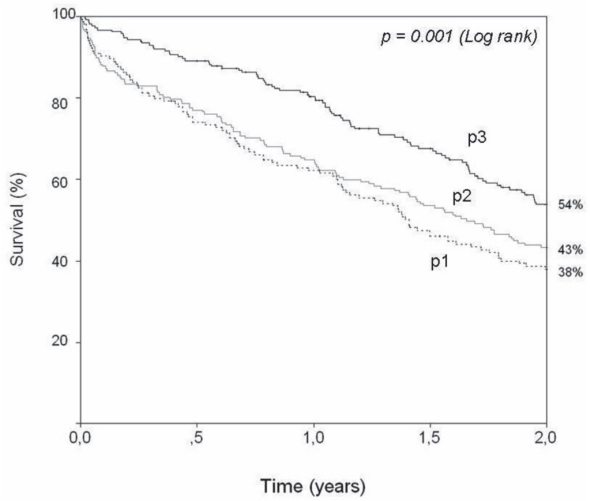


Figure 4.4.2 | Two-year survival after resection for all stages of esophageal carcinoma in three time periods (p1: 1990–1994, p2: 1995–1999, p3: 2000–2004), including hospital mortality

In **Table 4.4.5** patient, tumor, and treatment characteristics of patients operated on in hospitals with fewer than ten resections a year (low-volume hospitals LVH)

and with more than nine resections a year (high-volume hospitals HVH) are shown. Only patients operated in a year in which the procedural volume of the hospital concerned exceeded nine resections were included in the HVH group. In this group more patients with more comorbidity were operated, and the transhiatal approach was used more often than the transthoracic approach. Significantly more adverse events occurred in the LVH group, with a mortality rate of 6.3% in the LVH group and 2.9% in the HVH group (**Table 4.4.6**). After exclusion of the patients who died in hospital, median hospital stay was 8 days shorter in the HVH group. Survival analysis did not show a difference in 2-year survival between the LVH and HVH group (P=0.63).

Table 4.4.2 | Outcome after esophageal resections in region of CCCW (1990-994, 1995-1999, 2000-2004)

	1990-1994		1995-1999		2000-2004		
Outcome	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**P value**
Margins							0.57[a,c]
R0	107	69.5	140	74.9	156	72.9	
R1	34	22.1	21	11.2	39	18.2	
R2	10	6.5	25	13.4	12	5.6	
Unknown	3	1.9	1	0.5	7	3.3	
Complications							0.20[a]
No	43	27.9	46	24.6	70	32.7	
Yes	106	68.8	140	74.9	143	66.8	
Unknown	5	3.2	1	0.5	1	0.5	
Re-intervention							0.27[a,d]
None	115	74.4	155	82.9	163	76.2	
1	27	17.5	21	11.2	32	15.0	
2	5	3.2	7	3.7	12	5.6	
≥ 3	2	1.3	3	1.6	3	1.4	
Unknown	5	3.2	1	0.5	4	1.9	
Hospital stay (days)[b]							0.002
Median	20		21		17		
Range	(9-92)		(9-125)		(8-273)		
In-hospital mortality							0.003[a]
No	131	85.1	160	85.6	204	95.3	
Yes	22	14.3	23	12.3	10	4.7	
Unknown	1	0.6	4	2.1	-	-	
Total no. of patients	154		168		214		

[a] "Unknown" category excluded; [b] Patients who died during hospital stay were not included; [c] R0 versus R1 plus R2; [d] No reintervention versus others.

Table 4.4.3 | Cox multivariate model adjusted for the impact of covariates on the risk of dying (HR) for patients who underwent esophageal resection for cancer by period of surgery

	HR	95% CI
Univariate		
1990-1994	1.00	
1995-1999	0.89	0.69–1.14
2000-2004	0.66	0.50–0.86
Adjusted for stage[a] and co-morbidity[a]		
1990-1994	1.00	
1995-1999	0.82	0.61–1.11
2000-2004	0.57	0.42–0.77
Adjusted for stage[a], co-morbidity[a] and surgical approach[a]		
1990-1994	1.00	
1995-1999	0.85	0.62–1.15
2000-2004	0.60	0.43–0.84
Adjusted for stage[a], co-morbidity[a], surgical approach[a] and neo-adjuvant treatment[a]		
1990-1994	1.00	
1995-1999	0.85	0.63–1.16
2000-2004	0.61	0.44–0.86

HR hazards ratio, CI Confidence Interval; [a] "Unknown" categories excluded

Table 4.4.4 | Cox multivariate model adjusted for the impact of covariates on the risk of dying (HR) for patients who underwent esophageal resection for cancer by period of surgery (patients who died in hospital excluded)

	HR	95% CI
Univariate		
1990-1994	1.00	
1995-1999	0.87	0.64-1.20
2000-2004	0.67	0.48-0.91
Adjusted for stage[a]		
1990-1994	1.00	
1995-1999	0.90	0.65-1.24
2000-2004	0.67	0.48-0.93
Adjusted for stage[a], age and gender		
1990-1994	1.00	
1995-1999	0.88	0.64-1.22
2000-2004	0.67	0.48-0.93
Adjusted for stage[a], age, gender and co-morbidity[a]		
1990-1994	1.00	
1995-1999	0.88	0.64-1.22
2000-2004	0.67	0.48-0.93

Table 4.4.4 | *Continued*

	HR	95% CI
Adjusted for stage[a], age, gender, co-morbidity[a] and surgical approach[a]		
1990-1994	1.00	
1995-1999	0.92	0.66–1.29
2000-2004	0.75	0.52–1.07

HR hazards ratio, CI Confidence Interval; [a] "Unknown" categories excluded

Table 4.4.5 | Characteristics of patients who underwent esophageal resection by hospital volume in the 2000-2004 time period

	LVHs		HVHs		
Characteristics	**No. of patients**	**%**	**No. of patients**	**%**	**P value**
Age					0.24
median (yrs)	64		63		
range (yrs)	33-86		43-80		
Gender					0.53
Male	80	72.1	79	76.7	
Female	31	27.9	24	23.3	
Co-morbidity					0.001[a]
no	56	50.5	27	26.2	
1 organ system	35	31.5	50	48.5	
2 organ systems	18	16.2	23	22.3	
≥ 3 organ systems	1	0.9	3	2.9	
Unknown	1	0.9	-	-	
Histology					0.98[a,b]
Adenocarc.	73	65.8	71	68.9	
Squamous carc.	27	24.3	25	24.3	
Barrett's dysplasia	3	2.7	3	2.9	
Other	2	1.8	3	2.9	
Unknown	6	5.4	1	1.0	
Tumour localisation					0.61[a,c]
Cervical oesoph.	2	1.8	2	1.9	
Mid oesoph.	18	16.2	14	13.6	
Distal oesoph. / GE-junction	90	81.1	87	84.5	
Unknown	1	0.9	-	-	
Stage (pTNM)					0.90
0	3	2.7	3	2.9	
I	15	13.5	16	15.5	
II	43	38.7	39	37.9	
III	39	35.1	35	34.0	
IV	6	5.4	9	8.7	
Unknown	5	4.5	1	1.0	

Table 4.4.5 | *Continued*

	LVHs		HVHs		
Characteristics	**No. of patients**	**%**	**No. of patients**	**%**	**P value**
Neo-adj. treatment					0.27
No	90	81.1	70	68.0	
Chemo ± radiotherapy	21	18.9	33	32.0	
Surgical approach					<0.001[a,d]
Abdomino-cervical	66	59.5	90	87.4	
Thoraco-abdominal	10	9.0	1	1.0	
Abd-thor-cervical	17	15.3	10	9.7	
Abdominal	14	12.6	1	1.0	
Unknown	4	3.6	1	1.0	
Anastomoses					<0.001[e]
Cervical	86	77.5	101	98.1	
Thoracic	12	10.8	-	-	
Abdominal	13	11.7	2	1.9	
Total no. of patients	111		103		

LVHs low-volume hospitals (<10 resections/year), HVHs high-volume hospitals (≥10 resections/year), GE gastroesophageal; [a] "Unknown" category excluded; [b]Adenocarcinoma/Barrett's dysplasia versus squamous and others; [c]Distal esophagus/GE junction versus cervical/mid esophagus; [d]Abdomino-cervical versus others; [e]Cervical anastomoses versus others.

Table 4.4.6 | Outcome after esophageal resection by hospital volume in the 2000-2004 time period

	LVHs		HVHs		
Outcome	**No. of patients**	**%**	**No. of patients**	**%**	**P value**
Margins					0.35[b,c]
R0	77	69.4	79	76.7	
R1	19	17.1	20	19.4	
R2	10	9.0	2	1.9	
Unknown	5	4.5	2	1.9	
Complications					
No	24	21.6	46	44.7	0.001[b]
Yes	86	77.5	57	55.3	
Unknown	1	0.9	-	-	
Surgical complications					**0.05[b]**
No	54	48.6	64	62.1	
Yes	56	50.5	39	37.9	
Unknown	1	0.9	-	-	

Table 4.4.6 | *Continued*

	LVHs		HVHs		
Outcome	**No. of patients**	**%**	**No. of patients**	**%**	**P value**
General complications					**0.001**[b]
No	44	39.6	65	63.1	
Yes	66	59.5	38	36.9	
Unknown	1	0.9	-	-	
Reintervention					0.39[b,d]
None	82	73.9	81	78.6	
1	19	17.1	13	12.6	
2	7	6.3	5	4.9	
≥ 3	1	0.9	2	1.9	
Unknown	2	1.8	2	1.9	
Hospital stay (days)[a]					<0.001
Median	22		14		
Range	(10-273)		(8-104)		
In-hospital mortality					0.24
No	104	93.7	100	97.1	
Yes	7	6.3	3	2.9	
Total no. of patients	111		103		

LVHs low-volume hospitals (<10 resections/year), HVHs high-volume hospitals (≥10 resections/year); [a]Patients who died during hospital stay were not included; [b] "Unknown" category excluded; [c]R0 versus R1 plus R2; [d]No reintervention versus others.

DISCUSSION

In the last decade, many studies have been published that have addressed the volume-outcome relationship for complex surgical procedures.[106,117] The results of these studies focus on the rather high difference in mortality rates between high- and low-volume providers for esophageal resections for cancer.[112] As a consequence, these authors speculate that concentration of these high-risk surgical procedures in centers with adequate experience could avoid thousands of preventable deaths.[110,118] However, the present study is the first that shows an actual improvement in outcome after the process of centralization of esophageal resections for cancer.

Chowdhury et al. reviewed 163 studies that looked at the volume-outcome relationship for complex surgical procedures.[106] Seventy-three percent of these studies showed significant better outcomes in high-volume hospitals and for high-volume surgeons. However, most studies are registry-based and omit important

case-mix adjustments from clinical data. Moreover, hospital mortality is often presented as the sole outcome measure, without presenting other dimensions of quality of care. Therefore, there is solid criticism on the methodological issues, which hampers centralization initiatives for complex surgical procedures, especially in The Netherlands. Despite the expected benefits of centralizing complex surgical procedures at high-volume providers, there are few studies that show an actual improvement in clinical outcome after centralization of a specific procedure.[119] As a part of a broader initiative, the Leapfrog Group, a large coalition of private and public purchasers of health insurance in the USA, has been referring their patients to high-volume providers of esophagectomies since 2000. Although expectations about the beneficial effects of this intervention were high, no results have been published yet.[110,118]

Our study adds clinical proof to the effectiveness of concentrating complex surgical procedures: not only was hospital mortality reduced to a third of the original value, but also other outcome indicators, such as the number and severity of adverse events, showed improvement after centralization of esophagectomies in the CCCW region in The Netherlands. This was also reflected in a lower number of reinterventions and shorter length of stay. Remarkable is the significant improvement in survival that is already demonstrated after a limited concentration of esophageal resections (**Figure 4.4.2**). In our opinion, overall survival, adjusted for differences in tumor stages, should be the most important performance indicator in surgical oncology, being even more valuable than operative mortality.

In an earlier article from our group we showed that case mix is an important determinant of outcome and should be part of every study comparing outcome between providers.[115] Therefore we tried to study the effect of differences in case-mix between the hospitals. The identification of more patients with multiple comorbid diseases and more patients with stage IV disease in the last time period (**Table 4.4.1**) supports our conclusion that outcome improved with centralization of esophageal resections.

However, our study has several limitations. First, the accuracy of the registry database should be confirmed. This was done by comparing the results with the data of the independently retrieved information in the cancer registry of the CCCW. Only 3% of the patients operated on for esophageal cancer in our region were missing from our prospective database. The treatment and outcome characteristics of this small group of patients did not differ significantly from those of the original

group. An earlier report on a detailed medical audit confirms the accuracy of clinical outcomes databases on major fields such as operative mortality, major complications, and significant factors in risk stratification.[120]

Secondly, our dataset is still limited, though more (co)variables were included than in most volume-outcome studies. In contrast to the available data on case-mix variations, no information on structural changes in perioperative care was available. To our knowledge no important improvements in the treatment of esophageal cancer are known from the literature, nor within the region of the CCCW. Nevertheless, progress in anesthesiological techniques and postoperative care within the study period could have interfered with our findings. In addition, limited data were available on the survival of patients in the later time period (2-year survival). This could be insufficient to evaluate differences in disease control obtained by transthoracic and transhiatal procedures. Recently, the 5-year survival data of the Dutch randomized controlled trial comparing these surgical approaches were published.[121] No survival benefit was shown for either approach. Nevertheless, after introducing surgical approach in our multivariate analyses (**Table 4.4.4**), the statistical difference in survival between the time periods was lost, suggesting an important role for the choice of operative approach. In our opinion, the choice for a transhiatal or transthoracic procedure is made in a decision-making process in which careful interpretation of diagnostic images and surgical experience are combined. The increase in hospital volumes, as a result of the concentration of esophagectomies in our study, might have led to better surgical decision-making, especially in the choice of operative approaches.

The beneficial effects of the centralization process conducted in the last time period are further supported by the comparison of outcome between LVHs and the hospitals that acquired the status of HVH (C10 resections/year) in the last time period (**Table 4.4.6**). Although differences in operative mortality are not significant, they strongly suggest that the most important improvement in outcome is made in the HVHs, which now parallel the outcome in the nearest high-volume referral center (data not shown). Differences in case mix, especially comorbidities, are also in favor of the HVHs (**Table 4.4.5**). Continuation of the centralization process and the outcome registration in our region will lucidate the mechanisms behind these improvements in patient outcome. From 1st January 2005 esophagus resections in the region of the CCCW are concentrated in three hospitals with mean annual volume of more than 15 esophagus resections.

Finally, the feedback we gave to individual surgeons and hospital organizations on their performance (mirror information) could in itself have influenced practice patterns and dedication of the professionals. When outcomes data are used for internal peer review within institutions, changes in the process of care can be initiated by surgeons or hospitals themselves. A good example is the Veterans Affairs National Surgical Quality Improvement Program (NSQIP) in which feedback to providers and managers led to a decrease in the relative risk for postoperative mortality of 27% and a 45% decrease in postoperative morbidity.[122] However, this program was more detailed, consisting of outcome-based annual reports, periodic assessment of performance, self-assessment tools, structured site visits, and dissemination of best practices. Nevertheless, the observed improvements in outcome in our study could be not only a result of the concentration of services but also of the introduced feedback on surgical performance. This could explain the improved outcome that was also demonstrated in the LVHs, being of a lesser magnitude than the improvements in HVHs (**Table 4.4.6**).

Some authors believe that procedural volume, as a proxy for quality, is preferable above direct outcomes measurement.[123,124] The availability and easy access of these data and the avoidance of the statistical problem of small sample size are mentioned as important advantages.[125] However, in a study from our own country, van Heek et al. showed that, despite a 10-year-long "evidence- based" plea for centralization of pancreatic surgery, no reduction of mortality or change in referral pattern was seen in The Netherlands.[126] The problem is that provider volume as a quality measure only holds true on average, and is a poor predictor of quality in individual hospitals or surgeons.[127,128]

In our opinion, continuous monitoring of clinical outcomes not only has the ability to assess quality of care but can actually improve surgical performance. A number of methods for surgical monitoring, which take into account different levels of prior risk, have been described in the literature.[129,130] A routinely conducted medical audit, providing hospitals and surgeons with individualized and pooled outcome information, can be a stimulus for the introduction of a range of improvements in hospital and surgical care.[131-133] In addition, a national or regional approach, such as the example for esophageal cancer surgery in our study, clarifies important differences in quality of care. In a peer-review environment or when reliable, hospital-specific outcome information is made available to the public, actual changes in referral patterns can be made (outcome-based referral).

Acknowledgements

The authors thank the participating surgeons for their cooperative and selfless attitude in improving the quality of care for esophageal cancer patients in the region of the Comprehensive Cancer Center West.

REFERENCES

1. Gronberg H. Prostate cancer epidemiology. *Lancet.* 2003;361(9360):859-864.
2. Potosky AL, Kessler L, Gridley G, Brown CC, Horm JW. Rise in prostatic cancer incidence associated with increased use of transurethral resection. *J Natl Cancer Inst.* 1990;82(20):1624-1628.
3. Lee F, Gray JM, McLeary RD, et al. Transrectal ultrasound in the diagnosis of prostate cancer: location, echogenicity, histopathology, and staging. *Prostate.* 1985;7(2):117-129.
4. Lee F, Littrup PJ, McLeary RD, et al. Needle aspiration and core biopsy of prostate cancer: comparative evaluation with biplanar transrectal US guidance. *Radiology.* 1987;163(2):515-520.
5. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med.* 1987;317(15):909-916.
6. Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. *BJU international.* 2002;90(2):162-173.
7. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. *J Natl Cancer Inst.* 2009;101(19):1325-1329.
8. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med.* 2009;360(13):1320-1328.
9. Statistics Netherlands. Permanent research into the living situation – health inquiry (POLS) (Dutch). *http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=03799&D1=291&D2=0-17&D3=0&D4=a&VW=T.* (accessed January 2010).
10. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. *Lancet.* Mar 22 2003;361(9362):1045-1053.
11. Netherlands Cancer Registry. NCR data – incidence data. *http://www.ikcnet.nl/page.php?id=237&nav_id=97. (*accessed January 2010).
12. Siesling S, van Dijck JA, Visser O, Coebergh JW. Trends in incidence of and mortality from cancer in The Netherlands in the period 1989-1998. *Eur J Cancer.* 2003;39(17):2521-2530.
13. Post PN, Kil PJ, Crommelin MA, Schapers RF, Coebergh JW. Trends in incidence and mortality rates for prostate cancer before and after prostate-specific antigen introduction. A registry-based study in southeastern Netherlands, 1971-1995. *Eur J Cancer.* 1998;34(5):705-709.
14. Statistics Netherlands. Mortality data. *http://www.cbs.nl/. (*accessed January 2010).
15. Percy C, Fritz A, Jack A, al e. *International classification of diseases for oncology (ICD-O-3)*. 3rd ed. Geneva: WHO; 2000.
16. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol.* 1974;111(1):58-64.
17. Sobin L, Wittekind C. *TNM classification of malignant tumours.* 6th ed. New York: Wiley-Liss; 2002.
18. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med.* 2000;19(3):335-351.
19. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. *Comput Programs Biomed.* 1985;19(2-3):197-207.
20. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer.* 1996;78(9):2004-2010.

21. Giard RW, Coebergh JW, Casparie-van Velsen IJ. [A marked increase in the rate of diagnosed prostate cancer in the Netherlands during 1990-1996]. *Ned Tijdschr Geneeskd.* 1998;142(35):1958-1962.
22. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. *JAMA.* 1995;273(7):548-552.
23. Otto SJ, van der Cruijsen IW, Liem MK, et al. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. *Int J Cancer.* 2003;105(3):394-399.
24. Collin SM, Martin RM, Metcalfe C, et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncol.* 2008;9(5):445-452.
25. Melia J, Moss S, Johns L. Rates of prostate-specific antigen testing in general practice in England and Wales in asymptomatic and symptomatic patients: a cross-sectional study. *BJU international.* 2004;94(1):51-56.
26. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer.* 2008;44(10):1345-1389.
27. Visser O, Siesling S, van Dijck JA. *Incidence of cancer in the Netherlands 1999/2000*. Utrecht: Vereniging van Integrale Kankercentra; 2003.
28. Horner MJ, Ries LAG, Krapcho M, al. E. SEER cancer statistics review; 1975-2006. *http://seer.cancer.gov/csr/1975_2006/. (*accessed January 2010).
29. Merrill RM, Wiggins CL. Incidental detection of population-based prostate cancer incidence rates through transurethral resection of the prostate. *Urol Oncol.* 2002;7(5):213-219.
30. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med.* 1997;337(5):295-300.
31. Statistics Netherlands. Survival data. *http://www.cbs.nl/. (*accessed January 2010).
32. Epstein JI. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. *Am J Surg Pathol.* 2000;24(4):477-478.
33. Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol.* 2005;29(9):1228-1242.
34. Billis A, Guimaraes MS, Freitas LL, Meirelles L, Magna LA, Ferreira U. The impact of the 2005 international society of urological pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. *J Urol.* 2008;180(2):548-552; discussion 552-543.
35. Bouchardy C, Fioretta G, Rapiti E, et al. Recent trends in prostate cancer mortality show a continuous decrease in several countries. *Int J Cancer.* 2008;123(2):421-429.
36. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Changed trends of cancer mortality in the elderly. *Ann Oncol.* 2001;12(10):1467-1477.
37. Netherlands Cancer Registry. *http://cijfersoverkanker.nl/. (*accessed December 2011).
38. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol.* 2002;20(5):1248-1259.
39. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecol Oncol.* 2007;105(3):801-812.

40. du Bois A, Rochon J, Pfisterer J, Hoskins WJ. Variations in institutional infrastructure, physician specialization and experience, and outcome in ovarian cancer: a systematic review. *Gynecol Oncol.* 2009;112(2):422-436.

41. Balvert-Locht HR, Coebergh JW, Hop WC, et al. Improved prognosis of ovarian cancer in The Netherlands during the period 1975-1985: a registry-based study. *Gynecol Oncol.* 1991;42(1):3-8.

42. Fritz A, Percy C, Jack A, et al. *Classification of Diseases for Oncology, ed. 3rd* Geneva: World Health Organization; 2000.

43. Wittekind C, Green FL, Hutten RPV, Klimpfinger M, Sobin LH. *TNM Atlas*. 5th ed. Berlin: Springer-Verlag; 2005.

44. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet.* 2006;95 Suppl 1:S161-192.

45. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol.* 1993;22(3):369-376.

46. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med.* 2004;23(1):51-64.

47. Bjorge T, Engeland A, Hansen S, Trope CG. Prognosis of patients with ovarian cancer and borderline tumours diagnosed in Norway between 1954 and 1993. *Int J Cancer.* 1998;75(5):663-670.

48. Klint A, Tryggvadottir L, Bray F, et al. Trends in the survival of patients diagnosed with cancer in female genital organs in the Nordic countries 1964-2003 followed up to the end of 2006. *Acta Oncol.* 2010;49(5):632-643.

49. Barnholtz-Sloan JS, Schwartz AG, Qureshi F, Jacques S, Malone J, Munkarah AR. Ovarian cancer: changes in patterns at diagnosis and relative survival over the last three decades. *Am J Obstet Gynecol.* 2003;189(4):1120-1127.

50. Brenner H, Stegmaier C, Ziegler H. Trends in survival of patients with ovarian cancer in Saarland, Germany, 1976-1995. *J Cancer Res Clin Oncol.* 1999;125(2):109-113.

51. Engel J, Eckel R, Schubert-Fritschle G, et al. Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. *Eur J Cancer.* 2002;38(18):2435-2445.

52. Minelli L, Stracci F, Prandini S, Moffa IF, La Rosa F. Gynaecological cancers in Umbria (Italy): trends of incidence, mortality and survival, 1978-1998. *Eur J Obstet Gynecol Reprod Biol.* 2004;115(1):59-65.

53. Hannibal CG, Cortes R, Engholm G, Kjaer SK. Survival of ovarian cancer patients in Denmark: excess mortality risk analysis of five-year relative survival in the period 1978-2002. *Acta Obstet Gynecol Scand.* 2008;87(12):1353-1360.

54. Laurvick CL, Semmens JB, Holman CD, Leung YC. Ovarian cancer in Western Australia (1982-98): incidence, mortality and survival. *Aust N Z J Public Health.* 2003;27(6):588-595.

55. Chan JK, Cheung MK, Husain A, et al. Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol.* 2006;108(3 Pt 1):521-528.

56. Akhtar-Danesh N, Elit L, Lytwyn A. Temporal trends in the relative survival among patients diagnosed with ovarian cancer in Canada 1992-2005: a population-based study. *Gynecol Oncol.* 2011;123(2):192-195.

57. Chirlaque MD, Salmeron D, Ardanaz E, et al. Cancer survival in Spain: estimate for nine major cancers. *Ann Oncol.* 2010;21 Suppl 3:iii21-29.

58. Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet.* 2011;377(9760):127-138.

59. Neijt JP, ten Bokkel Huinink WW, van der Burg ME, et al. Randomised trial comparing two combination chemotherapy regimens (Hexa-CAF vs CHAP-5) in advanced ovarian carcinoma. *Lancet.* 1984;2(8403):594-600.

60. Omura G, Blessing JA, Ehrlich CE, et al. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group Study. *Cancer.* 1986;57(9):1725-1730.

61. Greimel ER, Bjelic-Radisic V, Pfisterer J, Hilpert F, Daghofer F, du Bois A. Randomized study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group comparing quality of life in patients with ovarian cancer treated with cisplatin/paclitaxel versus carboplatin/paclitaxel. *J Clin Oncol.* 2006;24(4):579-586.

62. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996;334(1):1-6.

63. Covens A, Carey M, Bryson P, Verma S, Fung Kee Fung M, Johnston M. Systematic review of first-line chemotherapy for newly diagnosed postoperative patients with stage II, III, or IV epithelial ovarian cancer. *Gynecol Oncol.* 2002;85(1):71-80.

64. Engelen MJ, Kos HE, Willemse PH, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer.* 2006;106(3):589-598.

65. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med.* 1985;312(25):1604-1608.

66. Bast RC, Jr., Badgwell D, Lu Z, et al. New tumor markers: CA125 and beyond. *Int J Gynecol Cancer.* 2005;15 Suppl 3:274-281.

67. Badgwell D, Bast RC, Jr. Early detection of ovarian cancer. *Dis Markers.* 2007;23(5-6):397-410.

68. Rosenthal AN, Menon U, Jacobs IJ. Screening for ovarian cancer. *Clin Obstet Gynecol.* 2006;49(3):433-447.

69. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA.* 2011;305(22):2295-2303.

70. Oei AL, Massuger LF, Bulten J, Ligtenberg MJ, Hoogerbrugge N, de Hullu JA. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. *Br J Cancer.* 2006;94(6):814-819.

71. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. *JAMA.* 2006;296(2):185-192.

72. Thigpen T, Brady MF, Omura GA, et al. Age as a prognostic factor in ovarian carcinoma. The Gynecologic Oncology Group experience. *Cancer.* 1993;71(2 Suppl):606-614.

73. Duska LR, Chang YC, Flynn CE, et al. Epithelial ovarian carcinoma in the reproductive age group. *Cancer.* 1999;85(12):2623-2629.

74. Maas HA, Kruitwagen RF, Lemmens VE, Goey SH, Janssen-Heijnen ML. The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study. *Gynecol Oncol.* 2005;97(1):104-109.

75. Brenner H, Steliarova-Foucher E, Arndt V. Up-to-date monitoring of childhood cancer long-term survival in Europe: methodology and application to all forms of cancer combined. *Ann Oncol.* 2007;18(9):1561-1568.

76. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol.* 2000;19(1):3-10.

77. Cannistra SA. Cancer of the ovary. *N Engl J Med.* 2004;351(24):2519-2529.

78. Hunter RW, Alexander ND, Soutter WP. Meta-analysis of surgery in advanced ovarian carcinoma: is maximum cytoreductive surgery an independent determinant of prognosis? *Am J Obstet Gynecol.* 1992;166(2):504-511.

79. Young RC, Decker DG, Wharton JT, et al. Staging laparotomy in early ovarian cancer. *JAMA.*1983;250(22):3072-3076.

80. Mayer AR, Chambers SK, Graves E, et al. Ovarian cancer staging: does it require a gynecologic oncologist? *Gynecol Oncol.* 1992;47(2):223-227.

81. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr.* 1975;42:101-104.

82. Griffiths CT, Parker LM, Fuller AF, Jr. Role of cytoreductive surgical treatment in the management of advanced ovarian cancer. *Cancer Treat Rep.* 1979;63(2):235-240.

83. Kehoe S, Powell J, Wilson S, Woodman C. The influence of the operating surgeon's specialisation on patient survival in ovarian carcinoma. *Br J Cancer.* 1994;70(5):1014-1017.

84. Nguyen HN, Averette HE, Hoskins W, Penalver M, Sevin BU, Steren A. National survey of ovarian carcinoma. Part V. The impact of physician's specialty on patients' survival. *Cancer.* 1993;72(12):3663-3670.

85. Woodman C, Baghdady A, Collins S, Clyma JA. What changes in the organisation of cancer services will improve the outcome for women with ovarian cancer? *Br J Obstet Gynaecol.* 1997;104(2):135-139.

86. Junor EJ, Hole DJ, Gillis CR. Management of ovarian cancer: referral to a multidisciplinary team matters. *Br J Cancer.* 1994;70(2):363-370.

87. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. *Gynecol Oncol.* 1992;47(2):203-209.

88. Carney ME, Lancaster JM, Ford C, Tsodikov A, Wiggins CL. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? *Gynecol Oncol.* 2002;84(1):36-42.

89. Junor EJ, Hole DJ, McNulty L, Mason M, Young J. Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish national study of 1866 patients. *Br J Obstet Gynaecol.* 1999;106(11):1130-1136.

90. Olaitan A, Weeks J, Mocroft A, Smith J, Howe K, Murdoch J. The surgical management of women with ovarian cancer in the south west of England. *Br J Cancer.* 2001;85(12):1824-1830.

91. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases.* 1987;40(5):373-383.

92. FIGO Cancer Committee. Staging announcement. *Gynecol Oncol.* 1986;25:383-385.

93. Tingulstad S, Skjeldestad FE, Hagen B. The effect of centralization of primary surgery on survival in ovarian cancer patients. *Obstet Gynecol.* 2003;102(3):499-505.

94. Junor E. The impact of specialist training for surgery in ovarian cancer. *Int J Gynecol Cancer.* 2000;10(S1):16-18.

95. Orr JW, Jr. What constitutes the "optimal" treatment environment of women with gynecologic cancer? *Gynecol Oncol.* 2003;89(1):1-3.

96. Eisenkop SM, Spirtos NM. What are the current surgical objectives, strategies, and technical capabilities of gynecologic oncologists treating advanced epithelial ovarian cancer? *Gynecol Oncol.* 2001;82(3):489-497.

97. Kitchener HC. Clinical practice guidelines: loss of clinical freedom or a coming of age? *Int J Gynecol Cancer.* 2002;12(4):332-336.

98. Wolfe CD, Tilling K, Raju KS. Management and survival of ovarian cancer patients in south east England. *Eur J Cancer.* 1997;33(11):1835-1840.

99. Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. *J Clin Oncol.* 2000;18(11):2327-2340.

100. Mol BW, Boll D, De Kanter M, et al. Distinguishing the benign and malignant adnexal mass: an external validation of prognostic models. *Gynecol Oncol.* 2001;80(2):162-167.

101. Im SS, Gordon AN, Buttin BM, et al. Validation of referral guidelines for women with pelvic masses. *Obstet Gynecol.* 2005;105(1):35-41.

102. Munstedt K, Franke FE. Role of primary surgery in advanced ovarian cancer. *World J Surg Oncol.* 2004;2:32.

103. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst.* 2003;95(2):113-125.

104. van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med.* 1995;332(10):629-634.

105. Rose PG, Nerenstone S, Brady MF, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med.* 2004;351(24):2489-2497.

106. Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. *Br J Surg.* 2007;94(2):145-161.

107. Urbach DR, Austin PC. Conventional models overestimate the statistical significance of volume-outcome associations, compared with multilevel models. *J Clin Epidemiol.* 2005;58(4):391-400.

108. Metzger R, Bollschweiler E, Vallbohmer D, Maish M, DeMeester TR, Holscher AH. High volume centers for esophagectomy: what is the number needed to achieve low postoperative mortality? *Dis Esophagus.* 2004;17(4):310-314.

109. Holscher AH, Metzger R, Brabender J, Vallbohmer D, Bollschweiler E. High-volume centers--effect of case load on outcome in cancer surgery. *Onkologie.* 2004;27(4):412-416.

110. Birkmeyer JD, Finlayson EV, Birkmeyer CM. Volume standards for high-risk surgical procedures: potential benefits of the Leapfrog initiative. *Surgery.* 2001;130(3):415-422.

111. Gandjour A, Bannenberg A, Lauterbach KW. Threshold volumes associated with higher survival in health care: a systematic review. *Med Care.* 2003;41(10):1129-1141.

112. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med.* 2002;346(15):1128-1137.

113. Killeen SD, O'Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. *Br J Surg.* 2005;92(4):389-402.

114. van Lanschot JJ, Hulscher JB, Buskens CJ, Tilanus HW, ten Kate FJ, Obertop H. Hospital volume and hospital mortality for esophagectomy. *Cancer.* 2001;91(8):1574-1578.

115. Wouters MW, Wijnhoven BP, Karim-Kos HE, et al. High-volume versus low-volume for esophageal resections for cancer: the essential role of case-mix adjustments based on clinical data. *Ann Surg Oncol.* 2008;15(1):80-87.

116. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355(1):11-20.

117. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med.* 2002;137(6):511-520.

118. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals: estimating potentially avoidable deaths. *JAMA.* 2000;283(9):1159-1166.

119. O'Connor GT, Plume SK, Olmstead EM, et al. A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. *JAMA.* 1996;275(11):841-846.

120. Herbert MA, Prince SL, Williams JL, Magee MJ, Mack MJ. Are unaudited records from an outcomes registry database accurate? *Ann Thorac Surg.* 2004;77(6):1960-1964; discussion 1964-1965.

121. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg.* 2007;246(6):992-1000; discussion 1000-1001.

122. Khuri SF, Daley J, Henderson WG. The comparative assessment and improvement of quality of surgical care in the Department of Veterans Affairs. *Arch Surg.* 2002;137(1):20-27.

123. Dimick JB, Birkmeyer JD, Upchurch GR, Jr. Measuring surgical quality: what's the role of provider volume? *World J Surg.* 2005;29(10):1217-1221.

124. Birkmeyer JD, Dimick JB, Staiger DO. Operative mortality and procedure volume as predictors of subsequent hospital performance. *Ann Surg.* 2006;243(3):411-417.

125. Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality: the problem with small sample size. *JAMA.* 2004;292(7):847-851.

126. van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg.* 2005;242(6):781-788, discussion 788-790.

127. Rathore SS, Epstein AJ, Volpp KG, Krumholz HM. Hospital coronary artery bypass graft surgery volume and patient mortality, 1998-2000. *Ann Surg.* 2004;239(1):110-117.

128. Birkmeyer JD, Dimick JB, Birkmeyer NJ. Measuring the quality of surgical care: structure, process, or outcomes? *J Am Coll Surg.* 2004;198(4):626-632.

129. Lovegrove J, Valencia O, Treasure T, Sherlaw-Johnson C, Gallivan S. Monitoring the results of cardiac surgery by variable life-adjusted display. *Lancet.* 1997;350(9085):1128-1130.

130. Steiner SH, Cook RJ, Farewell VT, Treasure T. Monitoring surgical performance using risk-adjusted cumulative sum charts. *Biostatistics.* 2000;1(4):441-452.

131. Jarman B, Bottle A, Aylin P, Browne M. Monitoring changes in hospital standardised mortality ratios. *BMJ.* 2005;330(7487):329.

132. Wright J, Dugdale B, Hammond I, et al. Learning from death: a hospital mortality reduction programme. *J R Soc Med.* 2006;99(6):303-308.

133. Reilly J, Mitchell A, Blue J, Thomson W. Breast cancer audit: adapting national audit frameworks for local review of clinical practice. *Health Bull (Edinb).* 2001;59(1):60-62.

CHAPTER 5

Framework for interpretations of changes in cancer trends

CHAPTER 5.1

Progress against cancer in the Netherlands since the late 1980s: an epidemiological evaluation

Henrike E. Karim-Kos
Lambertus A.L.M. Kiemeney
Marieke W.J. Louwman
Jan Willem W. Coebergh
Esther de Vries

Int J Cancer 2012 Jun;130(12):2981-9.

ABSTRACT

Progress against cancer through prevention and treatment is often measured by survival statistics only instead of analyzing trends in incidence, survival and mortality simultaneously because of interactive influences. This study combines these parameters of major cancers to provide an overview of the progress achieved in the Netherlands since 1989 and to establish in which areas action is needed. The population-based Netherlands Cancer Registry and Statistics Netherlands provided incidence, 5-year relative survival and mortality of 23 major cancer types. Incidence, survival and mortality changes were calculated as the estimated annual percentage change. Optimal progress was defined as decreasing incidence and/or improving survival accompanied by declining mortality, and deterioration as increasing incidence and/or deteriorating survival accompanied by increasing mortality rates. Optimal progress was observed in 12 of 19 cancer types among males: laryngeal, lung, stomach, gallbladder, colon, rectal, bladder, prostate and thyroid cancer, leukemia, Hodgkin and non-Hodgkin lymphoma. Among females, optimal progress was observed in 12 of 21 cancers: stomach, gallbladder, colon, rectal, breast, cervical, uterus, ovarian and thyroid cancer, leukemia, Hodgkin and non-Hodgkin lymphoma. Deterioration occurred in three cancer types among males: skin melanoma, esophageal and kidney cancer, and among females six cancer types: skin melanoma, oral cavity, pharyngeal, esophageal, pancreatic and lung cancer. Our conceptual framework limits misinterpretations from separate trends and generates a more balanced discussion on progress.

INTRODUCTION

A question frequently asked by professionals, policymakers and the public is whether or not we are making progress in combating cancer. Are there improvements or is there even deterioration? It seems that the war on cancer is far from won,[1,2] despite the investments since President R. Nixon declared the 'war on cancer' in 1971 in the United States and since the start of the 'Europe against Cancer' program in 1986.[3]

Cancer survival statistics are often used to measure progress against cancer achieved by early detection/screening and therapy, whereby comparisons between countries and regions receive special attention.[4-6] However, improved survival from cancer at the population level does not always imply progress in absolute terms of less suffering and fewer deaths due to cancer. This 'artificial' progress is often due to early detection and screening practices which result in length bias (increased survival time by more frequent diagnoses of indolent cancers) or lead-time bias (earlier diagnosis causing an increased survival time without postponing time of death) or incomplete incidence or follow-up data.[7-9]

Many parameters may indicate progress, such as less false positive and false negative screening exams, more effective therapies with fewer associated side effects, better quality of life, and improved organization of palliative care. All of these are difficult to measure and monitor through the standard surveillance instruments, mainly cancer registries. However, several of these parameters will influence incidence, survival and/or mortality of cancer, which can be monitored over time. We chose to focus on these three measures of cancer burden (*i.e.,* incidence, survival, and mortality) combined in order to achieve a more objective assessment of progress against cancer, while avoiding over-interpreting findings from one of these measures only.[7,9,10] Based on these three measures, two key situations of progress can be distinguished: (*i*) a decreasing incidence as a result of preceding lower risk factor prevalence or screening of pre-malignant lesions (e.g., of cervical and colorectal cancer), and (*ii*) an improving survival as a result of changes in incidence (i.e., shifts in cancer subsite/morphology distribution caused by changes in risk factor prevalence, and more favorable stage distribution due to earlier diagnosis and improved detection) and changes in therapy regimens. Both changes in incidence and survival had to ultimately affect mortality. Optimal progress should thus be reflected in a decreasing incidence and/or improving survival accompanied by decreasing mortality.

On the contrary, increasing incidence due to preceding increased risk factor prevalence, and/or a worsening survival as a result of unfavorable changes in incidence (i.e., shifts towards certain subtypes or morphologies with a poor prognosis) or deterioration of (access to) care leading to worsening survival will result in increasing mortality.[11]

Recently, American, European and worldwide data on incidence, mortality, and survival were published,[12-14] but none of these studies combined these three measures to assess progress. The present study shows the trends in incidence, survival and mortality to assess to what extent progress against cancer has been made in the Netherlands since 1989 and to establish where action needs to be taken. This approach can be used as a framework by others using routinely collected cancer registry data for (inter)national comparisons over time.

MATERIAL AND METHODS

Data on the following 23 cancer types were collected: oral cavity (ICD-10 code: C01-06), pharynx (C09-14), larynx (C32), esophagus (C15), stomach (C16), colon (C18), rectum (C19-20), gallbladder (C23), pancreas (C25), lung (C33-34), skin melanoma (C43), female breast (C50), cervix (C53), corpus uteri (C54-55), ovary (C56), prostate (C61), testis (C62), bladder (C65, invasive only), kidney (C64-66, C68), thyroid (C73), Hodgkin lymphoma (C81), non-Hodgkin lymphoma (C82-88), and leukemia (C91-95).

Incidence data from 1989 to 2009 were obtained from the population-based Netherlands Cancer Registry (NCR), which has complete national coverage and registers about 90,000 cases annually.[15] Mortality data from 1989 to 2009 were derived from Statistics Netherlands.[16] Information on the vital status of diagnosed cancer patients (necessary to calculate survival time) was initially obtained from municipal registries and from 1995 onward from the nationwide database of all municipal population registries. These registries provide virtually complete coverage of all deceased Dutch citizens. Follow-up was complete until 1 January 2010.

Trends in incidence, survival and mortality were categorized by all possible combinations of incidence and survival trends (either improving, stable or deteriorating) and were further classified by the mortality trend, which is a result of the incidence-survival combination. **Table 5.1.1** gives all the possible incidence-survival-mortality combinations and their outcome on progress against cancer.

Table 5.1.1 | Categories of trends in incidence, survival and mortality, and the progress classification

Category	Trends in			Progress classification
	Incidence	Survival	Mortality	
A-1	↓	↑	↓	Pr-Opt
	↓	↑	=	Pr-Inc/Pr-Surv
	↓	↑	↑	Pr-Inc/Pr-Surv
A-2	↓	=	↓	Pr-Opt
	↓	=	=	Pr-Inc
	↓	=	↑	Pr-Inc
A-3	↓	↓	↓	Pr-Opt/Non-Imp
	↓	↓	=	Pr-Inc/Non-Imp
	↓	↓	↑	Pr-Inc/Det
B-1	=	↑	↓	Pr-Opt
	=	↑	=	Pr-Surv
	=	↑	↑	Pr-Surv
B-2	=	=	↓	Oth
	=	=	=	Oth
	=	=	↑	Oth
B-3	=	↓	↓	Non-Imp
	=	↓	=	Non-Imp
	=	↓	↑	Det
C-1	↑	↑	↓	Pr-Opt /Non-Imp
	↑	↑	=	Pr-Surv/Non-Imp
	↑	↑	↑	Pr-Surv/Det
C-2	↑	=	↓	Non-Imp
	↑	=	=	Non-Imp
	↑	=	↑	Det
C-3	↑	↓	↓	Non-Imp
	↑	↓	=	Non-Imp
	↑	↓	↑	Det

Abbreviations: Pr-Inc: progress by decreasing incidence; Pr-Surv: progress by improved survival; Pr-Opt: optimal progress by decreasing incidence and/or improved survival accompanied by decreasing mortality; Det: deterioration by increasing incidence and/or worsening survival accompanied by increasing mortality; Non-Imp: non improvers because of an increasing incidence and/or worsening survival; Oth: other situations.

Optimal progress was defined as a decreasing incidence and/or improving survival accompanied by decreasing mortality (Pr-Opt). Decreasing incidence and/or improving survival without decreasing mortality were also seen as progress (Pr-

Inc and Pr-Surv). Deterioration (Det) was defined as increasing incidence and/or deteriorating survival accompanied by increasing mortality. Increasing incidence and/or deteriorating survival without increasing mortality were classified as 'non improvers' (Non-Imp). All other situations were classified as 'other' (Oth). We considered a trend as increasing or decreasing when the trend showed a statistically significant change; in other cases we considered a trend as stable.

Statistical analysis

Incidence and mortality rates were standardized to the European standard population. Changes in these rates were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (CI). A regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable [i.e., $y = mx + b$ where $y = \ln(\text{rate})$ and x = calendar year, then EAPC = $100 * (e^m - 1)$].

Five-year relative survival was used to estimate disease-specific survival. It reflects survival of cancer patients, adjusted for competing causes of death in the general population with the same age and gender distribution. Traditional cohort-based relative survival analysis was used for the period 1989-1991. Since follow-up was available until January 2010, period-based relative survival analysis was used for the most recent period 2007-2009, which gives the most up-to-date estimates for this period.[17] Survival trends were quantified as the mean annual percentage change within 1989-2009 estimated by a linear regression model. A positive value of the mean annual change reflects an upward trend in survival (*i.e.,* improving) and a negative value implies a negative trend (*i.e.,* deterioration). *p*-Values are two-sided, and $p<0.05$ was considered statistically significant. All statistical analyses were performed using SAS (version 9.2).

RESULTS

Tables 5.1.2 and **5.1.3** present data on tumor-specific incidence, survival and mortality for Dutch males and females separately. The tumor-specific relationship between incidence-mortality and survival-mortality is shown in **Figure 5.1.1**. The most important results are described below.

Progress against cancer among males

Optimal progress (Pr-Opt) was observed for 12 out of 19 studied male cancers: laryngeal, stomach, colon, rectal, gallbladder, lung, prostate, bladder and thyroid cancer, leukemia, Hodgkin and non-Hodgkin lymphoma. For oral cavity, pharyngeal, esophageal, pancreatic, testicular and kidney cancer, and skin melanoma progress was made through significant survival improvement (Pr-Surv) only. Progress made by significant decreasing incidence (Pr-Inc) only was not observed for any studied male cancer.

Deterioration (Det) was seen for 3 out of 19 studied male cancers: esophageal and kidney cancer and skin melanoma. However, the mortality increases were smaller than the incidence increases probably as a result of the above mentioned survival improvements. Oral cavity, pharyngeal, colon, rectal, prostate, testis and thyroid cancer, non-Hodgkin lymphoma and leukemia (9 out of 19 studied male cancers) were classified into the group non improvers (Non-Imp) because of a significantly increasing incidence. None of the studied male cancers showed a deteriorating survival trend.

Progress against cancer among females

Optimal progress (Pr-Opt) became manifest for 12 out of 21 studied female cancers: stomach, colon, rectal, gallbladder, breast, uterus, cervical, ovarian and thyroid cancer, leukemia, Hodgkin and non-Hodgkin lymphoma. For skin melanoma, oral cavity, esophageal, lung and kidney cancer progress was made by significant survival improvement (Pr-Surv) only. Progress made by significant decreasing incidence (Pr-Inc) only was not observed for any studied female cancer. Stable incidence, survival and mortality trends were seen for laryngeal cancer.

Deterioration (Det) was seen for 6 out of 21 studied female cancers: skin melanoma, oral cavity, pharyngeal, esophageal, pancreatic and lung cancer. For skin melanoma, oral cavity and esophageal cancer the mortality increases were smaller than the incidence increases probably as a result of the above mentioned survival improvements. Colon, rectal, breast, uterus, kidney, bladder and thyroid cancer, leukemia, Hodgkin and non-Hodgkin lymphoma (10 out of 21 studied female cancers) were classified as non improvers (Non-Imp) because of a significantly increasing incidence. None of the studied female cancers showed a deteriorating survival trend.

Table 5.1.2 | Changes in incidence, 5-year relative survival and mortality for 19 cancer types in males (≥15 years)

Tumor site (ICD-10)	Incidence (ESR)		EAPC (95% CI)	Incidence trend	5-year relative survival (%)		Annual trend (%) (95% CI)	Survival trend	Mortality (ESR)		EAPC (95% CI)	Mortality trend	Progress classification	Category
	1989-1991	2007-2009			1989-1991	2007-2009			1989-1991	2007-2009				
Oral cavity (C01-06)	6.1	7.4	1.0 (0.5, 1.6)	↑	50	55	0.3 (0.1, 0.5)	↑	2.0	2.0	0.2 (-0.3, 0.8)	=	Pr-Surv/Non-Imp	C-1
Pharynx (C09-14)	5.2	6.0	0.9 (0.5, 1.3)	↑	33	42	0.4 (0.2, 0.6)	↑	2.4	2.6	0.4 (-0.2, 1.1)	=	Pr-Surv/Non-Imp	C-1
Larynx (C32)	12.1	7.7	-2.3 (-2.6, -2.0)	↓	71	72	0.0 (-0.1, 0.2)	=	3.8	2.2	-2.7 (-3.4, -2.0)	↓	Pr-Opt	A-2
Esophagus (C15)	9.8	18.0	3.4 (3.1, 3.7)	↑	8	15	0.4 (0.3, 0.5)	↑	10.1	15.0	2.2 (1.8, 2.5)	↑	Pr-Surv/Det	C-1
Stomach (C16)	30.7	16.5	-3.4 (-3.6, -3.2)	↓	20	21	0.1 (0.0, 0.3)	↑	25.2	11.5	-4.4 (-4.6, -4.1)	↓	Pr-Opt	A-1
Colon (C18)	40.9	54.4	1.5 (1.3, 1.7)	↑	53	60	0.4 (0.3, 0.4)	↑	26.7	25.1	-0.5 (-0.8, -0.2)	↓	Pr-Opt/Non-Imp	C-1
Rectum (C19-20)	27.0	32.4	1.1 (0.9, 1.3)	↑	50	63	0.7 (0.5, 0.8)	↑	9.5	8.1	-0.8 (-1.2, -0.5)	↓	Pr-Opt/Non-Imp	C-1
Gallbladder (C23)	1.1	0.6	-4.7 (-5.9, -3.5)	↓	9	18	[1]	[1]	1.0	0.5	-3.8 (-5.1, -2.5)	↓	Pr-Opt	A
Pancreas (C25)	13.6	13.3	-0.1 (-0.6, 0.4)	=	3	5	0.1 (0.1, 0.2)	↑	15.8	15.3	-0.2 (-0.7, 0.3)	=	Pr-Surv	B-1
Lung (C33-34)	139.5	90.9	-2.5 (-2.7, -2.3)	↓	12	15	0.1 (0.1, 0.2)	↑	135.6	84.5	-2.7 (-2.8, -2.6)	↓	Pr-Opt	A-1
Skin melanoma (C43)	11.4	24.9	4.6 (4.2, 5.0)	↑	75	83	0.5 (0.4, 0.6)	↑	3.4	5.5	2.8 (2.4, 3.2)	↑	Pr-Surv/Det	C-1
Prostate (C61)	81.3	130.8	2.4 (1.9, 3.0)	↑	62	87	1.4 (1.2, 1.6)	↑	41.1	32.5	-1.5 (-1.9, -1.2)	↓	Pr-Opt/Non-Imp	C-1
Testis (C62)	5.2	10.5	4.0 (3.7, 4.4)	↑	94	97	0.2 (0.1, 0.2)	↑	0.6	0.4	-1.5 (-3.3, 0.2)	=	Pr-Surv/Non-Imp	C-1

Table 5.1.2 | *Continued*

Tumor site (ICD-10)	Incidence (ESR)		EAPC (95% CI)	Incidence trend	5-year relative survival (%)		Annual trend (%) (95% CI)	Survival trend	Mortality (ESR)		EAPC (95% CI)	Mortality trend	Progress classification	Category
	1989-1991	2007-2009			1989-1991	2007-2009			1989-1991	2007-2009				
Kidney & other urinary organs (C64-66, C68)	17.7	20.5	0.6 (0.2, 1.0)	↑	49	56	0.4 (0.3, 0.6)	↑	10.1	11.2	0.4 (0.0, 0.7)	↑	Pr-Surv/Det	C-1
Bladder, only invasive (C67)	29.7	27.7	-0.5 (-0.7, -0.3)	↓	56	55	-0.1 (-0.2, 0.1)	=	15.4	10.8	-1.8 (-2.1, -1.5)	↓	Pr-Opt	A-2
Thyroid (C73)	1.5	2.0	1.7 (0.7, 2.6)	↑	75	83	0.5 (0.1, 0.9)	↑	0.6	0.4	-2.2 (-4.1, -0.3)	↓	Pr-Opt/Non-Imp	C-1
Hodgkin lymphoma (C81)	3.3	3.7	0.6 (-0.0, 1.3)	=	77	85	0.4 (0.1, 0.6)	↑	1.2	0.7	-3.2 (-4.7, -1.7)	↓	Pr-Opt	B-1
Non-Hodgkin lymphoma (C82-88)	19.3	22.3	0.7 (0.4, 1.0)	↑	49	64	0.9 (0.7, 1.1)	↑	9.4	7.8	-0.9 (-1.5, -0.3)	↓	Pr-Opt/Non-Imp	C-1
Leukemia (C91-95)	13.0	19.9	2.8 (2.1, 3.4)	↑	35	52	0.9 (0.7, 1.1)	↑	10.0	8.4	-1.1 (-1.4, -0.7)	↓	Pr-Opt/Non-Imp	C-1

Abbreviations: ESR, European Standard Rate; EAPC, Estimated Annual Percentage Change; 95% CI, 95% Confidence Interval; Pr-Inc, progress by decreasing incidence; Pr-Surv, progress by improved survival; Pr-Opt, optimal progress by decreasing incidence and/or improved survival accompanied by decreasing mortality; Det, deterioration by increasing incidence and/or worsening survival accompanied by increasing mortality; Non-Imp, non-improvers because of increasing incidence and/or deteriorating survival; Oth, other situations; [1]annual survival trend could not be calculated because of less than 10 cases survived 5 years

Table 5.1.3 | Changes in incidence, 5-year relative survival, and mortality for 21 cancer types in females (≥15 years)

Tumor site (ICD-10)	Incidence (ESR)		EAPC (95% CI)	Incidence trend	5-year relative survival (%)		Annual trend (%) (95% CI)	Survival trend	Mortality (ESR)		EAPC (95% CI)	Mortality trend	Progress classification[a]	Category
	1989-1991	2007-2009			1989-1991	2007-2009			1989-1991	2007-2009				
Oral cavity (C01-06)	3.1	4.7	2.2 (1.5, 2.8)	↑	59	64	0.2 (0.1, 0.4)	↑	0.8	1.0	1.3 (0.3, 2.2)	↑	Pr-Surv/Det	C-1
Pharynx (C09-14)	1.7	2.2	1.8 1.1, 2.5)	↑	41	44	-0.0 (-0.4, 0.3)	=	0.8	0.9	1.1 (0.0, 2.3)	↑	Det	C-2
Larynx (C32)	1.4	1.5	0.1 (-0.8, 0.9)	=	74	70	-0.0 (-0.4, 0.3)	=	0.4	0.5	1.0 (-0.3, 2.3)	=	Oth	B-2
Esophagus (C15)	3.7	5.4	2.0 (1.5, 2.6)	↑	11	17	0.4 (0.2, 0.5)	↑	3.3	4.3	1.3 (0.8, 1.8)	↑	Pr-Surv/Det	C-1
Stomach (C16)	12.0	7.7	-2.5 (-2.9, -2.2)	↓	23	22	-0.0 (-0.2, 0.1)	=	10.1	5.7	-3.1 (-3.5, -2.7)	↓	Pr-Opt	A-2
Colon (C18)	34.9	41.5	0.9 (0.7, 1.1)	↑	55	59	0.3 (0.2, 0.4)	↑	21.2	18.0	-0.9 (-1.1, -0.8)	↓	Pr-Opt/Non-Imp	C-1
Rectum (C19-20)	15.9	18.7	0.9 (0.5, 1.2)	↑	52	64	0.6 (0.5, 0.8)	↑	5.2	4.5	-0.9 (-1.4, -0.5)	↓	Pr-Opt/Non-Imp	C-1
Gallbladder (C23)	3.0	1.2	-5.6 (-6.6, -4.7)	↓	14	11	[1]	[1]	2.3	0.9	-5.5 (-6.5, -4.5)	↓	Pr-Opt	A
Pancreas (C25)	9.2	10.4	0.5 (0.1, 1.0)	↑	3	5	0.0 (-0.0, 0.1)	=	11.1	11.8	0.5 (0.1, 0.8)	↑	Det	C-2
Lung (C33-34)	22.6	49.8	4.5 (4.3, 4.7)	↑	14	17	0.2 (0.1, 0.3)	↑	19.1	40.7	4.3 (4.0, 4.5)	↑	Pr-Surv/Det	C-1
Skin melanoma (C43)	15.7	30.2	3.8 (3.4, 4.3)	↑	88	91	0.2 (0.1, 0.3)	↑	2.6	3.6	1.7 (1.2, 2.2)	↑	Pr-Surv/Det	C-1
Breast (C50)	131.2	166.3	1.1 (0.9, 1.4)	↑	76	88	0.7 (0.6, 0.7)	↑	49.7	35.8	-1.9 (-2.1, -1.6)	↓	Pr-Opt/ Non-Imp	C-1
Cervix (C53)	11.8	9.8	-1.3 (-1.8, -0.8)	↓	66	73	0.3 (0.1, 0.4)	↑	4.3	2.5	-2.7 (-3.5, -2.0)	↓	Pr-Opt	A-1

Table 5.1.3 | *Continued*

Tumor site (ICD-10)	Incidence (ESR)		EAPC (95% CI)	Incidence trend	5-year relative survival (%)		Annual trend (%) (95% CI)	Survival trend	Mortality (ESR)		EAPC (95% CI)	Mortality trend	Progress classification[a]	Category
	1989-1991	2007-2009			1989-1991	2007-2009			1989-1991	2007-2009				
Uterus (C54-55)	20.0	22.0	0.6 (0.4, 0.9)	↑	77	80	0.2 (0.1, 0.3)	↑	4.9	4.1	-0.8 (-1.2, -0.3)	↓	Pr-Opt/Non-Imp	C-1
Ovary (C56)	19.6	14.3	-2.1 (-2.4, -1.8)	↓	36	41	0.4 (0.2, 0.5)	↑	14.7	10.7	-1.9 (-2.2, -1.6)	↓	Pr-Opt	A-1
Kidney & other urinary organs (C64-66, C68)	9.1	10.6	0.6 (0.2, 1.1)	↑	52	57	0.2 (0.1, 0.4)	↑	4.6	4.8	-0.1 (-0.5, 0.3)	=	Pr-Surv/Non-Imp	C-1
Bladder, only invasive (C67)	5.8	7.2	1.2 (0.8, 1.5)	↑	44	42	-0.1 (-0.3, 0.1)	=	3.5	3.4	-0.2 (-0.6, 0.3)	=	Non-Imp	C-2
Thyroid (C73)	3.6	4.9	1.8 (1.1, 2.5)	↑	78	83	0.3 (0.0, 0.5)	↑	1.0	0.7	-1.7 (-2.8, -0.7)	↓	Pr-Opt/Non-Imp	C-1
Hodgkin lymphoma (C81)	2.2	2.7	1.0 (0.4, 1.5)	↑	79	85	0.2 (0.0, 0.5)	↑	0.8	0.3	-4.3 (-6.2, -2.3)	↓	Pr-Opt/Non-Imp	C-1
Non-Hodgkin lymphoma (C82-88)	12.5	15.0	1.0 (0.8, 1.3)	↑	50	65	0.8 (0.6, 1.0)	↑	6.2	5.0	-1.0 (-1.6, -0.4)	↓	Pr-Opt/Non-Imp	C-1
Leukemia (C91-95)	7.2	12.3	3.5 (2.9, 4.1)	↑	38	54	0.9 (0.8, 1.1)	↑	6.1	5.1	-0.8 (-1.2, -0.4)	↓	Pr-Opt/Non-Imp	C-1

Abbreviations: ESR, European Standard Rate; EAPC, Estimated Annual Percentage Change; 95% CI, 95% Confidence Interval; Pr-Inc, progress by decreasing incidence; Pr-Surv, progress by improved survival; Pr-Opt, optimal progress by decreasing incidence and/or improved survival accompanied by decreasing mortality; Det, deterioration by increasing incidence and/or worsening survival accompanied by increasing mortality; Non-Imp, non-improvers because of increasing incidence and/or deteriorating survival; Oth, other situations; [1]annual survival trend could not be calculated because of less than 10 cases survived 5 years

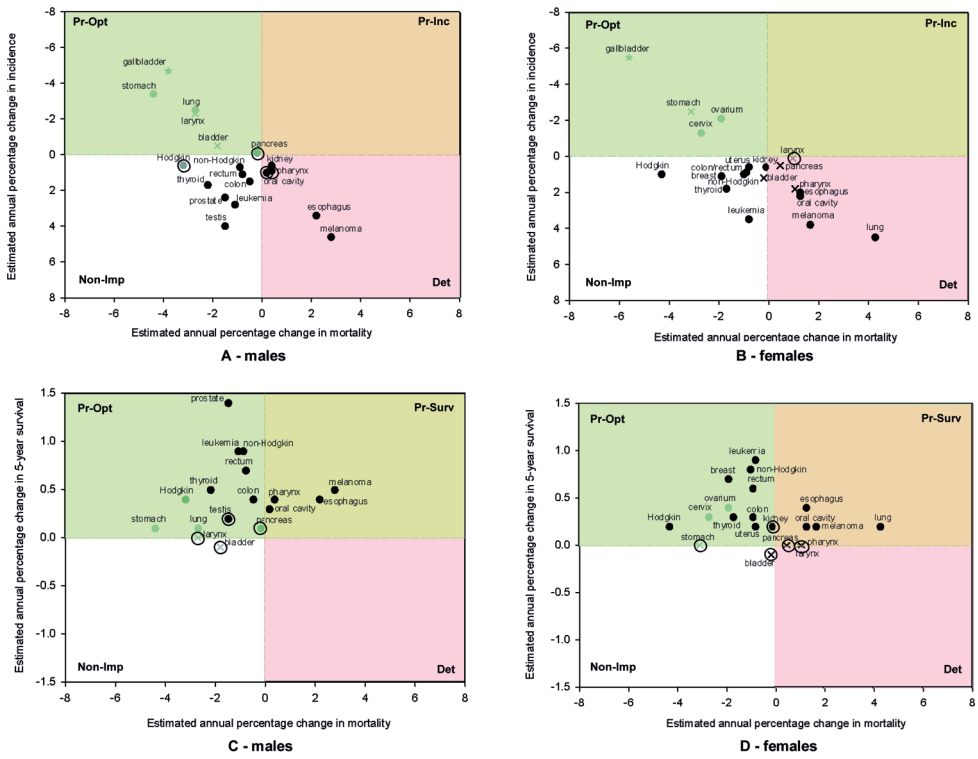


Figure 5.1.1 | Trends in incidence and mortality (a, b), and 5-year survival and mortality (c, d) for cancer in males and females, the Netherlands 1989–2009 (dots with a circle: mortality trend is not statistically significant; for 95% CIs of the point estimates, see Tables 2 and 3). See page 318 for color figure.

DISCUSSION

A largely positive pattern of progress against cancer was observed for the Netherlands in the last 20 years. Out of the 19 male and 21 female cancer types included in our study, optimal progress (Pr-Opt) was observed for 12 male and female cancers, and deterioration (Det) for three male and six female cancers only. Marked incidence increases were observed for nine male and ten female cancers without being accompanied by increasing mortality rates. These cancers and deteriorating cancers need our attention as well as cancers with a poor prognosis for which 5-year survival remained below 20% (*e.g.,* cancers of the esophagus, stomach, gallbladder, pancreas and lung).

Gender differences in progress against cancer

Out of the 17 studied cancers which occur in both sexes, all cancers showed progress (Pr-Opt or Pr-Surv) among males, while among women progress was seen for 13 of these cancers. This gender difference in progress is due to opposite trends in incidence of laryngeal, pancreatic and bladder cancer and a lack of progress in terms of survival for pharyngeal and pancreatic cancer among females. The opposite trends in incidence are most likely a result of opposing trends in smoking prevalence, as was already observed for lung cancer. While the smoking prevalence among adult males decreased from 90% in the late 1950s to 30% in 2009, it increased among females until the 1970s (about 40%) and slowly decreased to 26% in 2009.[18] This gender difference in smoking trends combined with alcohol intake is probably also the main cause of gender differences in deterioration that we have observed in this study: marked incidence and mortality increases were observed for cancers of the oral cavity, pharynx, pancreas and lung among females only.[19,20]

For pharyngeal cancer, males had a somewhat lower survival than females in 1989-1991 (survival gap of 8%), indicating more opportunity for improvement among males. However, large survival gaps of about 10% remained for skin melanoma, oral cavity and bladder cancer, where males had a worse survival, except for bladder cancer. Such gender differences have been reported before and it is known that (generally) males have a worse cancer survival than females, which was more pronounced in the past.[21] The survival benefit for women is generally thought to be due to earlier detection because of increased awareness, but for melanomas the survival benefit has been shown to be independent of stage and other tumor characteristics.[22,23]

Dutch progress against cancer in an international perspective

Observed cancer trends in this study resembled those in other developed countries.[13] Within Europe, the Netherlands has one of the strongest increases of esophageal cancer incidence, probably partly due to the marked increase of obesity prevalence although this prevalence is still one of the lowest in Europe.[24-26] Increases in prostate cancer incidence were more modest than in other European countries probably due to the lower frequency of PSA testing in the Netherlands.[24] This also explains why prostate cancer incidence in the US is much higher than in the Netherlands. Dutch ovarian cancer incidence showed one of the strongest declines within Europe

and is at a lower level than in the US, probably due to very common use of oral contraceptives in the Netherlands.[24, 27]

Survival improvements for the Netherlands are comparable with findings for the US, except for bladder cancer where only US data showed improvements. Survival for patients with laryngeal cancer deteriorated in the US, while it remained stable in the Netherlands.[14] Overall the 5-year survival rates were higher in the US than in the Netherlands, particularly for colorectal, thyroid, prostate and kidney cancer concurring with a comparison of European cancer survival results (EUROCARE) with US SEER data.[4] The higher frequency of screening of colorectal and prostate cancer in the US is largely responsible for these higher survival rates. However, there might also be a difference in completeness of follow-up in the cancer registries, being high in the Netherlands and which effects survival outcome negatively.[11]

Influence of prevention on progress

Prevention programs aimed to reduce exposure to risk factors (e.g., smoking, obesity and excessive sun exposure) and thereby to reduce cancer incidence. In this study, we observed marked incidence decreases for stomach, gallbladder, laryngeal (only males), lung (only males), bladder (only males), cervical and ovarian cancer. The decreases of laryngeal and lung cancer among males are good examples of the effect of decreasing smoking prevalence among males. The national screening program for cervical cancer successfully reduced cervical cancer incidence by detecting pre-malignancies.[28]

Prevention programs against smoking, obesity and excessive sun exposure remain important because of the enormous incidence increases of esophageal, oral cavity (only females), pharyngeal and lung cancer (only females), and skin melanoma.

Influence of shifts in stage distribution on progress

A shift in stage distribution can be an important cause of improving or deteriorating survival, although these shifts do not always become visible in overall incidence trends. They can be caused by changes in diagnostics, early detection (e.g., screening programs) and increased awareness among clinicians and the population. Among cancer types with improved survival, we observed a statistically significant rise in the occurrence of early stages (T1/2 N0 M0) for esophageal, rectal, skin melanoma, female breast, uterus, prostate, testis, kidney and thyroid cancer (Supporting

Information Figure). In case of skin melanoma this rise is probably also due to increased awareness in the population, although advanced stage melanomas also increased during the last decades.[29,30] The national breast cancer screening program in the Netherlands would explain the shift towards early breast cancer stages among women aged 50-75 years and probably part of the survival improvement,[31,32] to some extent also explained by increased use of adjuvant treatment.[32,33] Increasing use of PSA tests in the Netherlands partly explain the shift towards early stage and even latent prostate cancers, leading to artificially high survival rates.[34]

Improvements in diagnostics (*e.g.,* improved imaging techniques and increased number of examined lymph nodes) may also have led to a decrease in the occurrence of early stages resulting in the so-called stage migration. This is probably valid for laryngeal, stomach, lung, pancreatic, ovarian and bladder cancer for which a decrease in the occurrence of early stages was observed in the present study (Supporting Information Figure).

Influence of shifts in subsite/morphology distribution on progress

Shifts in the prognostic profile as determined by the subsite or morphology distribution can cause a deteriorating survival, which can be compensated by new therapies that improve survival at the same time. So, a stable survival does not always reflect a lack of progress. Shifts in subsite/morphology reflect changes in risk factor prevalence and are not necessarily visible in overall incidence trends. An example is the subsite shift from noncardia to cardia stomach cancers (cardia shifted from 26% to 32% for males and 13% to 18% for females in 1989-1991 and 2007-2009, respectively). Relative 5-year survival for patients with cardia tumors was only 15% compared to 24% of those with noncardia tumors despite ample attention for earlier detection due to more endoscopy and better surgery.[35]

Changes in therapy regimens and progress

In the Netherlands, progress was more often made in terms of survival than in terms of incidence, indicating a large role for changes in therapy. Changes in survival may be influenced by improved treatment but also by preceding changes in incidence. Unraveling and elucidating changes in incidence and therapy is often difficult, even when incidence remains stable, because there might be underlying proportional changes in age, subsite, morphology and stage distribution, whether or not following risk factor prevalence changes or early detection. Multivariable

relative survival analyses have been shown to be useful in unraveling the underlying mechanisms of improved survival, e.g., a study on colon carcinomas showed a marked improvement in survival for patients with stage III disease to be due to more adjuvant chemotherapy.[36]

Remarks on measuring progress

Because of the interdependence between survival and incidence, it has been suggested to define progress against cancer merely as decreasing mortality.[9,37,38] Using this definition, our results indicate progress in 12 of 19 male cancers and 12 of 21 female cancers. However, declining cancer mortality does not necessarily reflect recent progress, because mortality rates for a given year reflect the risk of cancer death among patients diagnosed over the preceding years depending on the prognosis of a certain cancer (e.g,. breast cancer mortality rates reflects deaths from the preceding 15-20 years).[10] Improvements in survival can also slow down an increase of mortality following the incidence trend. In this study, *e.g.,* EAPCs for mortality from skin melanoma, oral cavity and esophageal cancer were lower than those for incidence, most likely due to improved survival. Interestingly, certain cancers (melanoma and esophageal cancer for both sexes, oral cavity and lung cancer for females and kidney cancer for males) fall both into the Pr-Surv group and into the deterioration group which illustrates there can be progress in survival while incidence and mortality continue to rise. Therefore, it is important to consider information on incidence, survival and mortality simultaneously. Another reason not to use cancer mortality data only is that changes in mortality can also follow changes in coding practice of underlying cause–of-death. Therefore, we feel it is necessary to interpret mortality changes in combination with incidence and survival.

Welch et al.[8] attempted to measure progress against cancer in the USA by correlating both changes in incidence and changes in mortality with changes in 5-year survival. They concluded that the effectiveness of cancer care is tenuous, because of the small effect of survival changes on mortality, but much more influenced by changes in incidence. We did not focus on the strength of the association between incidence, survival and mortality, because of the difficulty of unraveling changes in incidence and therapy.

Limitations of this study

Using the progress model proposed in this study, one should realize that taking the same observation periods for incidence, survival and mortality it is not possible to observe the final effect of the incidence-survival combination on mortality: as it takes some time before changes in incidence and survival are reflected in the mortality statistics. An alternative could be taking a gap of *x* years between the observation periods of incidence/survival and mortality. However, this gap of *x* years would be different for different cancer types and it would mean not using the most recent trend information on incidence and survival, which would be a pity. Another important thing to realize is that studying a certain time period does not take into account the progress made before that period. For example, before 1990, much progress was made in the treatment of testicular cancer resulting in a decreasing and very low mortality rates.[39] In fact, mortality has become so low that there is hardly any room left for progress made by improved survival. In these situations progress made by improved survival only is the best progress one can expect.

In this study, changes in incidence and mortality were evaluated by EAPCs calculated over the whole study period. However, during a longer period, temporary trends in opposing directions are not taken into account. For example, in the Netherlands the incidence of cervical cancer decreased from 9.1 per 100,000 to 6.5 in 2001, but from 2001 it started to increase to 7.6 per 100,000 in 2009, but over the whole period there is still an overall decreasing incidence trend.[40] When studying longer time periods, one might have to use joinpoint analysis in order to take such effects more precisely into account.

To calculate 5-year relative survival we used two different methods, *i.e.,* cohort and period-based survival analyses. Although period-based results can differ slightly from the traditional cohort-based results, it has been repeatedly shown that they come very close to the later obtained cohort-based results. A difference between the two calendar periods based on the two different methods likely points to a change in prognosis.[41]

CONCLUSION

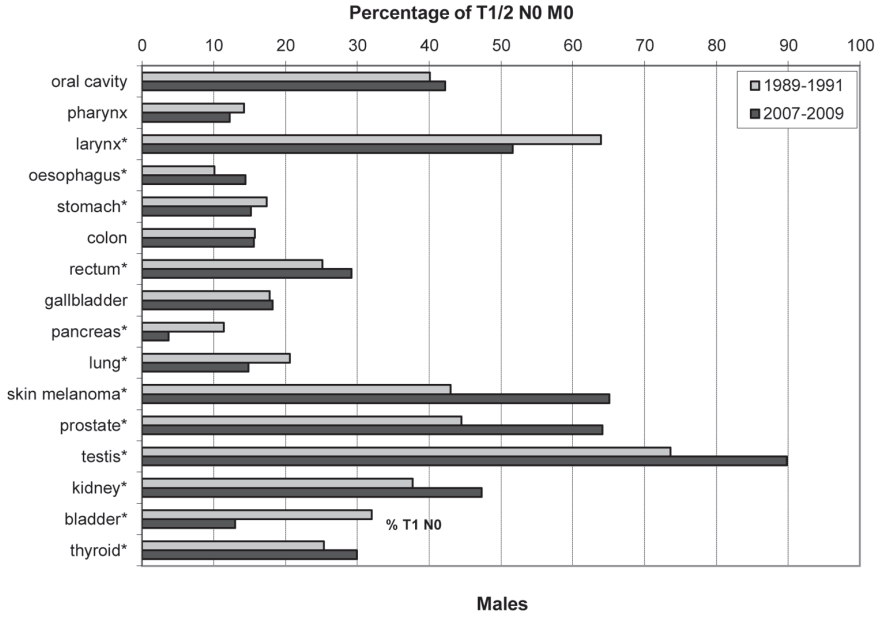
In conclusion, our conceptual framework limits misinterpretations from separate trends and generates a more balanced discussion on progress. The observed progress against cancer in the Netherlands is the result of successful prevention resulting in *e.g.,* decreasing smoking prevalence (particularly among males, *e.g.,* lung, laryngeal and bladder cancer), adequate screening of breast and cervical cancer (national coverage), other early detection (e.g., melanoma and PSA testing for prostate cancer), better staging by improved imaging techniques (e.g., lung and kidney cancer), improved staging and treatment (e.g., rectal cancer). Although, there is still much room left for improvement, smoking prevalence and incidence of smoking related cancers are still on the increase in women, incidence of obesity related cancers and melanomas continues increasing and survival of esophageal, lung, gallbladder, pancreatic and stomach cancer remains still poor.

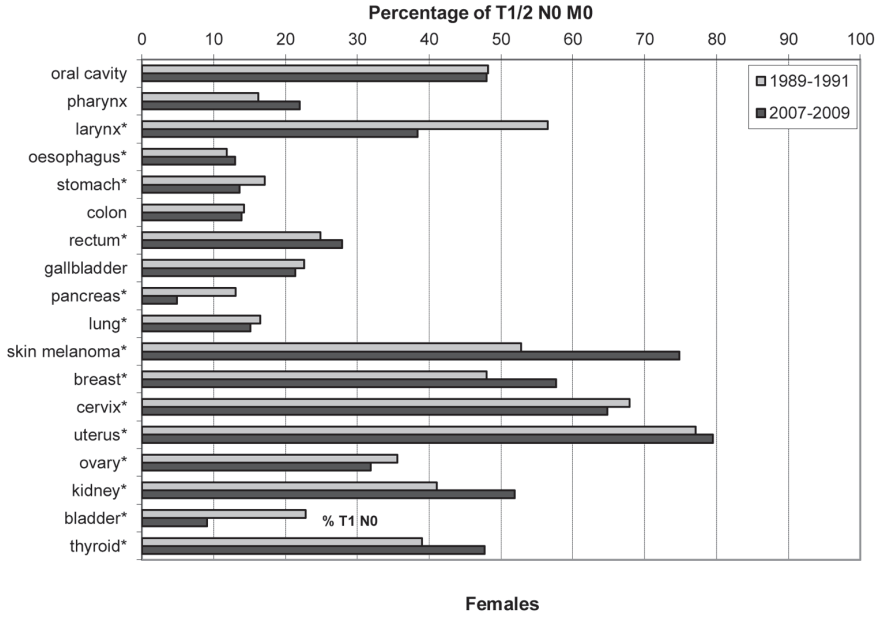
Acknowledgements

The work on this research was performed within the framework of the project "Progress against cancer in the Netherlands since the 1970?" funded by the Dutch Cancer Society (EMCR 2006-3489). The authors thank the registration clerks of the NCR for the dedicated data collection.

APPENDIX: SUPPORTING INFORMATION FIGURE

Percentage of low stages of studied cancer types among males and females





CHAPTER 5.2

Explanations for worsening cancer survival

Esther de Vries
Henrike E. Karim-Kos
Maryska L. Janssen-Heijnen
Isabelle Soerjomataram
Lambertus A.L.M. Kiemeney
Jan Willem W. Coebergh

Nat Rev Clin Oncol. 2010 Jan; 7(1):60-63.

ABSTRACT

If cancer survival is reported to be worsening over time or inferior compared to other countries, politicians and health-care workers may get blamed because suboptimal care is presumed to be the cause. Yet, a variety of reasons exist for cancer survival statistics to change for the worse, of which deterioration of care is only one. Another explanation is that the improved diagnosis of premalignant lesions causes survival statistics to reflect only the most aggressive cancers – those with the poorest prognosis. In addition, deleterious changes in the distribution of prognostic factors and in the distribution of sociodemographic characteristics may negatively affect survival proportions. In this article, we identify the pitfalls that might be encountered in comparisons of published, population-based survival data from different time periods or populations.

INTRODUCTION

Cancer survival statistics attract a lot of attention, particularly when comparisons between calendar periods or countries show that survival has decreased over time or is lower than expected based on the average found in surrounding countries. Population-based cancer survival tends to remain stable or increase over time in most industrialized countries and for most cancer types.[24,42] Such increases in survival, however, do not necessarily reflect true improvements in cancer treatment. For example, early detection and screening practices have artificial effects on survival statistics because of the presence of a lead time or length bias (**Box 1**).[7, 8]

Decreasing survival proportions are sometimes observed over time and can result from of a variety of causes, even after adjustment for age and all-cause mortality.[24, 43] Here, we briefly explain the principles underlying cancer survival calculations and illustrate that a decrease in survival can be attributed to four factors: deterioration of care or of access to it; improved diagnosis of premalignant lesions; deleterious changes in the distribution of prognostic factors; and changes in the distribution of socio-demographic characteristics. We identify possible pitfalls that might be encountered when published survival data from different time periods or different populations are compared.

Box 1. Lead time and length bias

Early detection or screening aims to diagnose a disease at an earlier stage than would happen without screening. When the moment of death is not postponed by screening and, therefore, no additional lifetime has been gained, the survival time since diagnosis is longer for a screened person than for an unscreened person. In this case, screening seems to increase survival time, and this gain is called 'lead time'.

Slow-growing tumors often have a better prognosis than rapidly growing ones. Early detection or screening is more likely to detect slow-growing tumors than fast-growing tumors, as slow-growing tumors exist for an extended time without causing symptoms, and some of these tumors might actually never cause clinical disease. In such cases, screen-detected tumors seem to be associated with improved survival because they represent a group of tumors that already had an inherently favorable prognosis. This effect is called 'length bias'.

DETERMINATION OF CANCER SURVIVAL

Cancer survival is estimated for cohorts of newly diagnosed patients, based on cytological or histological criteria and sometimes clinical criteria of patients when entered into a cohort study. Survival is measured as the time from cancer diagnosis until death; a 5-year follow-up period is most frequently used as an indicator of outcome, although survival at 10 years would be more suitable for many cancer types, such as those amenable to screening (for example, breast and prostate cancer). End points for calculating survival can vary. Death due to any cause is used to calculate all-cause survival, that is, the proportion of patients with cancer who are alive at a certain point in time after diagnosis. Death due to the cancer under study or its treatment is reflected by disease-specific survival.

Many practical problems are encountered in correctly determining and registering cause of death. For example, determining the correct underlying cause of death can be difficult.[3] Relative survival circumvents the need to determine the cause of death because it represents the ratio of the overall survival for a cohort of cancer patients and the expected overall survival for the general population with the same sex and age distribution as the cancer patient cohort. Relative survival measures the excess mortality associated directly and/or indirectly with the diagnosis of a cancer and, thus, includes deaths due to complications of cancer or its treatment. For relative survival to be interpreted as a measure of excess mortality individuals with cancer, an accurate estimation of the expected mortality for the general population is important and requires mortality data stratified by sex, age, and calendar year.[7] Cancer mortality and non-cancer mortality are assumed to be independent. Moreover, in theory, relative survival is dependent on trends in other causes of death in the general population. These assumptions, however, should sometimes be questioned. For example, a markedly decreased incidence and mortality from cardiovascular diseases (which would result in an increase in the expected overall survival for the general population) would lead to a decrease in the relative survival ratio of cancer, even when the observed disease-specific survival remains stable. In addition, patients with cancer are assumed to have had an average life expectancy if they had not been diagnosed with cancer. This is, of course, an arbitrary assumption for some types of cancer. For example, patients with lung cancer may have a lower life expectancy because the cause of their cancer (smoking) is also a strong risk factor for mortality from other diseases.

Relative survival ratios can be compared over time or between geographical regions, despite the ageing of populations, but the results are meaningful only when they are adjusted for age. In instances of differential period of observation, the most reliable survival comparisons are based on age-specific risks.[44] Relative survival ratios are very useful for specific cancer subsites, but this measure is not suitable for all cancers combined because the deaths due to all cancers represent a considerable proportion of deaths due to all causes. The 'expected' survival figures for relative survival calculations in this scenario are based on mortality data for the general population that are substantially influenced by cancer mortality, causing the 'expected' mortality figures to be overestimated. This causes the relative survival estimates to become less valid. Moreover, survival statistics for all cancer sites combined should not be compared directly because the various types of cancer and their distributions can differ greatly between distinct populations and time periods. To judge the quality of survival estimates given by a registry, the inclusion and exclusion rules of the registry database should be clear. If these rules of such criteria change, for example, in coding systems such as the ICD-O international classification of diseases or TNM staging system, survival estimates might change rapidly. When neoplasms that were previously considered noninvasive are reclassified as 'new' cancers (as happened, for example, with the change in classification of bladder papillomas into papillocarcinomas in 1978), survival estimates increase markedly.[45] Moreover, completeness of study follow-up is essential for accurate survival estimates. Unfortunately, administrative completeness can vary with time across and between countries. Survival proportions tend to decrease when the completeness of follow-up improves because many patients who were initially lost to follow-up are actually found to have died. The number of death-certificate only (DCO) cases in cancer registries depends on the quality of the registry and on access to death certificates. These cases are often excluded in survival analysis because the date of diagnosis (and hence survival time) of DCO cases is unknown.[46] Registries with a high proportion of DCO cases will overestimate survival; therefore, if the proportion of DCO cases decreases over time, survival estimates may seem to worsen.[47]

DETERIORATION OF ACCESS TO CARE

The most obvious reason for decreasing survival proportions is less-aggressive or substandard care that results in lack of early detection or less-effective treatment of cancer, although this situation is uncommon. For example, decreased relative survival ratios for patients with laryngeal cancer were observed in the mid-1990s in the US compared with the 1980s.[48] During the mid-1990s, many clinicians preferred to treat these patients with irradiation rather than laryngectomy. Detailed analyses over time revealed shorter survival for patients with laryngeal squamous-cell carcinoma who underwent nonsurgical treatment, compared with those who underwent surgery.[49]

Likewise, among patients with high-grade T1 bladder cancer who underwent radical surgery in the US, 5-year disease-free survival before 1998 was 70%, versus only 40% after 1998. During the 1990s, intravesical therapy (for example, immunotherapy and/or chemotherapy) facilitated bladder-sparing strategies for these patients. Before 1998, 74% of patients with high-grade T1 bladder cancer underwent radical surgery without prior intravesical therapy, while only 43% of such patients did so after 1998. The observed decrease in survival was attributed to the delay in scheduling radical surgery that resulted from increased use of intravesical therapy.[50]

The economic collapse of the former socialistic countries of Central Europe coincided with decreased cancer survival during the transition period; the survival of patients with ovarian, cervical and uterine cancer, childhood soft-tissue sarcomas, and hepatic and germ-cell tumours temporarily decreased between 1988–1992 and 1993-1997.[51,52] These temporary decreases were probably related to the disintegration of health-care systems and infrastructures.

When cancers are detected at a later stage or are mistakenly classified as low-stage disease because of deterioration in screening availability (for example, poor imaging capacity) treatment will be less effective and survival will decrease. Adjusting the survival calculations for stage at diagnosis is possible,[53] although improvements in staging methods and changes in stage-coding could still be problematic when stage-adjusted survival estimates are compared over time.

IMPROVED DIAGNOSIS OF PRECANCERS

Survival proportions can decrease while therapeutic options remain stable or improve over time and/or early detection remains unchanged or improves. This pattern occurred for cervical cancer in many European countries, where large-scale and high-quality population-based programs for cervical screening gradually became available (**Table 5.2.1**).[24] The same phenomenon might be observed in the future for colorectal cancer.

The aim of screening for cervical and colorectal cancers is not only the detection of cancers at an early stage but also the detection of premalignant lesions, which can be treated to prevent the development of 'invasive' cancer. However, the cancers that occur despite screening may consist of a select group of rapidly growing, aggressive tumors that are probably difficult to treat and, thus, might result in decreased survival proportions, preceded by a decreased cancer incidence.

Screening for most other types of cancer (for example, breast or prostate) detects early stages of cancer rather than premalignant lesions. For these cancers, survival proportions will increase as a result of screening because of lead time bias and even length bias (**Box 1**), and possibly as a result of improved efficacy of treatment. Survival proportions may decrease again, however, when individuals' awareness or willingness to participate in screening programs decreases, which can potentially lead to increased disease stage at diagnosis. If the date of death is not postponed by treatment, then the survival proportions worsen, leading to an inverse 'lead time' effect.

New and improved methods for cancer diagnosis frequently result in improved survival proportions because these methods are more precise and/or detect the cancers earlier than previous techniques, which is hoped to result in improved therapeutic options. Conversely, the introduction of a new diagnostic technique may temporarily decrease cancer survival proportions. Pancreatic cancer is difficult to diagnose and treat and is associated with a poor prognosis. New diagnostic technologies have resulted in more diagnoses of this cancer occurring during the patients' lifetimes, whereas previously the diagnosis would have been made at autopsy and recorded as a DCO. These tumors with a very bad prognosis will now be included in the survival statistics resulting in lower survival estimates.[7]

Table 5.2.1 | Relative survival proportions for cervical cancer in Europe

Region	Start of screening program (year)	Type of screening invitation	5-year relative survival ratios		Trends in survival
			1990-1994[54]	2000-2002[4,55,56]	
Austria (Tirol)	1970	PB/OP (regional)	63.6	64.2	Increased
Iceland	1964	NRS	68.6	70.6	Increased
Finland	1963	PB	66	65.8	No change
Italy	1982–1998	PB/OP (regional)	66.6	67	No change
Netherlands (three regions)	1980	PB	69.4	69.2	No change
Scotland	1988	NRS	60.6	61	No change
Norway	1995, pilot 1992	NRS	69	67.5	Decreased
Sweden	1967–1977	NRS	69.6	66.7	Decreased
Switzerland	No data	OP	68.7	66.8	Decreased
Czech republic	1966	OP	65.2	59.8	Large decrease
England	1988	NRS	63.8	58.6	Large decrease
Germany (Saarland)	1971	OP	63.5	55.5	Large decrease
Malta	No data	No data	64.4	46.5	Large decrease
Poland	No data	No data	48.2	56	Large increase
Slovenia	2003 (1995 opportunistic)	NRS	59.9	65.2	Large increase
Spain	1986 (regional)	PB/OP	68.7	60.4	Large decrease
Wales	1988	NRS	58.7	52.6	Large decrease

Abbreviations: NRS, invitation only, to women who did not recently have an opportunistic smear; OP, opportunistic only; PB, population-based, invitational program.

CHANGES IN PROGNOSTIC FACTORS

Subtypes and subsites

Changes in risk-factor exposure may lead to shifts in the distribution of cancer subtypes. In the Netherlands, relative survival ratios for adenocarcinomas of the lung decreased during the 1980s despite increased application of improved endoscopic techniques by lung physicians, which was accompanied by improved access to specialized care. This decrease in relative survival ratios was partly attributed to the termination of mass screening for tuberculosis in the early 1980s, which sometimes detected slow-growing peripheral adenocarcinomas. In addition, the higher concentration of carcinogens in the peripheral lung zone as a result of

the increased use of filter cigarettes and deep inhalation may have caused tumors to more metastasize rapidly.[57] Similar decreases in overall lung cancer survival from 1992 to 2005 were observed in Malta, where a stable overall incidence of and mortality from lung cancer was accompanied by a relative rise in the incidence rate of adenocarcinomas (R. Micallef, personal communication).

Shifts in cancer subtype and subsite distribution may need to be studied over time as a determinant of survival. This requirement is illustrated by a study of changes in incidence of and survival from gastric cancer in the southeastern part of the Netherlands. Despite marked improvements in the endoscopic early detection, staging, surgery, and perioperative mortality of gastric cancer, no improvement in gastric cancer survival occurred during the period 1982-1995 because the proportion of cardiac and diffuse cancers with a poor prognosis had increased.[58] Laryngeal cancers represent another example of the negative influence of shifts in cancer subsite on survival.[46] Laryngeal cancers of the glottis exhibit a 5-year relative survival of around 60-80%, and for supraglottal cancers this rate is at around 40%.[59] Cancers of the glottis are usually detected at early stages. Alcohol consumption and tobacco smoking have different etiological effects on tumor subsite, with alcohol consumption being more relevant for supraglottal tumors and smoking for glottal cancers. With the decreasing prevalence of smoking and the stable alcohol consumption rates in many European countries, the proportion of cancers of the poor prognostic subsite (supraglottal tumors) will increase and negatively affect the relative survival ratios of laryngeal cancer over time.

Comorbidity

Changes in the prevalence of risk factors can also affect overall survival because of the presence of concomitant diseases (comorbidity). If a concomitant condition becomes prevalent in the population as a whole, the relative survival ratio is corrected for this change. However, relative survival ratios are likely to be affected when the comorbid condition is strongly associated with the tumor (for example, chronic obstructive pulmonary disease in patients with lung or laryngeal cancer) or when the comorbid condition is not only life-threatening, but also influences the eligibility of patients to receive aggressive cancer treatments such as surgery or chemotherapy, as is the case for diabetes.[60]

Changes in behavioural risk factors, such as an increase in alcohol consumption, cause rises in alcohol-related cancer incidence, mortality and comorbidities, such as

ischemic heart disease, stroke, hypertension, diabetes, liver cirrhosis, and depression. An increased prevalence of such comorbid conditions will lead to decreased survival proportions.[61] Since alcohol consumption is an important risk factor for cancer, particularly for squamous-cell cancer of the esophagus and supraglottal cancer of the larynx, the above-mentioned comorbid conditions are likely to be prevalent among patients with esophageal and laryngeal cancer, and result in suboptimal treatment and increased complications. This phenomenon may also have contributed to the observed declines in survival of these cancers during the transition period in the former socialist countries in Central Europe.[24,62,63]

In a similar manner, the increased prevalence of infectious diseases related to cancer (including HIV and hepatitis B and C viruses)[64] may not only increase the incidence of tumors such as lymphomas and liver cancer, but may also have a negative effect on the survival of patients with these cancers.

SOCIODEMOGRAPHIC CHARACTERISTICS

When patient populations change rapidly, survival can also be affected; for example, when certain subgroups comprise a larger part of the cancer burden due to changes in the distribution of socio-economic status. Cancer survival among people of low socioeconomic status is generally lower than it is in those of mid or high socioeconomic status; the relative risk of death within 5 years of diagnosis in the most deprived groups is 1.3-1.5-fold higher than in the most affluent group.[65,66] Underlying causes of this worse prognosis are related to decreased awareness and unfavorable tumor characteristics (for example, later stage at diagnosis because of diagnostic delay); personal characteristics such as ethnicity, screening participation rates, psychosocial factors and comorbidity; and health-care factors including treatment, screening, and quality of medical care.[66] Changes in the distribution of socio-economic groups (for example, as a consequence of selective emigration of healthy and enterprising individuals) may lead to decreased survival proportions.

CONCLUSIONS

In conclusion, a variety of factors can lead to decreased cancer survival proportions, most of which do not represent deteriorating in care. Unfavorable changes in underlying risk factors and early detection or screening practices that lead to the identification of relatively less-aggressive lesions are often the cause of this phenomenon, as are the changing demographic profiles of populations of patients. Worsening survival proportions merit an in-depth investigation that takes into account preceding trends in incidence, particularly for tumor subtype or subsite.

Acknowledgments

The work on this research was performed within the framework of the project "Progress against cancer in the Netherlands since the 1970?" (Dutch Cancer Society grant EMCR 2006-3489) and co-funded by the Comprehensive Cancer Center South in Eindhoven, the Netherlands.

REFERENCES

1. Leaf C. Why we're losing the war on cancer (and how to win it). *Fortune.* 2004;149(6):76-82, 84-76, 88 passim.
2. Ness RB. Fear of failure: why American science is not winning the war on cancer. *Ann Epidemiol.* 2010;20(2):89-91.
3. Boyle P, Autier P, Bartelink H, et al. European Code Against Cancer and scientific justification: third version (2003). *Ann Oncol.* 2003;14(7):973-1005.
4. Verdecchia A, Francisci S, Brenner H, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol.* 2007;8(9):784-796.
5. Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol.* 2008;9(8):730-756.
6. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. *Lancet Oncol.* 2007;8(9):773-783.
7. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. *J Intern Med.* 2006;260(2):103-117.
8. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? *Jama.* 2000;283(22):2975-2978.
9. Autier P, Boniol M. Caution needed for country-specific cancer survival. *Lancet.* 2011;377(9760):99-101.
10. Sant M, Francisci S, Capocaccia R, Verdecchia A, Allemani C, Berrino F. Should we use incidence, survival or mortality to assess breast cancer trends in European women? *Nat Clin Pract Oncol.* 2006;3(5):228-229.
11. de Vries E, Karim-Kos HE, Janssen-Heijnen ML, Soerjomataram I, Kiemeney LA, Coebergh JW. Explanations for worsening cancer survival. *Nature reviews.* 2010;7(1):60-63.
12. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer.* 2010;46(4):765-781.
13. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127(12):2893-2917.
14. American Cancer Society. *Cancer Facts & Figures 2010.* American Cancer Society. 2010.
15. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol.* 1993;22(3):369-376.
16. Statistics Netherlands. *http://statline.cbs.nl.* (accessed September 2007).
17. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer.* 1996;78(9):2004-2010.
18. STIVORO. *http://www.stivoro.nl.(*accessed April 2011).
19. Marron M, Boffetta P, Zhang ZF, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *Int J Epidemiol.* 2010;39(1):182-196.
20. Baron AE, Franceschi S, Barra S, Talamini R, La Vecchia C. A comparison of the joint effects of alcohol and smoking on the risk of cancer across sites in the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev.* 1993;2(6):519-523.
21. Micheli A, Ciampichini R, Oberaigner W, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. *Eur J Cancer.* 2009;45(6):1017-1027.

22. de Vries E, Nijsten TE, Visser O, et al. Superior survival of females among 10,538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. *Ann Oncol.* 2008;19(3):583-589.

23. Joosse A, de Vries E, Eckel R, et al. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. *J Invest Dermatol.* 2011;131(3):719-726.

24. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer.* 2008;44(10):1345-1389.

25. van Blankenstein M, Looman CW, Siersema PD, Kuipers EJ, Coebergh JW. Trends in the incidence of adenocarcinoma of the oesophagus and cardia in the Netherlands 1989-2003. *Br J Cancer.* 2007;96(11):1767-1771.

26. Berghofer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. Obesity prevalence from a European perspective: a systematic review. *BMC Public Health.* 2008;8:200.

27. Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet.* 2008;371(9609):303-314.

28. van den Akker-van Marle ME, van Ballegooijen M, Habbema JD. Low risk of cervical cancer during a long period after negative screening in the Netherlands. *Br J Cancer.* 2003;88(7):1054-1057.

29. Hollestein LM, van den Akker SA, Nijsten T, Karim-Kos HE, Coebergh JW, de Vries E. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Ann Oncol.* 2012;23(2):524-530.

30. Welch HG, Woloshin S, Schwartz LM. Skin biopsy rates and incidence of melanoma: population based ecological study. *Bmj.* 2005;331(7515):481.

31. Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. *Br J Cancer.* 2004;91(5):861-867.

32. Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. *Br J Cancer.* 2004;91(2):242-247.

33. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;365(9472):1687-1717.

34. Cremers RG, Karim-Kos HE, Houterman S, et al. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. *Eur J Cancer.* 2010;46(11):2077-2087.

35. Hartgrink HH, Bonenkamp HJ, van de Velde CJ. Influence of surgery on outcomes in gastric cancer. *Surg Oncol Clin N Am.* 2000;9(1):97-117, vii-viii.

36. van Steenbergen LN, Elferink MA, Krijnen P, et al. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. *Ann Oncol.* 2010;21(11):2206-2212.

37. Measurement of progress against cancer. Extramural Committee to Assess Measures of Progress Against Cancer. *J Natl Cancer Inst.* 1990;82(10):825-835.

38. Boyle P, Ferlay J. Mortality and survival in breast and colorectal cancer. *Nat Clin Pract Oncol.* 2005;2(9):424-425.

39. Verhoeven RH, Coebergh JW, Kiemeney LA, 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(17):2553-2558.

40. de Kok IM, van der Aa MA, van Ballegooijen M, et al. Trends in cervical cancer in the Netherlands until 2007: Has the bottom been reached? *Int J Cancer.* 2011;128(9):2174-2181.
41. Brenner H, Steliarova-Foucher E, Arndt V. Up-to-date monitoring of childhood cancer long-term survival in Europe: methodology and application to all forms of cancer combined. *Ann Oncol.* 2007;18(9):1561-1568.
42. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin.* 2007;57(1):43-66.
43. Brenner H, Gondos A, Arndt V. Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. *J Clin Oncol.* 2007;25(22):3274-3280.
44. Pokhrel A, Hakulinen T. How to interpret the relative survival ratios of cancer patients. *Eur J Cancer.* 2008;44(17):2661-2667.
45. Kiemeney LA, Coebergh JW, Koper NP, et al. Bladder cancer incidence and survival in the south-eastern part of The Netherlands, 1975-1989. *Eur J Cancer.* 1994;30A(8):1134-1137.
46. Berrino F. The EUROCARE Study: strengths, limitations and perspectives of population-based, comparative survival studies. *Ann Oncol.* 2003;14 Suppl 5:v9-13.
47. Robinson D, Sankila R, Hakulinen T, Moller H. Interpreting international comparisons of cancer survival: the effects of incomplete registration and the presence of death certificate only cases on survival estimates. *Eur J Cancer.* 2007;43(5):909-913.
48. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med.* 1991;324(24):1685-1690.
49. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope.* 2006;116(9 Pt 2 Suppl 111):1-13.
50. Lambert EH, Pierorazio PM, Olsson CA, Benson MC, McKiernan JM, Poon S. The increasing use of intravesical therapies for stage T1 bladder cancer coincides with decreasing survival after cystectomy. *BJU international.* 2007;100(1):33-36.
51. Aareleid T, Brenner H. Trends in cancer patient survival in Estonia before and after the transition from a Soviet republic to an open-market economy. *Int J Cancer.* 2002;102(1):45-50.
52. Coebergh JW, Reedijk AM, de Vries E, et al. Leukaemia incidence and survival in children and adolescents in Europe during 1978-1997. Report from the Automated Childhood Cancer Information System project. *Eur J Cancer.* 2006;42(13):2019-2036.
53. Ciccolallo L, Capocaccia R, Coleman MP, et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut.* 2005;54(2):268-273.
54. Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990-94--results and commentary. *Ann Oncol.* 2003;14 Suppl 5:v61-118.
55. Anttila A, Ronco G, Clifford G, et al. Cervical cancer screening programmes and policies in 18 European countries. *Br J Cancer.* 2004;91(5):935-941.
56. Linos A, Riza E. Comparisons of cervical cancer screening programmes in the European Union. *Eur J Cancer.* 2000;36(17):2260-2265.
57. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. *Lung Cancer.* 2001;31(2-3):123-137.
58. Pinheiro PS, van der Heijden LH, Coebergh JW. Unchanged survival of gastric cancer in the southeastern Netherlands since 1982: result of differential trends in incidence according to Lauren type and subsite. *Int J Cancer.* 1999;84(1):28-32.

59. Berrino F, Gatta G. Variation in survival of patients with head and neck cancer in Europe by the site of origin of the tumours. EUROCARE Working Group. *Eur J Cancer.* 1998;34(14 Spec No):2154-2161.

60. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer.* 2007;120(9):1986-1992.

61. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol.* 2005;55(3):231-240.

62. Zaborskis A, Sumskas L, Maser M, Pudule I. Trends in drinking habits among adolescents in the Baltic countries over the period of transition: HBSC survey results, 1993-2002. *BMC Public Health.* 2006;6:67.

63. Zatonski W, Jha P. The health transformation in Eastern Europe after 1990: a second look. [online], *http://www.hem.home.pl/files/The_Health_Transformation_in_Eastern_Europe_after_1990_-_A_Second_Look.pdf* ed. Warsaw: Cancer Center and Institute of Oncology; 2009.

64. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer.* 2006;118(12):3030-3044.

65. Coleman MP, Babb P, Sloggett A, Quinn M, De Stavola B. Socioeconomic inequalities in cancer survival in England and Wales. *Cancer.* 2001;91(1 Suppl):208-216.

66. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Ann Oncol.* 2006;17(1):5-19.

CHAPTER 6

Discussion

For the first time it was possible to study long term trends in incidence and prognosis of and mortality from the diversity of cancer nationwide in the Netherlands because of recent availability of nationwide prognosis data in the Netherlands Cancer Registry. Combined analysis and presentation of incidence, prognosis and mortality potentially results in a more objective assessment of progress against cancer achieved in the Netherlands, while avoiding over-interpreting findings from one of these measures only.

First we described these cancer trends from 21 European countries, exploring the progress against cancer achieved in the Netherlands compared to other European countries. Secondly, we described cancer trends in more detail for oesophageal, lung, ovarian and prostate cancer in order to get an answer on our first research question: **'What was the impact of changes in risk factor prevalence, primary and secondary prevention, and cancer management on cancer trends?'** Because of the diversity of incidence, prognosis and mortality trends (e.g. incidence increases faster than mortality) we developed a quantitative framework of measuring progress against cancer to get a comprehensive overview of all cancer trends. Besides, we discussed the merits of this approach versus using only trends in survival or mortality as outcome and answered our second research question: **'How can we optimize the assessment of progress against cancer and what are the pitfalls?'**
In this final chapter results are summarized and discussed, followed by an overall conclusion on our main question: **'How much progress did we make against cancer in the Netherlands since the late 1980s?'**.

DUTCH CANCER TRENDS IN A EUROPEAN CONTEXT

The main conclusions from **Chapter 2** were that cancer rates among Dutch males were mostly equal or even lower than the European average, particularly for cancers of the oral cavity and pharynx, stomach, pancreas, testis and prostate. Dutch females showed to have more often higher cancer rates than the European average, particularly for skin melanoma and cancers of the oral cavity and pharynx, larynx, lung, oesophagus, colorectum and breast. **Table 6.1** gives an overview of incidence, survival and mortality rates of the Netherlands compared to European average rates in the mid-1990s and early 2000s.

Cancers that were more common among Dutch males and females than among other European males and females are those which are strongly associated with smoking, overweight and excessive sun exposure. The smoking prevalence among Dutch females became high during the 1970s and continues to be high compared to Europe in general.[1] This would explain the high incidence rates of cancers of the oral cavity and pharynx, larynx and lung among Dutch females. Remarkable is the enormous increase in the occurrence of oesophageal cancer since the mid-1990s among Dutch males compared to other European males, while the incidence rate was average in the mid-1990s. This incidence increase is due to the increase in adenocarcinomas, which are associated with reflux caused by obesity.[2] The prevalence of obesity among Dutch males tripled since the 1980s, although the prevalence remains relatively low compared to other European males.[1, 3] Increases in skin melanomas have been described for many developed countries, and are speculated to be largely due to overdiagnosis.[4] However, unlike the situation in many other countries, melanoma incidence rates of both thin and thick melanomas increased and mortality also increased since 1989. This makes clear that the incidence increases in the Netherlands are not merely due to overdiagnosis, but seems to be real, at least partly.[5] Compared to the European average, skin melanoma incidence was high, particularly among females. This is most likely due to high excessive sun exposure possibly as a result of less awareness about the risks of sunburn and use of sunbeds or a low risk perception of the seriousness of skin cancer in a population with predominantly sun-sensitive skin types.

The high breast cancer incidence among females is on the one hand possibly related to the gradual introduction of our successful national screening program in 1989 with an attendance rate of 82%, one of the highest worldwide.[6-8] On the other hand, it is plausible that the high incidence is related to changes in risk factors prevalence, like younger age at menarche, older age at menopause, increased age at first childbirth, lower parity and shorter lactation. The increased prevalence of obesity, diminishing physical activity and increased alcohol consumption are likely to have had a negative impact as well on the incidence of breast cancer.[6,9,10] However, the breast cancer incidence started to stabilize since 2007,[11] possibly as a result of levelling off of the screening effect and the decrease in hormone-replacement therapy since the early 2000s.[12]

Table 6.1 | Cancer incidence, survival and mortality rates of 17 common tumour types in the Netherlands compared to the average rates within Europe in the mid-1990s and early 2000s

Tumour type	Mid-1990s			Early 2000s			Remarks
	incidence	survival	mortality	incidence	Survival	Mortality	
Oral cavity and pharynx	**M < av** **F > av**	M/F = av	**M < av** F = av	**M < av** **F > av**	M/F = av	**M < av** **F > av**	Stable Inc and Mort in most EU countries, while rising Inc among Dutch females.
Oesophagus	M = av **F > av**	M/F = av	M = av **F > av**	**M/F > av**	M/F = av	**M/F > av**	Stable Inc and Mort in most EU countries, while rising Inc and Mort among Dutch males.
Stomach	**M/F < av**	M/F = av	**M/F < av**	**M/F < av**	M/F = av	**M/F < av**	Inc and Mort decreased in whole EU and Surv improved in some countries, but not in the Netherlands.
Colorectal	M = av **F > av**	**M/F > av**	**M < av** F = av	M = av **F > av**	M/F = av	M = av **F > av**	Inc increased modestly among males and remained stable among females in most EU countries (but increased in the Netherlands), Mort decreased and Surv improved in whole EU.
Pancreas	**M < av** F = av	M/F = av	M/F = av	**M/F < av**	M/F = av	M/F = av	Inc, Mort and Surv trends were quite stable over time in EU.
Larynx	**M < av** **F > av**	**M/F > av**	**M < av** F = av	**M < av** **F > av**	**M/F > av**	**M < av** **F > av**	Inc and Mort declined for males and remained stable for females in EU. Surv did not show marked improvements.
Lung	**M > av** F = av	M/F = av	**M > av** F = av	M = av **F > av**	M/F = av	**M/F > av**	Inc and Mort decreased among males and increased rapidly among females in most EU countries. Surv slightly improved.
Melanoma	M = av **F > av**	M/F=av	**M/F > av**	M = av **F > av**	**M/F>av**	**M/F > av**	Inc continued to increase, while Mort started to stabilize (but not in the Netherlands) and Surv improved in most EU countries
Female breast	**F > av**	F = av	**F > av**	**F > av**	F = av	**F > av**	Inc increased, Mort decreased and Surv improved in whole EU. Highest Inc rates were found in the Netherlands and Italy.
Cervix	**F < av**	**F > av**	**F < av**	**F < av**	**F > av**	**F < av**	Inc and Mort decreased in most EU countries. Surv remained stable (case in the Netherlands) or even decreased.

Table 6.1 | *Continued*

Tumour type	Mid-1990s			Early 2000s			Remarks
	incidence	survival	mortality	incidence	Survival	Mortality	
Corpus uteri	F = av	F = av	**F < av**	**F < av**	F = av	**F < av**	Inc increased in Northern Europe and Mort decreased in Southern and Central Europe due to improved Surv. The Netherlands showed stable trends.
Ovarium	**F < av**	M/F = av	F = av	**F < av**	M/F = av	**F < av**	Inc and Mort were stable or decreasing (case in the Netherlands) and Surv slightly improved over time in EU.
Prostate	**M > av**	**M > av**	**M > av**	**M < av**	M = av	M = av	Inc markedly increased in EU, except for the Netherlands. Mort decreased and Surv improved in most EU countries.
Testis	**M < av**	M = av	**M < av**	**M < av**	M = av	**M < av**	Inc increased , Mort remained stable and Surv slightly improved in most EU countries.
Kidney	M/F = av	M/F = av	M = av **F > av**	M/F = av	M/F = av	M/F = av	Inc and Mort remained stable in EU, but declined in the Netherlands. Surv improved across EU.
Bladder	*	*	M/F = av	*	*	M/F = av	Mort decreased for EU males and remained stable for EU females.
Hodgkin's lymphoma	**M < av** F = av	M/F = av	**M < av** F = av	**M > av** F = av	M/F = av	**M/F < av**	Inc and Mort remained stable or slightly decreased and Surv improved in all EU countries. For Dutch males, Inc increased.

Av: average rate in Europe; M: males; F: females; Inc : Incidence, Mort: Mortality; Surv: Survival; EU: Europe/European
< av: incidence and mortality ≥ 10% lower than average rate; survival ≥ 5% lower than average rate
> av: incidence and mortality ≥ 10% higher than average rate; survival ≥ 5% higher than average rate
*comparison with other European countries was not possible because of different inclusion criteria

IMPACT OF CHANGES IN RISK FACTOR PREVALENCE, PRIMARY AND SECONDARY PREVENTION AND CANCER MANAGEMENT ON CANCER TRENDS

Many efforts have been made to lower cancer incidence and mortality and improve cancer prognosis by primary and secondary prevention programs and changes in cancer management (e.g. changes in diagnostics and therapies) as described in **Chapter 1**. **Table 6.2** gives an overview of changes in incidence, prognosis and mortality trends from all cancer types studied in the project 'Progress against cancer in the Netherlands since the 1970s' and the main cause(s) for these changes. From this **Table 6.2** we can conclude that changes in risk factor prevalence are one of the most important causes of changes in cancer trends. In **Chapter 3.2** we showed that the ovarian cancer mortality rate decreased since the 1970s with a reduction of 36%, particularly among women born after the 1920s. The ovarian cancer incidence rate reduced by 30% between 1989 and 2009, which was one of the largest reductions observed within Europe.[13] Both changes were mainly caused by the introduction of oral contraceptives in the mid-1960s, which showed to be protective against ovarian cancer.[14] Another example of a change in cancer risk upon spontaneous changes in risk factor prevalence is stomach cancer. Due to changes in dietary patterns, improved food preservation techniques (e.g. refrigerator) and a decline in *Helicobacter pylori* infections incidence of and mortality from stomach cancer declined dramatically.[15, 16]

These two examples of successes in lowering cancer incidence and mortality were reached without prevention campaigns, but show the potential room for primary prevention. From different studies it appeared that 25-50% of cancer is avoidable in the long run through lifestyle changes.[17, 18] In **Chapter 3.1** we showed the effect of lowering smoking prevalence rates on lung cancer incidence and mortality trends among females, as had already been seen for men in the past.[19] The total lung cancer incidence among females is not yet decreasing and neither are the other smoking related cancers, but we are expecting a levelling off or decrease soon. These developments as a result of decreasing smoking prevalence among the Dutch population illustrate that primary prevention against smoking can be considered as a success. However, much less has been achieved than in neighbouring countries, as illustrated by the relatively high levels of smoking related cancers compared to the European average.

Table 6.2 | Overview of changes in incidence, 5-year relative survival, and mortality between 1989 and 2009 for cancer types studied in the project 'Progress against cancer in the Netherlands since the 1970s?' [20]

Cancer type	Males			Females			Changes mainly caused by
	Incidence[a]	Survival[b]	Mortality[a]	Incidence[a]	Survival[b]	Mortality[a]	
Oral cavity	↑	↑	=	↑↑↑	↑	↑↑	RISK (alcohol, smoking, HPV, EBV) ↑ particularly among females
Pharynx	↑	↑	=	↑↑	=	↑↑	RISK (alcohol, smoking) ↑ particularly among females and by immigration[21]
Larynx	↓↓↓	=	↓↓↓	=	=	=	PRIM → RISK (smoking) ↓ among males **Remark**: Surv supraglottis < Surv glottis and % supraglottis females > males[22]
Oesophagus	↑↑↑	↑	↑↑↑	↑↑	↑	↑↑	RISK (obesity) ↑ causing ↑ adenocarcinomas CANC (improved treatment, regionalization of surgery)[23,24] **Remark:** Surv adenocarcinomas > Surv squamous cell carcinomas
Stomach	↓↓↓	↑	↓↓↓	↓↓↓	=	↓↓↓	RISK (Helicobacter Pylori) ↓ + improved methods of food preservation + dietary pattern CANC (earlier detection by endoscopy, centralisation surgery)[16,24] **Remark:** cardia tumours ↑ and Surv cardia < Surv non-cardia
Colon	↑↑	↑	↓	↑	↑	↓	RISK (overweight, unhealthy diet, low physical activity) ↑ CANC (earlier detection by endoscopy, more often (adjuvant) chemotherapy for late stages)[25]
Rectum	↑↑	↑↑	↓	↑	↑↑	↓	RISK (overweight, unhealthy diet, low physical activity) ↑ CANC (earlier detection, TME surgery, increased use of pre-operative RT)[26]
Gallbladder	↓↓↓	=	↓↓↓	↓↓↓	=	↓↓↓	SEC (cholecystectomies) ↑ by the introduction of ultrasonography and laparoscopic surgery[27]
Pancreas	=	↑	=	↑	=	↑	CANC (improved diagnostics : CT and endoscopic ultrasound; improved surgical techniques/centralisation)[28]
Lung	↓↓↓	↑	↓↓↓	↑↑↑	↑	↑↑↑	PRIM → RISK (smoking): males ↓, females ↑[29] CANC (improved staging and treatment strategies): *NSCLC* - receiving standard treatment ↑, chemotherapy for late stages ↑[30] *SCLC* (only for ages 45-59 yr) – chemoradiation for limited disease ↑, chemotherapy for extensive disease ↑[31]
Skin melanoma	↑↑↑	↑	↑↑↑	↑↑↑	↑	↑↑	RISK (excessive sun exposure) ↑ PRIM (awareness) ↑ → earlier detection **Remark:** both thin and thick melanomas ↑[5]
Breast				↑↑	↑↑	↓↓	RISK (e.g. age at first childbirth, low parity, short lactation period, earlier age at menarche) ↑[9] SEC (screening since 1989) → earlier detection[7,32] CANC (improved treatment)[6]

Table 6.2 | *Continued*

Cancer type	Males			Females			Changes mainly caused by
	Incidence[a]	Survival[b]	Mortality[a]	Incidence[a]	Survival[b]	Mortality[a]	
Cervix				↓↓	↑	↓↓↓	SEC (screening since the 1980s) → premalignancies ↑[33] CANC(improved staging and treatment, e.g. chemoradiation ↑, radical surgery + less RT for early stages)[34,35] **Remark:** RISK (HPV) ↑
Uterus				↑	↑	↓	RISK (obesity, low parity) ↑ CANC (RT ↓ for middle-age women, chemotherapy ↓ for FIGO I-III)[35]
Ovary				↓↓	↑	↓↓	OC use and late age at first childbirth ↑[36] CANC (improved staging, debulking surgery + chemotherapy ↑, complete chemotherapy schedules ↑, centralisation surgery)[37-40] **Remark:** adenocarcinomas NOS ↓ and serous carcinomas ↑ Surv adenocarcinomas NOS < Surv serous carcinomas
Prostate	↑↑↑	↑↑	↓↓				SEC (PSA testing) ↑ → earlier (over)detection CANC (brachytherapy) ↑[35,41]
Testis	↑↑↑	↑	=				RISK (late maternal age at first birth, low parity, low number of children/women) ↑ + improved awareness CANC (improved staging, chemotherapy, centralisation treatment)[42]
Kidney and other urinary organs	↑	↑	↑	↑	↑	=	RISK (obesity, hypertension) ↑ CANC (use of diagnostic imaging techniques ↑, targeted therapies)[43]
Bladder, only invasive	↓	=	↓↓	↑↑	=	=	PRIM → RISK (smoking): males ↓, females ↑ CANC (earlier detection + improved treatment of non-invasive tumours) **Remark:** stage II ↓ and stage III/IV ↑[44]
Thyroid	↑↑	↑	↓↓↓	↑↑	↑	↓↓	CANC (fine needle aspiration biopsies) ↑[45]
Hodgkin lymphoma	=	↑	↓↓↓	↑	↑	↓↓↓	RISK (decrease of infections in children) CANC (combined radio-chemotherapy) ↑[35]
NonHodgkin lymphoma	↑	↑↑	↓	↑	↑↑	↓	RISK (autoimmune, chronic inflammatory disorders) ↑ CANC (improved diagnostics, targeted therapies (only for B-cell neoplasms)) **Remark:** indolent mature B-cell, mature T- and NK-cell neoplasms ↑, aggressive neoplasms =[46]
Leukaemia	↑↑↑	↑↑	↓↓	↑↑↑	↑↑	↓	RISK (autoimmune, chronic inflammatory disorders, former cancer treatment) ↑ SEC (breast cancer screening, only for chronic lymphocytic leukaemia) CANC (improved staging and therapy)[47]

[a] = stable incidence; ↑ / ↓ estimated annual % change is ≤1%; ↑↑ / ↓↓ estimated annual % change is between 1.1-2%; ↑↑↑ / ↓↓↓ estimated annual % change is >2%.
[b] = stable survival; ↑ / ↓ % annual trend is ≤0.5%; ↑↑/ ↓↓ % annual trend is >0.5%
RISK risk factor prevalence; PRIM primary prevention; SEC secondary prevention; CANC cancer management
Surv Survival; HPV human papilloma virus; EBV Epstein-Barr virus; TME Total Mesorectal Excision; RT Radiotherapy; CT computed tomography; NOS not otherwise specified

For lung cancer we know that on average 57% is avoidable by reducing smoking to the lowest prevalence levels observed in Europe.[17] For most cancer types, the association with a risk factor is much less strong than for smoking and lung cancer, hence potential effects of primary interventions are expected to be less clear-cut. From a public health perspective it is however important to keep in mind that primary prevention against a risk factor often affecting multiple chronic or non-communicable diseases simultaneously, including certain cancer types (for instance, anti-smoking campaigns are also affecting trends of head and neck, oesophageal and bladder cancer, vascular diseases and COPD). Another example of primary prevention activities is the information campaigns on the risk of excessive sunbathing and sunburns especially for younger people by the Dutch Cancer Society. However, the incidence of skin melanomas is still rising, not only thin melanomas, but also thick melanomas, which results in a modest, but continuing increasing mortality.[48] But we have to keep in mind that it takes a long time before positive effects of primary prevention campaigns are visible in terms of cancer rates because of long latency times, e.g. for lung cancer it is about 30 years.[49] The time between scientific evidence for a risk factor and governmental action can take even longer (lag time).[50] Despite such long latency times it remains important to invest in primary prevention, especially when we consider the increasing prevalence of obesity and the increased use of alcohol during the 1970s and early 1980s. The increase in overweight/obesity is likely to be partly responsible for the observed incidence increases of non-Hodgkin lymphoma, leukaemia, oesophageal, colorectal, female breast (postmenopausal), corpus uteri, kidney and thyroid cancer between 1989 and 2009.[20,51] The observed increases in incidence of cancer of the oral cavity, pharynx, female breast and colorectal cancer are partly due to the increased use of alcohol.[20,52] While costs of primary prevention are lower than developments of new treatments, only 2% of all cancer research funding of the European Commission was spent on cancer prevention in 2002-2006.[53] Especially in this time of the financial crisis with lower health budgets, we should focus more on primary prevention.[54] Besides, it is important that governments become faster in taking action against upcoming risk factors and not waiting so long as they did against smoking and asbestos in the past.

Two examples of secondary prevention in the Netherlands are the national screening programmes for breast and cervical cancer. Because of the different nature of the lesions detected (early stage invasive cancer and premalignant lesions), these two screening programmes had different effects on cancer trends.

While breast cancer screening caused at first an increasing incidence until 2007, particularly an increase in early stages and a decline in advanced stages,[55,56] cervical cancer screening caused a decreasing incidence during 1989-2001.[33]

Before the introduction of the nationwide mass-screening program for breast cancer in the 1990s, increasing trends were already found in the Southeastern Netherlands and breast cancer mortality started to decrease since the early 1990s, particularly for women younger than 70. A decrease in mortality as a result of population screening would not be expected to become visible within such a short time-frame.[6] However, a recent case-control study showed that early detection by mammography screening might reduce breast cancer mortality by 50%.[57] On the other hand, improvements in adjuvant treatment of breast cancer patients played also a role in the mortality decrease by improving survival of these patients.[58-60]

The incidence of cervical cancer decreased during 1989-1998, followed by a more rapid fall in the period 1998-2001, although the incidence started to increase afterwards. The observed incidence trend followed the trend in age group 35-54 years (the invited screening group before 1996) suggesting that screening was likely to underlie the observed incidence trends. Since 1996, the screening program was restructured and during the conversion period 1996-1998 several extra birth cohorts were invited followed by a period with normal, but less intensive screening (screening interval was lengthened from 3 to 5 years and age group was broadened to 30-60 years). This conversion period of intensive screening is probably the reason for the rapid incidence decrease in 1998-2001 followed by a compensating modest increase in incidence. Besides changes in the screening program, other underlying causes, such as an increase in HPV infections in young people, might also be responsible for the increasing incidence.[33]

The Dutch Minister of Health decided in 2011 to start colorectal cancer screening from 2013 using the immunochemical faecal occult blood test (iFOBT).[61] All persons aged 55-75 will be invited every 2 years for this national screening program. As this screening program, like the one for cervical cancer, is detecting pre-malignant polyps it is expected that the incidence trend will decrease on the long-term, while during the first 4-5 years the incidence will slightly increase. Furthermore, it was calculated that every year 1,428 deaths from colorectal cancer will be prevented during the first 30 years of screening with an attendance rate of 60%.[62] In 2010, about 5,000 patients died from colorectal cancer in the Netherlands.[11] With the increase in therapy costs for advanced colorectal cancer, screening is not only a

good approach to lower the incidence and mortality, but also to control the costs of colorectal cancer treatment.[63] As a result of detecting pre-malignant polyps survival will not improve or even deteriorate if nothing changed.

A negative effect of screening is overdiagnosis and overtreatment. In **Chapter 4.1** we gave an example of this negative screening effect by studying the prostate cancer trends and increased use of testing serum prostate-specific antigen level (PSA). Prostate cancer incidence increased and survival improved enormously by mainly detecting of indolent cancers which increased especially since 2000.

If a certain cancer type is a huge public health problem and there is a valid screening test which can detect pre-malignancies or early stages of cancer with better treatment options than would be available if the cancer was diagnosed later, and good prognosis, screening is a definitely good option to prevent (late stage) cancer and also saving treatment costs.

Improvements in diagnostics and treatment can result in improved cancer survival as we illustrated in **Chapter 4.2** for ovarian cancer. Five-year relative survival in advanced stage ovarian cancer patients increased from 18% in 1989-1993 to 28% in 2004-2009. Part of this improvement was caused by changes in treatment: more patients received (neo)adjuvant chemotherapy and underwent an optimal debulking surgery over time. Other examples of (new) effective therapies that we could relate to improvements in survival are the total mesorectal excision (TME) surgery, increased use of pre-operative radiotherapy and adjuvant chemotherapy for patients with rectal cancer since the mid 1990s. Five-year relative survival of rectal cancer, stage II and III were recently about 70% and 55%, and increased for male patients with 9 and 12 percent-points between 1989 and 2006, and for female patients with 12 and 16 percent-points, respectively. This marked improvement in prognosis is largely due to the improvements in therapy besides earlier detection by increased use of endoscopy since the 1980s.[26] For small cell lung cancer, we observed some first modest survival improvements since the early 1990s, particularly at age 45-59. This survival improvement is probably due to the increased use of chemoradiation for limited disease and the introduction of prophylactic cranial irradiation (PCI) since the early 2000s besides improved staging.[31]

In **Chapter 4.3** we showed that ovarian cancer surgery (including staging) in the North Netherlands during the period 1994-1997 was better performed by an oncological gynaecologist than by a general gynaecologist. For oesophageal cancer, we found a reduction in postoperative morbidity, length of hospital stay, in-hospital

mortality which declined from 14% to 4.7% and 2-year survival improved from 38% to 54% after centralisation of oesophageal resections in the mid-western part of the Netherlands (**Chapter 4.4**). These findings were confirmed by other studies performed in the Netherlands.[24, 64] Discussions regarding the need for centralisation of treatment, particularly surgery, are also ongoing for cancers of the stomach, liver, pancreas, prostate, bladder and lung.[65]

Changes in cancer management can improve cancer survival. However, the costs to develop new diagnostics and therapies are likely to become very high which is visible in the increasing national health budget during the last years. For the future, it is important to study the cost-effectiveness of these new (targeted) therapies and to look for opportunities to improve existing therapies (e.g. improving effectiveness of systemic therapies).

THE NEW PROPOSED FRAMEWORK AND PITFALLS OF MEASURING PROGRESS AGAINST CANCER

Measuring progress against cancer is important to evaluate progress in clinical management and public health programs as often mentioned in (national) cancer programs. There are many parameters which can indicate progress, such as less false-positive and false-negative screening exams, more effective therapies with fewer associated side effects, better quality of life and improved organization of palliative care. These parameters are difficult to measure and monitor through the standard surveillance instruments, mainly cancer registries. However, several of these parameters influence cancer incidence, survival and mortality, which can be monitored over time.

In this thesis, we proposed a conceptual framework to measure progress against cancer where we combined incidence, survival and mortality to achieve an objective assessment of progress against cancer in the Netherlands, while avoiding misinterpreting findings from one of these measures (**Chapter 5.1**). However, it remains a challenge to unravel and elucidate coinciding changes in incidence and therapy, because changes in survival can be influenced by combinations of changes in treatment and incidence. Multivariable relative survival analyses showed to be useful in unravelling the relative importance of the potential underlying reasons of improved survival of rectal cancer.[25]

So far, progress against cancer on a population level has usually been expressed by trends in mortality or survival of cancer. As mortality is influenced by both incidence and survival, there are strong advocates of expressing progress in terms of changes in mortality rates.[66,67] However, changes in mortality rates do not necessarily reflect recent progress, as mortality in a given year reflects the risk of cancer death among patients diagnosed over the preceding years depending on the prognosis of a certain cancer (e.g. breast cancer mortality rate in a given year reflects deaths from the preceding 15-20 years).[68] Secondly, trends in competing risks of death, particularly among the elderly, may complicate the interpretation of cancer mortality trends.[69] Thirdly, mortality statistics are usually based on cause-of-death statistics, which have their problems in terms of reliability, such as correct coding of underlying cause of death and changing coding practices in time. Fortunately, in the Netherlands, the reliability of coding the underlying cause of death turned out to be high (>90%) for major causes of death such as cancer.[70] Finally, not all cancer patients die from cancer and changes in cancer mortality often does not reflect the possible progress made for these patients at all.

Others advocate using cancer survival only as a measure of progress over time and between countries. Indeed, survival is often used and interpreted as a measure of progress made by changes in cancer management. However, survival is also influenced by stage at diagnosis that may differ over time and between countries.[71] This makes that survival is not a good measure either to evaluate screening programs because of the increased detection of (indolent) low-stage cancer (e.g. PSA screening) or premalignant lesions (e.g. cervical cancer screening). In **Chapter 5.2** we listed more phenomena which can influence survival and even can cause deteriorations in survival, such as changes in risk factor exposures which can lead to shifts in the distribution of cancer subtypes with different prognosis, changes in the prevalence of concomitant diseases (comorbidity) in the population and changes in the sociodemographic characteristics of a population. Inclusion of patients with multiple tumours in survival analyses can also lower survival.[72]

Trends in cancer mortality and survival are sometimes contrasting and if studied separately, can cause a lot of debate about data quality and how to interpret cancer trends. Recently, this was the case in the United Kingdom where breast cancer mortality showed one of the strongest declines within Europe, but survival remained worse than elsewhere in Western Europe.[73-75] Another example is that survival is improving, while mortality keeps on rising. For the Netherlands, we observed this

for skin melanoma, oral cavity and oesophageal cancer. These examples show that expressing progress in terms of either mortality or survival only gives a very limited impression of progress and show the need of including cancer incidence and combine them all three to avoid misinterpreting findings from one of these cancer trends.[68,76,77] To add to current possibilities of assessing progress against cancer, it would be useful to have information on causes of death, in order to know if cancer patients are dying from their cancer or from other diseases/causes. This information will be extremely useful for getting more insight on long-term side effects of cancer treatment among long-term survivors of cancer.[78,79] Unfortunately, the information on death causes are currently not routinely linked to the NCR.

CONCLUSIONS

- The proposed conceptual framework for measuring progress against cancer can be useful to evaluate (national) cancer programs and to prioritize and monitor activities in the field of prevention and clinical research.
- A largely positive, but mixed pattern of progress against cancer was observed for the Netherlands since the late 1980s:
  - Optimal progress (defined as decreasing incidence and/or improving survival accompanied by declining mortality) was observed in 12 of 19 cancer types among males: laryngeal, lung, stomach, gallbladder, colon, rectal, bladder, prostate and thyroid cancer, leukaemia, Hodgkin and non-Hodgkin lymphoma. Among females, optimal progress was observed in 12 of 21 cancers: stomach, gallbladder, colon, rectal, breast, cervical, uterus, ovarian and thyroid cancer, leukaemia, Hodgkin and non-Hodgkin lymphoma.
  - Deterioration (defined as increasing incidence and/or deteriorating survival accompanied by increasing mortality rates) occurred in three cancer types among males: skin melanoma, oesophageal and kidney cancer, and among females in six cancer types: skin melanoma, oral cavity, pharyngeal, oesophageal, pancreatic and lung cancer.
- Primary and secondary prevention showed to have bigger impact on cancer trends than new diagnostics and treatment.
  - Anti-smoking campaigns can be considered as a success of primary prevention resulting in decreasing incidence and mortality of smoking related cancers.

However smoking prevalence rates are still high, particularly among Dutch women who showed to have higher rates of smoking related cancers than the average rates among European women.
  - Screening for cancer can have different effects on cancer trends depending on detection of pre-malignancies (decreasing incidence and sometimes even deteriorating survival) or early stages of disease (increasing incidence and improving survival). It is not certain what will happen to colorectal cancer incidence after introduction of screening.
- New effective diagnostics or treatment showed to improve cancer survival often coinciding with subspecialisation of clinicians and regionalisation of cancer care showed to be effective to improve survival (for instance ovarian and oesophageal cancer).

RECOMMENDATIONS FOR POLICY AND FURTHER RESEARCH

- The proposed conceptual framework for measuring progress against cancer should be used to monitor cancer trends as a basis for future scenarios which can be useful to determine clinical capacity and to prioritize activities in the field of prevention and clinical research.
- Cancer epidemiologists should make sure that policy makers are well informed on newly occurring trends in occurrence, mortality or prognosis from cancer, and should also inform them on (new/emerging) risk factors, in order to try and minimize delays in taking action when new risk factors are detected.
- Primary prevention needs to be back on the governmental agenda, e.g. campaigns against smoking, obesity and excessive sun exposure remain important to lower future cancer incidence. Particularly, the incidence of obesity related cancers such as oesophageal and colorectal cancer is high compared to other European countries.
- Cancers of the oesophagus, stomach, gallbladder, pancreas and lung need our attention because of their stable poor prognosis (5-year relative survival below 25%). What are the possibilities to lower the risk factor prevalence, increase earlier detection and improve treatment? And would centralisation/regionalisation of cancer care help? Scenario calculations could be useful to get more insight in the possibilities of prevention, early detection and improved cancer management.

- In the future it is important to evaluate the colorectal cancer screening by monitoring incidence and prognosis of and mortality from colorectal cancer, over time and also by birth cohort. The same is valid for evaluating the effects of using HPV DNA test as primary screen test in the cervical screening program and HPV vaccination among 12-year old girls since 2009 to prevent cervical cancer.
- The cost-effectiveness of new targeted (often expensive) therapies should be studied and their effect on the overall cancer prognosis and mortality.
- To give possible new directions for development of new therapies we should study also potential gender differences in incidence, prognosis and mortality in more detail.
- It is important to assess progress against cancer by age (e.g., <20, 20-35, 35-49, 50-69, 70-79, ≥80) to see whether special attention is needed for certain age groups. It is particularly interesting to know how much progress we are making among the elderly, because the age group of 75 and older is estimated to double until 2040.[80] Birth cohort approaches will also be interesting when lifestyle risk factors play a role.
- Assessing progress against cancer by socioeconomic status (SES) should be also interesting to monitor the gap between SES groups. Recently, it was found that those with low SES had highest incidence rates of common cancers, less favourable stage of disease, less likely to receive curative treatment and invasive therapies and had lower survival rates compared to those with high SES.[77]
- To make the assessment of progress against cancer more complete it will be interesting to incorporate disease-specific mortality (especially for the long-term side effects of cancer treatment and therefore linking death causes with the NCR is highly recommended), quality of life (e.g. differs between stage of disease, cancer treatments)[78,79] and/or costs invested in prevention programs and spent on (new) diagnostics and therapies. Recently, it was found that the US cancer mortality rates fall faster than cancer mortality rates in Europe and that US survival rates were on a higher level than European ones, possibly as consequence of higher health care spending.[80]

REFERENCES

1. Boniol M, Autier P. Prevalence of main cancer lifestyle risk factors in Europe in 2000. *Eur J Cancer*. 2010;46(14):2534-2544.
2. van Blankenstein M, Looman CW, Siersema PD, Kuipers EJ, Coebergh JW. Trends in the incidence of adenocarcinoma of the oesophagus and cardia in the Netherlands 1989-2003. *Br J Cancer*. 2007;96(11):1767-1771.
3. Visscher TL, Kromhout D, Seidell JC. Long-term and recent time trends in the prevalence of obesity among Dutch men and women. *Int J Obes Relat Metab Disord*. 2002;26(9):1218-1224.
4. Erickson C, Driscoll MS. Melanoma epidemic: Facts and controversies. *Clin Dermatol*. 2010;28(3):281-286.
5. Hollestein LM, van den Akker SA, Nijsten T, Karim-Kos HE, Coebergh JW, de Vries E. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Ann Oncol*. 2012;23(2):524-530.
6. Louwman WJ, Voogd AC, van Dijck JA, et al. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. *Cancer Causes Control*. 2008;19(1):97-106.
7. Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verbeek AL. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006. *Int J Cancer*. 2008;123(8):1929-1934.
8. Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R. Breast and cervical cancer screening programme implementation in 16 countries. *J Med Screen*. 2010;17(3):139-146.
9. Soerjomataram I, Pukkala E, Brenner H, Coebergh JW. On the avoidability of breast cancer in industrialized societies: older mean age at first birth as an indicator of excess breast cancer risk. *Breast Cancer Res Treat*. 2008;111(2):297-302.
10. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 European countries. *Eur J Cancer*. 2003;39(12):1718-1729.
11. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55(2):74-108.
12. Soerjomataram I, Coebergh JW, Louwman MW, Visser O, van Leeuwen FE. Does the decrease in hormone replacement therapy also affect breast cancer risk in the Netherlands? *J Clin Oncol*. 2007;25(31):5038-5039; author reply 5039-5040.
13. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer*. 2008;44(10):1345-1389.
14. Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet*. 2008;371(9609):303-314.
15. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol*. 2006;20(4):633-649.
16. Dassen AE, Lemmens VE, van de Poll-Franse LV, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. *Eur J Cancer*. 2010;46(6):1101-1110.
17. Soerjomataram I, de Vries E, Pukkala E, Coebergh JW. Excess of cancers in Europe: a study of eleven major cancers amenable to lifestyle change. *Int J Cancer*. 2007;120(6):1336-1343.

18. Olsen JH, Andersen A, Dreyer L, et al. Summary of avoidable cancers in the Nordic countries. *APMIS Suppl*. 1997;76:141-146.

19. Verbeek AL, Peeters PH, Sturmans F. [Has the lung cancer epidemic in the Netherlands reached its peak?]. *Ned Tijdschr Geneeskd*. Dec 7 1985;129(49):2365-2369.

20. Karim-Kos HE, Kiemeney LA, Louwman MW, Coebergh JW, de Vries E. Progress against cancer in the Netherlands since the late 1980s: an epidemiological evaluation. *Int J Cancer*. 2012;130(12):2981-2989.

21. Arnold M, Wildeman MA, Visser O, et al. *Lower mortality from nasopharyngeal cancer in the Netherlands since 1970 with differential incidence trends in histopathology*. (submitted).

22. van Dijk BAC, Karim-Kos HE, Coebergh JW, Marres HAM, De Vries E. *Progress against laryngeal cancer in the Netherlands: deteriorating 5-year relative survival rates for supraglottic cancer and no change for glottic cancer*. (in preparation).

23. Crane LM, Schaapveld M, Visser O, Louwman MW, Plukker JT, van Dam GM. Oesophageal cancer in The Netherlands: Increasing incidence and mortality but improving survival. *Eur J Cancer*. Jun 2007;43(9):1445-1451.

24. van de Poll-Franse LV, Lemmens VE, Roukema JA, Coebergh JW, Nieuwenhuijzen GA. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival. *Br J Surg*. 2011;98(7):956-963.

25. van Steenbergen LN, Elferink MA, Krijnen P, et al. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. *Ann Oncol.* Nov;21(11):2206-2212.

26. Elferink MA, van Steenbergen LN, Krijnen P, et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989-2006. *Eur J Cancer.* 2010;46(8):1421-1429.

27. Witjes CD, van den Akker SA, Visser O, et al. Gallbladder Cancer in the Netherlands: Incidence, Treatment and Survival Patterns since 1989. *Dig Surg*. 2012;29(2):92-98.

28. Nienhuijs SW, van den Akker SA, de Vries E, de Hingh IH, Visser O, Lemmens VE. Nationwide improvement of only short-term survival after resection for pancreatic cancer in The Netherlands. *Pancreas* 2012;41(7):1063-1066.

29. Karim-Kos HE, Janssen-Heijnen ML, van Iersel CA, van der Meer RM, de Vries E, Coebergh JW. The beginning of the end of the lung cancer epidemic in Dutch women? *Int J Cancer.* 2008;123(6):1472-1475.

30. van der Drift MA, Karim-Kos HE, Siesling S, et al. Progress in standard of care therapy and modest survival benefits in the treatment of non-small cell lung cancer patients in the Netherlands in the last 20 years. *J Thorac Oncol*. 2012;7(2):291-298.

31. Janssen-Heijnen ML, Karim-Kos HE, van der Drift MA, et al. Modest improvements of survival for patients with small cell lung cancer aged 45 to 59 years only, diagnosed in the Netherlands, 1989 to 2008. *J Thorac Oncol*. 2012;7(1):227-232.

32. Otto SJ, Fracheboud J, Verbeek AL, et al. Mammography screening and risk of breast cancer death: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2012;21(1):66-73.

33. de Kok IM, van der Aa MA, van Ballegooijen M, et al. Trends in cervical cancer in the Netherlands until 2007: has the bottom been reached? *Int J Cancer.* 2011;128(9):2174-2181.

34. Van der Aa MA, De Kok IMCM, Kruitwagen RFPM, Jobsen JJ, Coebergh JWW, Karim-Kos HE. *Improvements in treatment and survival of cervical cancer in the Netherlands, 1989-2009*. (in preparation).

35. Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW, eds. Van meten naar weten: 50 jaar kankerregistratie. Eindhoven: *Comprehensive Cancer Center South*; 2005.

36. Karim-Kos HE, van Altena AM, Massuger LFHG, Mourits MJE, Coebergh JWW, *De Vries E. Progress against ovarian cancer in the Netherlands: decreased incidence and mortality due to previous changes in risk factors, coinciding with improved survival*. (submitted).
37. van Altena AM, Karim-Kos HE, de Vries E, Kruitwagen RF, Massuger LF, Kiemeney LA. Trends in therapy and survival of advanced stage epithelial ovarian cancer patients in the Netherlands. *Gynecol Oncol*. 2012;125(3):649-654.
38. Engelen MJ, Kos HE, Willemse PH, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer*. 2006;106(3):589-598.
39. Vernooij F, Heintz AP, Witteveen PO, van der Heiden-van der Loo M, Coebergh JW, van der Graaf Y. Specialized care and survival of ovarian cancer patients in The Netherlands: nationwide cohort study. *J Natl Cancer Inst*. 2008;100(6):399-406.
40. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecol Oncol*. 2007;105(3):801-812.
41. Cremers RG, Karim-Kos HE, Houterman S, et al. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. *Eur J Cancer*. 2010;46(11):2077-2087.
42. Verhoeven RHA, Karim-Kos HE, Coebergh JWW, et al. *Markedly increased incidence and improved survival of testicular cancer in the Netherlands*. (submitted).
43. van de Schans SA, Aben KK, Mulders PF, et al. Modest improvement in 20 years of kidney cancer care in the Netherlands. *Eur J Cancer*. 2012;48(12):1822-1830.
44. de Vries RR, Visser O, Karim-Kos HE, Kiemeney LA, Horenblas S. *Trends in incidence and survival among Dutch bladder cancer patients: a population-based study between 1989-2009*. (submitted).
45. Netea-Maier RT, Aben KK, Casparie MK, et al. Trends in incidence and mortality of thyroid carcinoma in The Netherlands between 1989 and 2003: correlation with thyroid fine-needle aspiration cytology and thyroid surgery. *Int J Cancer*. 2008;123(7):1681-1684.
46. van de Schans SA, Issa DE, Visser O, et al. Diverging trends in incidence and mortality, and improved survival of non-Hodgkin's lymphoma, in the Netherlands, 1989-2007. *Ann Oncol.* 2012;23(1):171-182.
47. van den Broek EC, Kater AP, van de Schans SA, et al. Chronic Lymphocytic Leukaemia in the Netherlands: Trends in incidence, treatment and survival, 1989-2008. *Eur J Cancer*. 2012;48(6):889-895.
48. Hollestein LM, van den Akker SA, Nijsten T, Karim-Kos HE, Coebergh JW, de Vries E. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Ann Oncol*. 2012;23(2):524-530.
49. Weiss W. Cigarette smoking and lung cancer trends. A light at the end of the tunnel? *Chest.* May 1997;111(5):1414-1416.
50. Coebergh JW, Martin-Moreno JM, Soerjomataram I, Renehan AG. The long road towards cancer prevention: 4 steps backward and 8 forward. *Eur J Cancer*. 2010;46(14):2660-2662.
51. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578.
52. World Cancer Research Fund / American Institute for Cancer Research. *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*. Washington D.C.: AICR; 2007.
53. Eckhouse S, Lewison G, Sullivan R. Trends in the global funding and activity of cancer research. *Mol Oncol*. 2008;2(1):20-32.
54. Martin-Moreno JM, Alfonso-Sanchez JL, Harris M, Lopez-Valcarcel BG. The effects of the financial crisis on primary prevention of cancer. *Eur J Cancer*. 2010;46(14):2525-2533.

55. van Dijck JA, Hendriks JH, Holland R, Schouten LJ, Verbeek AL. [Alterations of stage distribution for breast cancer since the implementation of national screening program in the Netherlands during 1989-1995]. *Ned Tijdschr Geneeskd*. 2000;144(23):1119-1124.
56. Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. *Br J Cancer.* 2004;91(5):861-867.
57. Otto SJ, Fracheboud J, Verbeek ALM, et al. Mammography Screening and Risk of Breast Cancer Death: A Population-Based Case-Control Study. *Cancer Epidemiol Biomarkers Prev.* 2012;21(1):66-73.
58. Ernst MF, van de Poll-Franse LV, Roukema JA, et al. Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002. *Breast*. 2007;16(4):344-351.
59. Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. *Br J Cancer*. 2004;91(2):242-247.
60. Voogd AC, van Beek MW, Crommelin MA, Kluck HM, Repelaer van Driel OJ, Coebergh JW. Management of early breast cancer in southeast Netherlands since 1984. A population-based study. Regional Breast Cancer Study Group. *Acta Oncol*. 1994;33(7):753-757.
61. Schippers EI. [Final decision of introduction national colorectal cancer screening]. *Letter of the ministry of Public Health, Welfare and Sport* (PG/OGZ 3065362). June 1, 2011.
62. Health Council of the Netherlands. [*Population screening for colorectal cancer*]. The Hague: Health Council of the Netherlands; 2009.
63. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. *J Natl Cancer Inst.* 2009;101(20):1412-1422.
64. Dikken JL, Wouters MW, Lemmens VE, et al. Influence of hospital type on outcomes after oesophageal and gastric cancer surgery. *Br J Surg*. 2012;99(7):954-963.
65. Signaleringscommissie Kanker van KWF Kankerbestrijding. [*Quality of cancer care in the Netherlands*]. Amsterdam: Dutch Cancer Society; 2010.
66. Boyle P, Ferlay J. Mortality and survival in breast and colorectal cancer. *Nat Clin Pract Oncol*. 2005;2(9):424-425.
67. Measurement of progress against cancer. Extramural Committee to Assess Measures of Progress Against Cancer. *J Natl Cancer Inst*.1990;82(10):825-835.
68. Sant M, Francisci S, Capocaccia R, Verdecchia A, Allemani C, Berrino F. Should we use incidence, survival or mortality to assess breast cancer trends in European women? *Nat Clin Pract Oncol.* May 2006;3(5):228-229.
69. Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. Trends in cancer incidence and mortality. *IARC Sci Publ*. 1993(121):1-806.
70. Harteloh P, de Bruin K, Kardaun J. The reliability of cause-of-death coding in The Netherlands. *Eur J Epidemiol*. 2010;25(8):531-538.
71. Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer.* 2003;106(3):416-422.
72. Rosso S, Zanetti R. A further caveat in interpreting cancer survival. *Nature reviews*. Apr 2010;7(4):184-c181; author reply 184-c182.
73. Autier P, Boniol M, La Vecchia C, et al. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. *BMJ*. 2010;341:c3620.

74. Beral V, Peto R. UK cancer survival statistics. *BMJ*. 2010;341:c4112.

75. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. Lancet Oncol. 2007;8(9):773-783.

76. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. J Intern Med. 2006;260(2):103-117.

77. *Autier P, Boniol M. Caution needed for country-specific cancer survival.* Lancet. 2011;377(9760):99-101.

78. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. *International journal of radiation oncology, biology, physics*. 2006;64(4):1081-1091.

79. Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*. 2007;99(5):365-375.

80. Signaleringscommissie Kanker van KWF Kankerbestrijding. [*Cancer in the Netherlands up to 2020, trends and prognosis*]. Amsterdam: Dutch Cancer Society; 2011.

Summary
Nederlandse samenvatting
Dankwoord
Curriculum Vitae
List of publications
PhD Portfolio

SUMMARY

During the second part of the 20th century, cancer has become an important health problem worldwide. In the Netherlands, cancer incidence increased with 50% since the 1970s. Fortunately, mortality from cancer started to decrease from the 1980s onwards. Impressive improvements in cancer survival started to occur since the 1970s, first for the younger patients and later on also for the elderly. To evaluate progress against cancer, incidence and prognosis of and mortality from cancer are useful outcome measures. The work in this thesis shows which progress has been achieved against cancer in the Netherlands since the late 1980s, also in comparison with other European countries. It shows the impact of changes in risk factor prevalence, primary and secondary prevention and cancer management on cancer trends and how we can optimize assessment of progress against cancer

Dutch cancer trends in a European context

In **Chapter 2** we describe the main cancer trends within Europe from the mid 1990s to early 2000. The cancer incidence trends were generally favourable in the more prosperous countries from Northern and Western Europe, except for obesity related cancers, which showed increases in incidence. Whereas incidence of and mortality from tobacco-related cancers decreased for males in Northern, Western and Southern Europe, they increased for both sexes in Central Europe and for females nearly everywhere in Europe. Survival rates generally improved, probably due to better access to specialized diagnostics, staging and treatment. Marked effects of more early detection, organized or opportunistic screening became visible for breast, prostate and melanoma in the wealthier countries. Mortality trends were generally favourable, except for smoking related cancers.

Dutch males had comparable cancer rates, while Dutch females had more often higher cancer rates compared to the European average. In the beginning of this century, the incidence rates of cancer of the oral cavity and pharynx, larynx, stomach, pancreas, prostate and testis were lower among Dutch males than the European average. Whereas incidence rate of male lung cancer was higher than the European average during the mid 1990s, it is now on the European average. More common among Dutch males than the European average were oesophageal cancer and Hodgkin lymphoma. During the early 2000, the incidence of cancer of the stomach,

pancreas, cervix, corpus uteri and ovary was lower than the European average. In the mid 1990s, the incidence rate of female lung cancer was about the European, but has risen so dramatically between the mid 1990s and early 2000 and is now above the European average. Cancers of the oral cavity and pharynx, oesophagus, colorectal, larynx, skin melanoma and breast were also more common among Dutch females than average among European females. Relative survival of Dutch cancer patients was in general about the same as the average in Europe and higher than average for patients with laryngeal and cervical cancer and skin melanoma.

Impact of changes in risk factor prevalence, primary and secondary prevention and cancer management on cancer trends

Many efforts were made to lower the cancer incidence and mortality and improve the cancer prognosis by primary and secondary prevention programs and changes in cancer management (e.g. changes in diagnostics and therapies). In **Chapter 3 and 4** we illustrate how such efforts can influence cancer trends by using examples of cancer of the oesophagus, lung, ovary and prostate. We found in **Chapter 3.1** indications that the lung cancer epidemic among females is beginning to come to an end: Lung cancer incidence and mortality trends were flattening out among young females (20-49 yrs) since 1999 as a result of an observed decrease among females born after the 1950s. The same birth cohort trend was seen for the smoking prevalence, which also declined among females born after the 1950s. This shows that lowering the risk factor prevalence by primary prevention (e.g. smoking prevention) does have a positive effect on the incidence and mortality trends although it takes a long time before the positive effects are visible because of the long latency times.

Cancer incidence and mortality can also decrease as a result of changes in behaviour among the population without the aid of any prevention campaign, as illustrated in **Chapter 3.2** by the introduction of oral contraceptives in the mid-1960s. In the Netherlands, we observed that ovarian cancer mortality rate decreased since the 1970s, coinciding with the introduction of the oral contraceptives, with a reduction of 36%, particularly among females born after the 1920s. Ovarian cancer incidence was reduced by 30% between 1989 and 2009, which was one of the largest reductions observed within Europe.

In **Chapter 4.1** we studied the prostate cancer trends and increased use of testing serum prostate-specific antigen level (PSA). Whether PSA testing is responsible for the observed decrease in the incidence of metastasized tumours and mortality in

the Netherlands was still questionable. We observed two periods of increasing incidence rates, at first, an increase in cT2-tumours (palpable tumours) between 1989 and 1995 and secondly, an increase of cT1c-tumours (screen-detected tumours) since 2001. The incidence of metastasized tumours (cT4/N+/M+) decreased between 1993 and 2006 and prostate cancer mortality started to decrease from 1996. The increase of prostate cancer incidence in the early 1990s was probably caused by increased prostate cancer awareness among clinicians combined with diagnostic improvements (transrectal ultrasound, (thin) needle biopsies), but not caused by PSA testing, which was not widely used at the time. PSA testing must have caused the second period of incidence increase in the 2000s. The decline in mortality from 1996 onwards is probably due to the increased detection of cT2-tumours in the early 1990s; it remains unclear what the contribution is of the increase of cT1c-tumours to the decreasing mortality.

At last, changes in cancer management showed to be effective to improve survival of cancer patients. For example, over the last two decades treatment of epithelial ovarian cancer patients with advanced disease improved; more patients received (neo-)adjuvant chemotherapy and underwent optimal debulking surgery. These changes in treatment partly explained the survival improvement of ten percent of ovarian cancer (**Chapter 4.2**). In **Chapter 4.3**, we found that surgery by a consultant gynaecologist oncologist also improved survival in ovarian cancer patients. For patients younger than 75 years operated by a gynaecologist oncologist the reduction in risk of dying was almost 30% adjusted for age, stage, type of hospital and chemotherapy compared to patients operated by a general gynaecologist. For oesophageal cancer, we found in **Chapter 4.4** a reduction in postoperative morbidity, length of hospital stay, in-hospital mortality which declined from 14% to 4.7% and 2-year survival improved from 38% to 54% after centralisation of oesophageal resections in the mid-western part of the Netherlands.

Framework for interpretations of changes in cancer trends

Measuring progress against cancer has become an important issue to evaluate (national) cancer programs during recent decades. There are many parameters which can indicate progress, most of which are difficult to measure and monitor with the standard surveillance instruments: mainly cancer registries. Several of these parameters are influencing cancer incidence, survival and mortality, which can be monitored over time. In **Chapter 5.1** we proposed a conceptual framework where

we combined incidence, survival and mortality to achieve an objective assessment of progress against cancer while avoiding misinterpreting findings from one of these measures separately. In the Netherlands, a largely positive pattern of progress against cancer since the late 1980s was observed. Optimal progress (defined as decreasing incidence and/or improving survival accompanied by declining mortality) was observed in 12 of 19 cancer types among males: laryngeal, lung, stomach, gallbladder, colon, rectal, bladder, prostate and thyroid cancer, leukaemia, Hodgkin and non-Hodgkin lymphoma. Among females, optimal progress was observed in 12 of 21 cancers: stomach, gallbladder, colon, rectal, breast, cervical, uterus, ovarian and thyroid cancer, leukaemia, Hodgkin and non-Hodgkin lymphoma. Deterioration (defined as increasing incidence and/or deteriorating survival accompanied by increasing mortality rates) occurred in three cancer types among males: skin melanoma, oesophageal and kidney cancer, and among females in six cancer types: skin melanoma, oral cavity, pharyngeal, oesophageal, pancreatic and lung cancer.

In **Chapter 5.2** we showed the possible causes of a deteriorating survival over time or of inferior survival rates compared to other countries. First of all, deterioration of care is the worse cause of deteriorating survival, but almost never occurs in practice. Another, more common, cause of deteriorating survival rates is improved diagnosis of premalignant lesions, which causes survival statistics to reflect only the most aggressive cancers-those with the poorest prognosis. In addition, deleterious changes in the distribution of prognostic factors and in the distribution of sociodemographic characteristics may negatively affect cancer survival, as well as changes in completeness and quality of the cancer registry.

Conclusions

- The proposed conceptual framework for measuring progress against cancer can be useful to evaluate (national) cancer programs and to prioritize and monitor activities in the field of prevention and clinical research.
- A largely positive, but mixed pattern of progress against cancer was observed for the Netherlands since the late 1980s:
  - Optimal progress (defined as decreasing incidence and/or improving survival accompanied by declining mortality) was observed in 12 of 19 cancer types among males: laryngeal, lung, stomach, gallbladder, colon, rectal, bladder, prostate and thyroid cancer, leukaemia, Hodgkin and non-Hodgkin lymphoma. Among females, optimal progress was observed in 12 of 21 cancers: stomach,

gallbladder, colon, rectal, breast, cervical, uterus, ovarian and thyroid cancer, leukaemia, Hodgkin and non-Hodgkin lymphoma.
  - Deterioration (defined as increasing incidence and/or deteriorating survival accompanied by increasing mortality rates) occurred in three cancer types among males: skin melanoma, oesophageal and kidney cancer, and among females in six cancer types: skin melanoma, oral cavity, pharyngeal, oesophageal, pancreatic and lung cancer.
- Primary and secondary prevention showed to have bigger impact on cancer trends than new diagnostics and treatment.
  - Anti-smoking campaigns can be considered as a success of primary prevention resulting in decreasing incidence and mortality of smoking related cancers. However smoking prevalence rates are still high, particularly among Dutch women who showed to have higher rates of smoking related cancers than the average rates among European women.
  - Screening for cancer can have different effects on cancer trends depending on detection of pre-malignancies (decreasing incidence and sometimes even deteriorating survival) or early stages of disease (increasing incidence and improving survival). It is not certain what will happen to colorectal cancer incidence after introduction of screening.
- New effective diagnostics or treatment showed to improve cancer survival often coinciding with subspecialisation of clinicians and regionalisation of cancer care showed to be effective to improve survival (for instance ovarian and oesophageal cancer).

Recommendations

- The proposed conceptual framework for measuring progress against cancer should be used to monitor cancer trends as a basis for future scenarios which can be useful to determine clinical capacity and to prioritize activities in the field of prevention and clinical research.
- Cancer epidemiologists should make sure that policy makers are well informed on newly occurring trends in occurrence, mortality or prognosis from cancer, and should also inform them on (new/emerging) risk factors, in order to try and minimize delays in taking action when new risk factors are detected.
- Primary prevention needs to be back on the governmental agenda, e.g. campaigns against smoking, obesity and excessive sun exposure remain important to lower

future cancer incidence. Particularly, the incidence of obesity related cancers such as oesophageal and colorectal cancer is high compared to other European countries.

- Cancers of the oesophagus, stomach, gallbladder, pancreas and lung need our attention because of their stable poor prognosis (5-year relative survival below 25%). Scenario calculations could be useful to get more insight in the possibilities of prevention, early detection and improved cancer management.
- In the future it is important to evaluate the colorectal cancer screening by monitoring incidence and prognosis of and mortality from colorectal cancer, over time and also by birth cohort. The same is valid for evaluating the effects of using HPV DNA test as primary screen test in the cervical screening program and HPV vaccination among 12-year old girls since 2009 to prevent cervical cancer.
- The cost-effectiveness of new targeted (often expensive) therapies should be studied and their effect on the overall cancer prognosis and mortality.
- It is important to assess progress against cancer by age and gender because of the diversity on causes, detection and treatment, and to see whether special attention is needed for certain groups.
- Assessing progress against cancer by socioeconomic status (SES) should be also interesting to monitor the gap between SES groups which was found recently.
- To make the assessment of progress against cancer more complete it will be interesting to incorporate disease-specific mortality (especially for the long-term side effects of cancer treatment and therefore linking death causes with the NCR is highly recommended), quality of life (e.g. differs between stage of disease, cancer treatments) and/or costs invested in prevention programs and spent on (new) diagnostics and therapies.

NEDERLANDSE SAMENVATTING

Vanaf de tweede helft van de vorige eeuw is kanker uitgegroeid tot een belangrijk gezondheidsprobleem. In Nederland is het vóórkomen (incidentie) van kanker met 50% gestegen sinds de jaren '70. Echter de overleving van kankerpatiënten is enorm verbeterd sinds de jaren '70 (gemiddeld met 20%) en vanaf eind jaren '80 is de sterfte aan kanker in de bevolking gedaald met 20%.

Vanaf de jaren '70 is in Nederland veel geld en energie geïnvesteerd in de verbetering van het vroeg ontdekken en de behandeling van kankerpatiënten en preventiecampagnes. Een veel voorkomende vraag is dan ook of deze investeringen wat hebben opgeleverd. In dit proefschrift wordt een poging gedaan om een antwoord op deze vraag te krijgen op basis van geobserveerde trends in drie belangrijke parameters: incidentie en overleving van en sterfte aan kanker.

Allereerst hebben we de trends in incidentie, overleving en sterfte van 21 Europese landen beschreven om daarmee een beeld te krijgen hoe Nederland er voor staat binnen Europa. Vervolgens zijn in dit proefschrift de Nederlandse trends van slokdarmkanker, longkanker, eierstokkanker en prostaatkanker in meer detail bestudeerd om zo meer inzicht te krijgen in de impact van veranderingen in het vóórkomen van risicofactoren, primaire en secundaire preventie, diagnostiek en behandeling op kankertrends. Binnen het project 'Progress against cancer in the Netherlands since the 1970s' (gefinancieerd door de KWF Kankerbestrijding) zijn ook de trends van 21 andere kankersoorten in meer detail bestudeerd. Vanwege de diversiteit van de trends in incidentie, overleving en sterfte (bijv. de incidentie stijgt harder dan de sterfte) laten we tot slot zien hoe belangrijk het is om naar deze drie trends gecombineerd te kijken en geven we een overzicht van de vooruitgang die geboekt is in onze strijd tegen kanker in Nederland vanaf eind jaren '80.

Waar staat Nederland binnen Europa?

In **Hoofdstuk 2** worden trends in incidentie, prognose en sterfte van 17 kankersoorten binnen Europa beschreven van midden jaren '90 tot begin 2000. De trends in kankerincidentie zijn over het algemeen het meest gunstig in Noord- en West-Europa, behalve voor de kankersoorten die gerelateerd zijn aan obesitas. De trends in incidentie en sterfte van rookgerelateerde kankersoorten (met name longkanker) lieten een daling zien bij mannen in Noord-, West- en Zuid-Europa,

maar stegen juist voor mannen in Centraal Europa. In vrijwel geheel Europa stegen de incidentie en sterfte van deze kankersoorten bij vrouwen. Over de gehele linie verbeterde de prognose van kanker, waarschijnlijk door een betere toegang tot gespecialiseerde diagnostiek en behandeling. De effecten van vroege opsporing, mede door screening, waren te zien voor melanoom, borstkanker en prostaatkanker in de rijkere landen. Trends in kankersterfte waren over het algemeen ook gunstig, behalve voor rookgerelateerde kankers bij vrouwen.

Bij Nederlandse vrouwen komen melanomen en kanker van de mond- en keelholte, strottenhoofd, slokdarm, long en borst vaker voor dan onder andere Europese vrouwen. Zo kwam longkanker in de midden jaren '90 bij Nederlandse vrouwen net zo vaak voor als elders in Europa, maar na een enorme stijging in de longkankerincidentie zitten ze nu boven het Europese gemiddelde. Daarentegen komen kanker van de maag, alvleesklier, baarmoeder, baarmoederhals en eierstok minder vaak voor bij Nederlandse vrouwen. Bij Nederlandse mannen is een positiever beeld te zien. Kwam midden jaren '90 longkanker vaker voor bij Nederlandse mannen dan bij andere Europese mannen, begin 2000 zaten ze op het Europese gemiddelde. Kanker van de mond- en keelholte, strottenhoofd, maag, alvleesklier, prostaat en testis komen minder vaak voor bij Nederlandse mannen. Daarentegen komen slokdarmkanker en Hodgkin lymfoom vaker voor onder Nederlandse mannen. De relatieve overleving van kankerpatiënten in Nederland was over het algemeen gelijk aan de gemiddelde overleving in Europa en was zelfs hoger dan het gemiddelde voor patiënten met melanoom, strottenhoofdkanker en baarmoederhalskanker.

Impact van veranderingen in het vóórkomen van risicofactoren, primaire en secundaire preventie, diagnostiek en behandeling op kankertrends

In de **Hoofdstukken 3 en 4** laten we zien hoe veranderingen in het vóórkomen van risicofactoren, preventie, diagnostiek en behandeling kankertrends kunnen beïnvloeden aan de hand van 4 voorbeelden: slokdarmkanker, longkanker, eierstokkanker en prostaatkanker.

In **Hoofdstuk 3.1** beschrijven we indicaties die aantonen dat het einde van de longkankerepidemie bij vrouwen in zicht is, ondanks de alsmaar stijgende incidentie. De longkankerincidentie en –sterfte bij jonge vrouwen (20-49 jaar) stabiliseerde vanaf 1999. Dalende longkankersterfte en rookprevalentie werd waargenomen bij vrouwen geboren ná 1950. Dit is een duidelijk voorbeeld van hoe het terugdringen

van een bepaalde risicofactor door primaire preventie (bijv. anti-rook campagnes) uiteindelijk zijn vruchten afwerpt: een dalende incidentie en sterfte.

Kankerincidentie en -sterfte kunnen ook dalen doordat veranderingen in het gedrag van de bevolking plaatsvinden zonder de hulp van preventiecampagnes. **Hoofdstuk 3.2** laat hier een voorbeeld van zien. In Nederland zien we vanaf de jaren '70 een enorme daling in de eierstokkankersterfte van 36%, met name bij vrouwen die geboren zijn ná 1920. Deze daling gaat gepaard met de toename in het gebruik van de pil als anticonceptiemiddel. De incidentie van eierstokkanker daalde met 27% tussen 1989 en 2009, een van de sterkste dalingen binnen Europa.

In **Hoofdstuk 4.1** hebben we de prostaatkankertrends en de mogelijke invloed van het toegenomen gebruik van de PSA-test daarop bestudeerd. Het is namelijk nog steeds de vraag of de afname van de gemetastaseerde prostaatkankertumoren en sterfte in Nederland toe te schrijven is aan de toename in het aantal PSA-testen over de tijd. Wij vonden twee perioden van stijgingen in de prostaatkankerincidentie. Ten eerste een stijging van cT2-tumoren (tumoren die door de huisarts of uroloog voelbaar zijn bij rectaal onderzoek) in de periode 1989-1995 en als tweede een stijging van cT1c-tumoren (tumoren die opgespoord kunnen worden via een PSA-test) vanaf 2001. Zowel cT1c- en cT2-tumoren worden beschouwd als 'vroege' prostaattumoren, en hebben een zeer gunstige prognose. De incidentie van gemetastaseerde tumoren (cT4/N+/M+) daalde tussen 1993 en 2006. De prostaatkankersterfte begon te dalen vanaf 1996. De eerste van bovengenoemde stijgingen in de incidentie, die van begin jaren '90, is waarschijnlijk veroorzaakt door een toename in de bewustwording onder medici gecombineerd met verbeteringen in de diagnostiek. Deze stijging is nog te vroeg om als effect te zien van de PSA test, want die werd op dat moment nog niet vaak gebruikt werd in Nederland. De tweede stijging vanaf 2001 lijkt echter wel veroorzaakt te zijn door het toegenomen gebruik van de PSA test. De dalende prostaatkankersterfte vanaf 1996 is zeer waarschijnlijk een gevolg van de eerste stijging van cT2-tumoren. Het blijft vooralsnog onduidelijk wat de bijdrage is van de stijging in cT1c-tumoren op de prostaatkankersterfte.

Verandering in diagnostiek en behandeling kunnen van veel betekenis zijn voor het (verder) verbeteren van de overleving van kankerpatiënten. Een voorbeeld hiervan is eierstokkanker. De laatste 20 jaar is de behandeling van patiënten met gemetastaseerde epitheliale eierstokkanker verbeterd: meer patiënten kregen (neo-)adjuvante chemotherapie en ondergingen een chirurgische ingreep met optimale debulking. Deze veranderingen verklaren voor een deel de verbetering

in de 5-jaars overleving van deze patiënten die steeg van 18% naar 28% in de periode 1989-2009 (**Hoofdstuk 4.2**). In **Hoofdstuk 4.3** vonden we dat wanneer de chirurgische ingreep werd uitgevoerd door een gynaecologisch oncoloog de overleving verbeterde voor de patiënten met eierstokkanker. Bij patiënten jonger dan 75 jaar, geopereerd door een gynaecologisch oncoloog daalde het risico op sterfte met bijna 30% in vergelijking met patiënten die geopereerd waren door een algemeen gynaecoloog, gecorrigeerd voor leeftijd, stadium van de ziekte, type ziekenhuis en al dan niet behandeling met chemotherapie. Voor patiënten met slokdarmkanker vonden we in **Hoofdstuk 4.4** een daling in de post-operatieve morbiditeit, lengte van ziekenhuisverblijf, sterfte tijdens het ziekenhuisverblijf nadat het chirurgisch verwijderen van de slokdarm werd gecentraliseerd in bepaalde ziekenhuizen in de regio Leiden-Den Haag. Voor deze chirurgische ingreep komt slechts ongeveer 30% van de slokdarmkankerpatiënten in aanmerking. De sterfte tijdens het ziekenhuisverblijf daalde van 14% naar 5% en de 2-jaars overleving van deze beperkte groep slokdarmkankerpatiënten verbeterde zelfs van 38% naar 54%.

Meten van vooruitgang in de strijd tegen kanker

Om kankerbestrijdingprogramma's die opgesteld zijn door (regionale) overheden te kunnen evalueren is het meten van verbetering belangrijk geworden, juist omdat er zo gemakkelijk schijnbare vooruitgang kan worden geboekt door bijvoorbeeld vroege opsporing van kanker. Er zijn vele parameters waarmee vooruitgang is te meten, maar de meeste (zoals kwaliteit van leven) zijn niet zonder meer te meten en te monitoren door kankerregistraties. Echter de parameters incidentie, prognose en sterfte kunnen wel gemeten worden door de meeste kankerregistraties. Om een goed overzicht te krijgen van de voor- of achteruitgang in de strijd tegen kanker is het van belang om deze drie parameters per tumorsoort te laten zien. Vaak wordt slechts naar één van deze parameters gekeken en worden verkeerde interpretaties gedaan.

In Nederland is vanaf eind jaren '80 voor 16 veel voorkomende kankersoorten vooruitgang geboekt (**Hoofdstuk 5.1**). Maagkanker en galblaaskanker kwamen steeds minder vaak voor bij zowel mannen als vrouwen sinds eind jaren '80. Daarnaast was een daling in incidentie zichtbaar bij mannen voor strottenhoofdkanker, longkanker en blaaskanker en bij vrouwen voor baarmoederhalskanker en eierstokkanker. Het percentage patiënten dat 5 jaar na diagnose nog in leven is, was toegenomen bij zowel mannen als vrouwen voor dikke darmkanker, rectumkanker, schildklierkanker,

longkanker, leukemie, Hodgkin en non-Hodgkin lymfomen. Bij mannen was eenzelfde verbetering zichtbaar voor maagkanker en prostaatkanker en bij vrouwen voor borstkanker, baarmoederhalskanker, baarmoederkanker en eierstokkanker. Al deze verbeteringen leidden ertoe dat steeds minder mensen overleden aan deze kankersoorten. Voor sommige vormen van kanker werd achteruitgang gemeten: bij zowel mannen als vrouwen bleek dat slokdarmkanker en melanoom steeds vaker voorkomen. Gelukkig was de overleving van deze kankersoorten wel sterk verbeterd sinds eind jaren '80, waardoor de sterfte niet in gelijke mate steeg. Daarnaast kwam bij mannen nierkanker steeds vaker voor en bij vrouwen mondholte- en keelholtekanker, alvleesklierkanker en longkanker. Bij geen van de kankersoorten werd een verslechtering van de overleving geobserveerd. Al blijven slokdarmkanker, maagkanker, alvleesklierkanker, galblaaskanker en longkanker onze aandacht vereisen vanwege hun slechte prognose (5-jaars overleving < 25%).

In **Hoofdstuk 5.2** wordt een overzicht gegeven van de mogelijke oorzaken van een verslechtering in de overleving over de tijd of wanneer overleving verschilt tussen landen. Vaak wordt alleen gedacht aan het slechtste scenario, namelijk verslechtering van de zorg. In de praktijk is dit echter gelukkig bijna nooit het geval. Een vaker voorkomende oorzaak is dat tumoren vaker in een goedaardig stadium worden ontdekt (bijvoorbeeld bij baarmoederhalskankerscreening). Hierdoor neemt het aantal tumoren af die worden geregistreerd in de kankerregistratie en neemt verhoudingsgewijs het aandeel agressieve kwaadaardige tumoren met een slechte prognose toe ten opzichte van het totaal aantal geregistreerde tumoren waarop de overleving wordt berekend. Dit leidt logischerwijze tot slechtere overlevingscijfers. Veranderingen in de stadiumverdeling en verdeling van subtypes van tumoren, veranderingen in het vóórkomen van bijkomende ziektes (bijv. diabetes), veranderingen in socio-demografische karakteristieken (bijv. toename van bevolkingsgroep met laag sociaal economische status), toename van compleetheid en/of kwaliteit van een kankerregistratie kunnen de overleving van kankerpatiënten ook nadelig beïnvloeden.

Conclusies

– Het meten van vooruitgang in de strijd tegen kanker door middel van incidentie, prognose en sterfte is zeer bruikbaar bij het evalueren van (nationale) kankerbestrijdingsprogramma's. Discussie over prioriteiten en gericht monitoren

van activiteiten ten behoeve van preventie en klinisch onderzoek kunnen hierdoor op een hoger niveau plaatsvinden.

- In Nederland is vanaf eind jaren '80 over het algemeen veel vooruitgang geboekt in onze strijd tegen kanker.
  - Een dalende incidentie en/of verbetering in de overleving samengaand met een dalende sterfte werd bij 12 van de 19 onderzochte kankersoorten geobserveerd voor mannen: kanker van het strottenhoofd, long, maag, galblaas, dikke darm, blaas, prostaat en schildklier, leukemie, Hodgkin en non-Hodgkin lymfomen.
  - Voor vrouwen werd dit bij 12 van 21 onderzochte kankersoorten geconstateerd: kanker van de maag, galblaas, dikke darm, borst, baarmoederhals, baarmoeder, eierstok en schildklier, leukemie, Hodgkin en non-Hodgkin lymfomen.
- Primaire en secundaire preventie (vroege opsporing van kanker) hebben laten zien een grotere impact te kunnen hebben op kankertrends dan nieuwe diagnostiek en behandeling.
  - Anti-rook campagnes als primaire preventive kunnen als succesvol worden bestempeld omdat ze geleid hebben tot een afname van incidentie en sterfte van rookgerelateerde kankersoorten. Echter, vergeleken met veel andere landen is de prevalentie van roken nog steeds hoog in Nederland, met name bij de vrouwen. Dit is een van de oorzaken waarom kankersoorten zoals longkanker, strottenhoofdkanker en mond- en keelholtekanker vaker vóórkomen bij Nederlandse vrouwen dan in andere Europese landen.
  - Kankerscreening kan verschillende effecten hebben op kankertrends afhankelijk van het feit of er gescreend wordt op voorstadia van kanker (met als resultaat een dalende incidentie en soms zelfs een verslechterde overleving) of vroege stadia van kanker (met als resultaat een stijgende incidentie en verbeterde overleving).
- Nieuwe effectieve diagnostiek en behandeling bleken buiten de trials ook tot verbeteringen te hebben geleid in de overleving van kankerpatiënten. Deze ontwikkelingen gaan vaak samen met subspecialisatie van clinici en regionalisatie/centralisatie van de behandeling (zoals bij eierstokkanker en slokdarmkanker).

Aanbevelingen

- Primaire preventie moet weer terug op de politieke agenda (zoals campagnes tegen roken, obesitas en te veel blootstelling aan UV-licht) om zo de

kankerincidentie en ook andere chronische ziekten terug te dringen. Dit geldt met name voor de obesitas-gerelateerde kankersoorten: slokdarm- en dikke darmkanker die veel vóórkomen in Nederland vergeleken met andere Europese landen.

- Slokdarmkanker, maagkanker, alvleesklierkanker, galblaaskanker en longkanker vereisen onze aandacht vanwege hun slechte prognose (5-jaars overleving < 25%). Belangrijk hierbij is het exploreren van de mogelijkheden op het gebied van primaire preventie (blootstelling aan risicofactoren terugdringen), secundaire preventie (vroege opsporing), behandeling en centralisatie/regionalisatie van de zorg.
- Het monitoren van trends in incidentie, prognose en sterfte is van belang bij het evalueren van de nieuwe ontwikkelingen op het gebied van secundaire preventie, zoals bevolkingsonderzoek dikke darmkanker, HPV tests binnen het bevolkingsonderzoek baarmoederhalskanker en HPV- vaccinatie van 12-jarige meisjes.
- Het is belangrijk om de kosten-effectiviteit van nieuwe kankertherapieën (vaak de zgn. dure geneesmiddelen) te bestuderen, maar ook de impact van deze therapieën op de trends in overleving van en sterfte aan kanker op bevolkingsniveau.
- Om meer inzicht te krijgen in de vooruitgang of achteruitgang is het interessant om ook naar kankertrends te kijken in de diverse leeftijdsgroepen (bijvoorbeeld kinderen, adolescenten, mensen van middelbare leeftijd en ouderen) en naar geslacht vanwege de diversiteit in de oorzaken, detectie en behandeling.
- Het meten van vooruitgang zou ook voor de verschillende sociaaleconomische groepen in de bevolking gedaan moeten worden om zo de geconstateerde verschillen tussen deze groepen te kunnen monitoren. Recent is namelijk gebleken dat in Nederland bij mensen met een laag sociaaleconomische status vaker kanker vóórkomt, kanker vaker gediagnosticeerd wordt met een vergevorderd stadium en dat deze groep een slechtere overleving heeft dan de hoge sociaaleconomische groepen.
- Bij het meten van vooruitgang in de strijd tegen kanker is het interessant om als uitkomstmaten toe te voegen:
  - ziekte-specifieke sterfte, met name om meer inzicht te krijgen in de lange termijn effecten van kankertherapieën (hiervoor is wel noodzakelijk dat de kankerregistratie toegang heeft tot het doodsoorzakenregister!)

- kwaliteit van leven, dit verschilt per stadium en therapie
- geïnvesteerde kosten in preventie, (nieuwe) diagnostiek en behandeling. Recent is namelijk gebleken dat de sterfte aan kanker in de VS sterker gedaald is dan in Europa en dat de overlevingscijfers hoger zijn in de VS mogelijk als een gevolg van een hogere investering in de gezondheidszorg.

DANKWOORD

En nu is het zover, het is af! Wie had dat ooit kunnen denken. Zelf was ik degene die het hardst heeft geroepen dat promoveren niet mijn ding is en heb bij mijn start in 2007 tegen vrijwel niemand gezegd dat het om een promotietraject ging. Sommigen van jullie weten pas sinds kort dat ik druk bezig was met een 'boekje'. Maar ik zal eerlijk bekennen: ik ben gezwicht toen dit interessante project voorbij kwam en ik niet anders kon dan er gewoon heel enthousiast in te stappen met dit proefschrift als resultaat!

Mijn promotoren, prof.dr. Jan Willem Coebergh, prof.dr. Bart Kiemeney en co-promotor dr. Esther de Vries, wil ik allereerst bedanken voor alle steun en het vertrouwen dat zij in mij hadden. Zij hebben er zeker aan bijgedragen dat ik enthousiast bleef. Jan-Willem wat heb ik veel van je geleerd. We hadden heerlijke gesprekken die gingen over verklaren van kankertrends tot dure medicijnen, van promoveren tot bevallingen en zo kan ik nog wel even doorgaan. Bart, jij zat fysiek verder weg, maar dat was niet te merken als ik je om hulp vroeg. Ik ben je erg dankbaar voor de altijd kritische blik en je wist me altijd terug te brengen tot de essentie waar het om draaide. Een mooiere combinatie van promotoren had ik me niet kunnen wensen! Esther, bij jou kon ik altijd terecht met mijn vragen of voor een gezellig 'onderonsje' eerst bij je op de kamer en later via de skype (en wat mis ik dat nu zeg!). Ik heb onze samenwerking als ontzettend fijn ervaren en je enthousiasme voor het onderzoek werkte altijd aanstekelijk en dat doet het nog steeds. Ik hoop dat we in de toekomst nog eens wat samen gaan doen, is het niet op het gebied van onderzoek dan wel met de kinderen. En van die nominatie tot co-promotor van het jaar is het nooit gekomen, maar ik roep je hierbij uit tot beste co-promotor aller tijden!

Begin juli 2012 was het dan zover, het proefschrift kon verstuurd worden ter goedkeuring. Ik wil de leden van de kleine commissie, prof.dr.ir. Floor van Leeuwen, prof.dr. Jaap Verweij en prof.dr. Curt Burger bedanken voor de tijd en de energie die zij gestoken hebben in het kritisch bekijken van mijn proefschrift. De andere leden van de promotiecommissie wil ik danken voor deelname aan de oppositie. Special thanks to Dr. David Forman for his visit to the Netherlands to take place in my defence commission.

Al de artikelen die binnen het grote 'Progress against cancer'-project zijn gepubliceerd, waarvan een aantal in dit proefschrift staan, zouden niet tot stand gekomen zijn zonder de enthousiaste inzet van alle (co)auteurs die er te veel zijn om op te noemen. Bedankt voor het kritisch meedenken en schrijven! Ruben Cremers, Anne van Altena, Mirjam Engelen, Michel Wouters en Esther de Vries als eerste auteurs van artikelen die in dit proefschrift staan, wil ik jullie nog even extra in 't zonnetje zetten. Ontzettend bedankt voor jullie bijdrage aan dit mooie geheel en het enthousiasme, waarmee jullie altijd je (klinische) kennis met mij deelden. Maar ook met Dorry Boll (leuk dat je langs kwam in Wenen!), Carlijn Witjes en Miep van der Drift als eerste auteurs van de andere artikelen heb ik een speciale band opgebouwd. Bedankt voor de fijne samenwerking!

Zonder onze registratiemedewerkers die dag in en uit in de ziekenhuizen de medische dossiers napluizen, zouden we geen enkel artikel over kankertrends kunnen schrijven. Dat laat zien hoe belangrijk hun werk is. Bedankt voor jullie inzet en ga zo door!

De KWF Kankerbestrijding wil ik hartelijk bedanken voor het mogelijk maken van het project ' Progress against cancer' door middel van financiële ondersteuning.

Mijn MGZ collega's wil ik bedanken voor de fijne tijd in Rotterdam. Er was altijd wel een gezellig moment in het keukentje of op de gang. Yvonne, jou wil ik bedanken voor al je hulp rondom mijn proefschrift. Mijn 'koffiemaatjes', Ida, Hein, Inge en Meeke, bedankt voor de gezellige wandelingen naar de DE. Eefje, met jou deelde ik kamer AE-107 en wat heb ik het met jou getroffen. Inge, jij was onze vaste stamgast. We deelden lief en leed en hadden vaak de grootste lol, dank daarvoor. En Eefje, wat ik ben blij dat je vandaag naast me staat!

In Eindhoven voelde ik me ook altijd welkom en daarvoor wil ik mijn IKZ-collega's bedanken. Ook voor de interessante, stimulerende en gezellige brainstorms die we samen hadden.

Wat was het heerlijk om naast het werk afleiding te hebben. We zagen elkaar helaas niet veel, maar als we elkaar zagen was het weer als vanouds. Marieke, Corina en Carla, bedankt voor jullie onvoorwaardelijke vriendschap! Corina, jou wil ik nog extra bedanken voor het mooie ontwerp van de voorkant. Carla, leuk dat je vandaag mijn paranimf wil zijn. We begonnen onze middelbare schoolcarrière in dezelfde schoolbank en dat is goed afgelopen, dus dat moet vandaag ook goed komen met jou naast me!

Also thanks to the Vienna Baby Club-moms, Christiana, Katherina, Emanouella, Mary-Jane, San-San, Barbara and Verena for our nice time together with our kids. Every week, I looked forward to seeing you for a chat in one of the great playgrounds in Vienna. Hopefully, see you soon again and it's time for a ladies night to celebrate this event!

Thea, bij jou kon ik na een drukke werkdag altijd mijn verhaal kwijt en vaak kon ik nog een hapje mee-eten ook. Je stond samen met Wim en Lisanne altijd voor me klaar. Eind vorig jaar kwam je zelfs een week langs in Wenen om te komen oppassen, zodat ik nog hard aan de slag kon met dit boekwerk, bedankt daarvoor!

Paps en mams, jullie horen eigenlijk als eersten genoemd te worden. Maar ik zou willen zeggen: de laatsten zullen de eersten zijn. Jullie hebben me altijd de vrijheid gegeven om te doen wat ik wilde en me daarin gesteund, ook al was dat niet altijd even makkelijk. En dan de rest van de familie. Bij wie moet ik beginnen, want ondertussen zijn we uitgegroeid tot een twintigtal. Ons samenzijn betekent altijd een gezellige drukke boel. Iedereen bedankt voor alle afleiding! Joost en Jantine, jullie hebben je 'kleine zusje' altijd van goede adviezen voorzien, dank daarvoor. Zus, we moeten vooral doorgaan met onze interessante discussies over de zorg! En dan m'n maatje en 'broertje' Pieter. Samen hebben we elkaar weten te stimuleren. Jij mij bij dit boekwerk en ik jou bij het schrijven van jouw masterscriptie. Jij hebt je bul al binnen en nu ik nog. En dan op naar ons volgend doel, jij als minister-president en ik als minister van Volksgezondheid (knipoog).

Tot slot, mijn lieve Reza, waar was ik zonder jou. Jij hebt me gestimuleerd om deze stap te wagen en wat riep je vaak bij weer een publicatie: 'Ik word toch maar huisman'. Je hebt er veel voor over gehad, want de laatste 1,5 jaar heb je veel avonden aaneen jezelf moeten vermaken. Ik beloof je dat het komend jaar echt vaker een gezellig avondje op het balkon wordt of ergens op het terras in het mooie Wenen. Lieve Norah, mama's 'meissie', je snapt er waarschijnlijk nog niks van, maar mama is je ontzettend dankbaar. De laatste 1,5 jaar heb ook jij je heel wat ochtenden zelf moeten vermaken, terwijl mama hard aan het werk was in de studeerkamer. Afgezien van een keer brandje stoken in de keuken, ben je heel braaf geweest, dikke kus! En dan als allerlaatste een dikke knuffel voor mijn kleine lieve kereltje, Ruben. Alsof je het aanvoelde dat mama klaar was met schrijven, want tot dat moment sliep je heerlijk 's avonds en 's nachts door en daarna was het over.

CURRICULUM VITAE

Henrike Kos was born on January 18, 1979 in Zeist, the Netherlands. In 1997, she completed her secondary eductation (VWO) at Van Lodenstein college in Amersfoort. From 1997 to 2002 she studied Nutrition and Epidemiology at Wageningen University. She obtained her MSc degree in 2002 with two theses, one on the influence of GSTM1-genotype in the association between vegetable consumption and colorectal adenomas at Wageningen University and one on validation of a 24-hour activity recall to measure physical activity of pregnant women in rural Bangladesh at the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh. In December 2002, she started working as an epidemiologist at the Comprehensive Cancer Centre North in Groningen (now called Comprehensive Cancer Centre the Netherlands, location Groningen) where she worked mainly on the following two projects: the effect of surgery of by consultant gynaecologist oncologist on survival in ovarian cancer patients and the effect of latent Epstein-Barr virus infection of tumour cells and HLA class II expression by Hodgkin Reed-Sternberg cells on survival in Hodgkin's lymphoma patients. Between November 2005 and February 2007 she worked for three months as an epidemiologist at the municipal health service Amstelland- de Meerlanden in Amstelveen and for one year as epidemiologist at the Comprehensive Cancer Centre West in Leiden (now called Comprehensive Cancer Centre the Netherlands, location Leiden). In Leiden she worked mainly on a project which studied the effect of centralisation of oesophageal cancer surgery on prognosis of oesophageal cancer patients. In March 2007, she started a PhD project on progress against cancer in the Netherlands at the Department of Public Health of Erasmus MC under supervision of prof. dr. Jan Willem Coebergh, dr. Esther de Vries and prof. dr. Bart Kiemeney (Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre), resulting in this thesis.

Since September 2005 she is married with Reza Karim and in February 2010 their daughter Norah was born, in January 2012 followed by their son Ruben.

LIST OF PUBLICATIONS

Publications in this thesis

1. **Karim-Kos HE**, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer.* 2008;44(10):1345-1389.
2. **Karim-Kos HE**, Janssen-Heijnen ML, van Iersel CA, van der Meer RM, de Vries E, Coebergh JW. The beginning of the end of the lung cancer epidemic in Dutch women? *Int J Cancer.* 2008;123(6):1472-1475.
3. **Karim-Kos HE**, van Altena AM, Massuger LFHG, Mourits MJE, Coebergh JWW, de Vries E. Progress against ovarian cancer in the Netherlands: decreased incidence and mortality due to previous changes in risk factors, coinciding with improved survival. (submitted).
4. Cremers RG, **Karim-Kos HE**, Houterman S, Verhoeven RH, Schröder FH, van der Kwast TH, Kil PJ, Coebergh JW, Kiemeney LA. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. *Eur J Cancer.* 2010;46(11):2077-2087.
5. van Altena AM, **Karim-Kos HE**, de Vries E, Kruitwagen RF, Massuger LF, Kiemeney LA. Trends in therapy and survival of advanced stage epithelial ovarian cancer patients in the Netherlands. *Gynecol Oncol.* 2012;125(3):649-654.
6. Engelen MJ, **Kos HE**, Willemse PH, Aalders GJ, de Vries EG, Schaapveld M, Otter R, van der Zee AG. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer.* 1 2006;106(3):589-598.
7. Wouters MW, **Karim-Kos HE**, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, Tilanus HW, Tollenaar RA. Centralization of esophageal cancer surgery: does it improve clinical outcome? *Ann Surg Oncol.* 2009;16(7):1789-1798.
8. **Karim-Kos HE**, Kiemeney LA, Louwman MW, Coebergh JW, de Vries E. Progress against cancer in the Netherlands since the late 1980s: an epidemiological evaluation. *Int J Cancer.* 15 2012;130(12):2981-2989.
9. de Vries E, **Karim-Kos HE**, Janssen-Heijnen ML, Soerjomataram I, Kiemeney LA, Coebergh JW. Explanations for worsening cancer survival. *Nat Rev Clin Oncol.* 2010;7(1):60-63.

Publications from the project 'Progress against cancer in the Netherlands since the 1970s?'

10. van der Aa MA, de Kok IM, Kruitwagen RF, Jobsen JJ, **Karim-Kos HE**, Coebergh JW. Improvements in treatment and survival of cervical cancer in the Netherlands, 1989-2009. (in preparation).
11. Boll D, **Karim-Kos HE**, Verhoeven RHA, Liu L, van de Poll-Franse LV, Burger CW, Coebergh JW, van Doorn HC. Progress against endometrial cancer in the Netherlands since the 1970s: incidence, survival and mortality. (in preparation).
12. Dassen AE, Bosscha K, Dikken JL, Wouters MW, van de Velde CJ, Coebergh JW, Lemmens VE. Trends in incidence and survival of gastric cancer in the Netherlands 1989-2009: a nation-wide population-based study. (in preparation).
13. van Dijk BA, **Karim-Kos HE**, Coebergh JW, Marres HM, de Vries E.. Diverging trends in incidence and mortality of laryngeal cancer by gender in the Netherlands: decreases for males, increasing for females.(in preparation).
14. Husson O, Haak HR, van Steenbergen LN, Nieuwlaat W-A,van Dijk BA, Nieuwenhuijzen GA, **Karim-Kos HE**, Kuijpens J, van de Poll-Franse LV, Coebergh JW. Trends in incidence and survival of and mortality from thyroid cancer in the Netherlands since 1989. (in preparation).
15. Verhoeven RH, **Karim-Kos HE**, Coebergh JW, Brink M, Horenblas S, de Wit R, Kiemeney LA. Markedly increased incidence and improved survival of testicular cancer in the Netherlands. (submitted).
16. de Vries RR, Visser O, **Karim-Kos HE**, Kiemeney LA, Horenblas S. Trends in incidence and survival among Dutch bladder cancer patients: a population-based study between 1989-2009. (submitted).
17. Arnold M, Wildeman MA, Visser O, **Karim-Kos HE**, Middeldorp JM, Fles R, Bing Tan I, Coebergh JW. Lower mortality from nasopharyngeal cancer in the Netherlands since 1970 with differential incidence trends in histopathology. *Oral Oncol.* (in press).
18. Faiz Z, Lemmens VEPP, Siersma PD, Nieuwenhuijzen GA, Wouters MW, Rozema T, Coebergh JW, Wijhoven BP. Increased resection rates and survival among patients with esophageal cancer aged 75 years and older with esophageal cancer: a Dutch nationwide population-based study. *World J Surg*. (in press).
19. Kuijpens JH, Louwman MW, Peters R, Janssens GO, Burdorf AL, Coebergh JW. Trends in sinonasal cancer in the Netherlands: more squamous cell cancer, less adenocarinoma: a population-based study 1973-2009. *Eur J Cancer.* (in press).

20. Witjes CD, **Karim-Kos HE**, Visser O, de Vries E, IJzermans JN, de Man RA, Coebergh JW, Verhoef C. Intrahepatic cholangiocarcinoma in a low-endemic area: rising incidence and improved survival. *HPB*. (in press).
21. Boll D, Verhoeven RH, van der Aa MA, Pauwels P, **Karim-Kos HE**, Coebergh JW, van Doorn HC. Incidence and survival trends of uncommon corpus uteri malignancies in the Netherlands, 1989-2008. *Int J Gynecol Cancer.* 2012;22(4):599-606.
22. van den Broek EC, Kater AP, van de Schans SA, **Karim-Kos HE**, Janssen-Heijnen ML, Peters WG, Nooijen PT, Coebergh JW, Posthuma EF. Chronic lymphocytic leukaemia in the Netherlands: trends in incidence, treatment and survival, 1989-2008. *Eur J Cancer. 2012*;48(6):889-895.
23. Dikken JL, Lemmens VE, Wouters MW, Wijhoven BP, Siersema PD, Nieuwenhuijzen GA, van Sandick JW, Cats A, Verheij M. Coebergh JW, van de Velde CJ. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands. *Eur J Cancer* 2012;48(11):1624-1632.
24. van der Drift MA, **Karim-Kos HE**, Siesling S, et al. Progress in standard of care therapy and modest survival benefits in the treatment of non-small cell lung cancer patients in the Netherlands in the last 20 years. *J Thorac Oncol.* 2012;7(2):291-298.
25. Hollestein LM, van den Akker SA, Nijsten T, **Karim-Kos HE**, Coebergh JW, de Vries E. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Ann Oncol.* 2012;23(2):524-530.
26. Janssen-Heijnen ML, **Karim-Kos HE**, van der Drift MA, et al. Modest improvements of survival for patients with small cell lung cancer aged 45 to 59 years only, diagnosed in the Netherlands, 1989 to 2008. *J Thorac Oncol*. 2012;7(1):227-232.
27. Nienhuijs SW, van den Akker SA, de Vries E, de Hingh IH, Visser O, Lemmens VE. Nationwide improvement of short-term survival after resection for pancreatic cancer in The Netherlands. *Pancreas* 2012;41(7):1063-1066.
28. van de Schans SA, Aben KK, Mulders PF, Haanen JB, van Herpen C, Verhoeven RH, **Karim-Kos HE**, Oosterwijk E, Kiemeney LA. Modest improvement in 20 years of kidney cancer care in the Netherlands. *Eur J Cancer.* 2012;48(12):1822-1830.
29. van de Schans SA, Issa DE, Visser O, Nooijen P, Huijgens PC, **Karim-Kos HE**, Janssen-Heijnen ML, Coebergh JW. Diverging trends in incidence and mortality, and improved survival of non-Hodgkin's lymphoma, in the Netherlands, 1989-2007. *Ann Oncol.* 2012;23(1):171-182.

30. Witjes CD, **Karim-Kos HE**, Visser O, van den Akker SA, de Vries E. IJzermans JN, de Man RA, Coebergh JW, Verhoef C. Hepatocellular carcinoma in a low-endemic area: rising incidence and improved survival. *Eur J Gastroenterol Hepatol.* 2012;24(4):450-457.
31. Witjes CD, van den Akker SA, Visser O, **Karim-Kos HE**, de Vries E, IJzermans JN, de Man RA, Coebergh JW, Verhoef C. Gallbladder Cancer in the Netherlands: Incidence, Treatment and Survival Patterns since 1989. *Dig Surg.* 2012;29(2):92-98.
32. Asadzadeh Vostakolaei F, **Karim-Kos HE**, Janssen-Heijnen ML, Visser O, Verbeek AL, Kiemeney LA. The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival. *Eur J Public Health.* 2011;21(5):573-577.
33. de Kok IM, van der Aa MA, van Ballegooijen M, Siesling S, **Karim-Kos HE**, van Kemenade FJ, Coebergh JW. Trends in cervical cancer in the Netherlands until 2007: has the bottom been reached? *Int J Cancer.* 2011;128(9):2174-2181.
34. Siesling S, Visser O, Luth TK, **Karim-Kos HE**, van de Poll-Franse LV, Aben KK, Damhuis RA. [Adult cancer patients are surviving longer in the Netherlands: 5-year survival rate increased by 12% between the periods 1989-1993 and 2004-2008]. *Ned Tijdschr Geneeskd.* 2011;155:A3169.
35. Elferink MA, van Steenbergen LN, Krijnen P, Lemmens VE, Rutten HJ, Marijnen CA, Nagtegaal ID, **Karim-Kos HE**, de Vries E, Siesling S. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989-2006. *Eur J Cancer.* 2010;46(8):1421-1429.
36. van Steenbergen LN, Elferink MA, Krijnen P, Lemmens VE, Siesling S, Rutten HJ, Richel DJ, **Karim-Kos HE**, Coebergh JW. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. *Ann Oncol.* 2010;21(11):2206-2212.
37. **Karim-Kos HE**, Janssen-Heijnen ML, van Iersel CA, van der Meer RM, de Vries E, Coebergh JW. [The beginning of the end of the lung cancer epidemic among Dutch women]. *Ned Tijdschr Geneeskd.* 2008;152(26):1473-1477.

Contributed to report from the Signaleringscommissie Kanker van KWF Kankerbestrijding. *[Cancer in the Netherlands up to 2020, trends and prognosis]* Amsterdam: Dutch Cancer Society; 2011.

Other publications

38. Diepstra A, van Imhoff GW, Schaapveld M, **Karim-Kos H**, van den Berg A, Vellenga E, Poppema S. Latent Epstein-Barr virus infection of tumor cells in classical Hodgkin's lymphoma predicts adverse outcome in older adult patients. *J Clin Oncol.* 2009;27(23):3815-3821.
39. van der Zee AG, Engelen MJ, Schaapveld M, **Karim-Kos HE**, de Vries EG, Willemse PH, Otter R. [Primary surgery by a gynecological oncologist improves the prognosis in patients with ovarian carcinoma]. *Ned Tijdschr Geneeskd.* 2009;153(1-2):15-19.
40. Wouters MW, Wijnhoven BP, **Karim-Kos HE**, et al. High-volume versus low-volume for esophageal resections for cancer: the essential role of case-mix adjustments based on clinical data. *Ann Surg Oncol.* 2008;15(1):80-87.
41. Diepstra A, van Imhoff GW, **Karim-Kos HE**, et al. HLA class II expression by Hodgkin Reed-Sternberg cells is an independent prognostic factor in classical Hodgkin's lymphoma. *J Clin Oncol.* 2007;25(21):3101-3108.

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Henrike Karim-Kos	PhD period: March 2007 – December 2011
Erasmus MC Department: Public Health	Promotors: Prof. dr. J.W.W. Coebergh / Prof.dr. L.A.L.M. Kiemeney
	Co-promotor: Dr. E. de Vries

1. PhD training

	Year	Workload (Hours/ECTS)
Courses		
– Relative survival: approaches to advanced modelling, London School of Hygiene & Tropical Medicine, London	2007	28 hours (1.0 ECTS)
– Cancer epidemiology, Netherlands Institute for Health Sciences (NIHES), Amsterdam	2007	40 hours (1.4 ECTS)
– Planning and evaluation of screening, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2007	40 hours (1.4 ECTS)
– Conceptual foundation of epidemiologic study design, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2007	20 hours (0.7 ECTS)
– Introduction to decision making in medicine, Netherlands Institute for Health (NIHES), Rotterdam	2007	20 hours (0.7 ECTS)
– Career development, Federatie van medisch wetenschappelijke verenigingen (FEDERA), Utrecht	2008	4 hours (0.1 ECTS)
– Basic didactic course, Onderwijs Expertise Centrum Rotterdam (OECR)/RISBO, Rotterdam	2008	84 hours (3 ECTS)
– Docententraining voor Vaardigheidsonderwijs, dept Public Health, Erasmus MC, Rotterdam	2008	4 hours (0.1 ECTS)
– Biomedical English writing and communication	2008	112 hours (4 ECTS)
– Principles of Epidemiologic Data-analysis, Netherlands Institute for Health Sciences (NIHES), Lunteren	2008	40 hours (1.4 ECTS)
– Advanced analysis of prognosis studies, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2009	25 hours (0.9 ECTS)
– Ethnicity, health and health care, Netherlands Insitute for Health Sciences (NIHES), Rotterdam	2009	32 hours (1.1 ECTS)
– Health Status Measurements, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2009	28 hours (1.0 ECTS)
– Principles of genetic epidemiology, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2009	20 hours (0.7 ECTS)

Seminars and workshops		
– Seminars of the department Public Health, Rotterdam	2007-2010	100 hours (3.6 ECTS)
– Seminars Netherlands Cancer Registry, Utrecht	2007-2010	16 hours (0.6 ECTS)
– PhD day, Erasmus MC, Rotterdam	2008	8 hours (0.3 ECTS)
– Federatie van medisch wetenschappelijke verenigingen (FEDERA) day, Leiden	2008	8 hours (0.3 ECTS)
– Vereniging van Integrale Kanker Centra (VIKC) research day	2009	8 hours (0.3 ECTS)
Presentations		
– Oral presentations within the project 'Progress against cancer in the Netherlands since the 1970s?'	2008-2010	200 hours (7 ECTS)
– Oral presentation, Research meeting dept Public Health, Erasmus MC, Rotterdam	2008	32 hours (1.1 ECTS)
– Poster presentation WEON, Groningen	2008	32 hours (1.1 ECTS)
– Poster presentation WEON, Amsterdam	2009	32 hours (1.1 ECTS)
– Poster presentation ECCO/ESMO congress, Berlin	2009	32 hours (1.1 ECTS)
– Oral presentation Research meeting Netherlands Cancer Registry, Utrecht	2009	20 hours (0.7 ECTS)
– Oral presentation Lustrum symposium Netherlands Cancer Registry, Utrecht	2011	32 hours (1.1 ECTS)
(Inter)national conferences		
– Werkgroep Epidemiologisch Onderzoek Nederland (WEON), Groningen/Amsterdam	2008-2009	64 hours (2.2 ECTS)
– ECCO 15 – 34th ESMO Multidisciplinary Congress, Berlin	2009	36 hours (1.3 ECTS)
Other		
– Member of the working group ´Monitoring van Kanker in Nederland´ from the Dutch Cancer Society	2010-2011	40 hours (1.4 ECTS)
2. Teaching		
Lecturing		
– Curriculum medical students, 4th year, Theme 4.2: 'De populatie als patiënt?'	2009	20 hours (0.7 ECTS)
Supervising practicals and excursions, Tutoring		84 hours (1.5 ECTS)
– Curriculum medical students, 4th year, Theme 4.2: 'Kanker in Nederland: de populatie als patiënt?'	2008-2009	
Total	**1261 hours (42.9 ECTS)**	