Variation in incidence and outcome of cervical cancer in the Netherlands

Studies based on cancer registry data

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Variation in Incidence and Outcome of Cervical Cancer in the Netherlands

Studies based on cancer registry data

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Studies gebaseerd op data van de kankerregistratie

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Chapter 1

Introduction

1.1 Epidemiology of cervical cancer

Worldwide, cancer of the cervix uteri is the second most common cancer in women, accounting for 15% of all malignancies. The incidence and mortality rates vary between countries, the highest rates being recorded in the developing countries (figure 1) [1]. In Europe, variation between countries is higher in incidence than in mortality. In 2002, age-standardized incidence rates varied between the lowest rate 4.3 per 100,000 person-years in Finland and the highest of 27.4 per 100,000 person-years in Serbia and Montenegro. Age-standardized mortality rates varied between 1.6 per 100,000 person-years in Malta and 13.0 per 100,000 person-years in Romania [1].

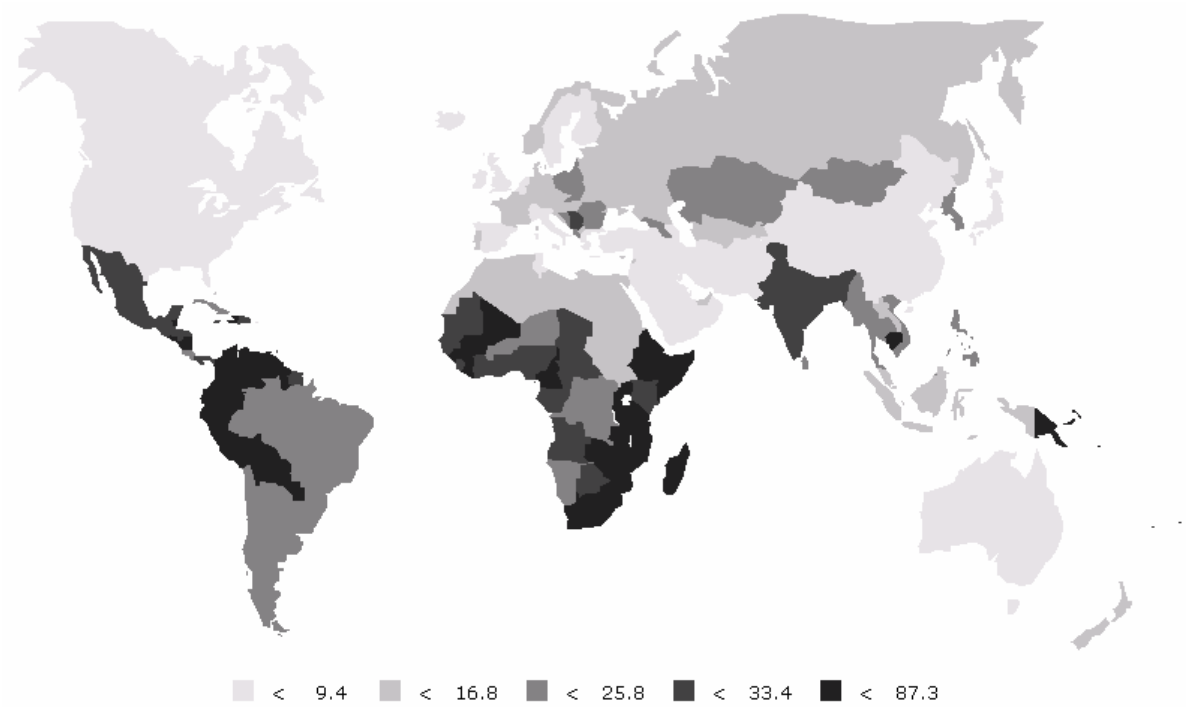

Figure 1 Incidence of cervical cancer worldwide, Globocan IARC 2002 [2]

In the Netherlands, approximately 2% of all newly diagnosed malignant tumours in women are cancers of the uterine cervix, corresponding to about 700 new cases of invasive carcinoma per year [3]. Putting this in perspective, cervical cancer is not in the top ten of most frequent cancers in the Netherlands: breast cancer is found yearly in 11,800 women, colon cancer in 4,750 women and lung cancer in 2,900 women. A general practitioner sees cervical cancer only once in 15 years. Every year about 250 women die from cervical cancer, which is about 1.5% of all deaths in women caused by cancer [3,4].

There are two main types of cervical cancer: squamous cell carcinoma (accounting for 90-95% of all cervical cancers) and adenocarcinoma, or glandular cell carcinoma (accounting for 5-10% of all cervical cancers) [4;5]. Each is named according to the type of cells from which the cancer develops. In particular, the development of squamous cell cervical cancer is an example of a classic multistage disease beginning with the acquisition of preinvasive lesions. Preinvasive lesions may regress, persist, or progress into invasive carcinoma. Higher grade lesions are more likely to persist or progress and spontaneous regression is infrequent (seen in 28%), while low-grade lesions often regress (seen in 90%) without treatment [6;7].

It is now well established that human papillomavirus (HPV) infection is the central causal factor in cervical cancer [8;9]. HPV is a common sexually transmitted infection and both women and men are exposed to the virus after the onset of sexual intercourse. The risk of infection with HPV and thus the risk of cervical cancer increases with the number of sexual partners, age at first intercourse and promiscuity of male partners [8;10].

Cervical cancer in the Netherlands is mostly a problem of the lower socioeconomic class, including migrants [11-13]. The main explanations for the excess risk among lower socioeconomic groups are social circumstances leading to the greater chance to acquire the human papillomavirus (HPV) and/or become chronic carriers of HPV. Currently, 15 HPV types are considered to be oncogenic of which HPV16, HPV18, HPV31 and HPV33 are the most important types [8]. In the Netherlands the proportions of the lowest social strata tend to be largest in the cities: the well-to-do people generally prefer living outside of the cities. Furthermore, the incidence of cancer in general is higher in areas with high population density [14], which in cervical cancer is partly related to lower participation in the mass screening programme [15;16]. Regional differences in the incidence of cervical cancer therefore exist within the Netherlands with the highest incidence rates of cervical cancer in the areas with the highest proportions of people with low SES. These regional differences are very well visualised in maps which can be found on www.ikcnet.nl.

1.2 Early detection and screening

Since the introduction in 1928 of a cervical smear test by George Papanicolaou (Pap smear), cervical cytology has become the main diagnostic tool for detecting (pre-invasive) cervical cancer [17].

Therefore the use of the Pap smear test can prevent the progression to invasive cervical cancer and thus can result in a decline in incidence and mortality. Local

and national population-based cervical cancer screening programmes based on Pap smear testing have therefore been introduced in the past 30 to 50 years in many countries, including Canada, the United States, UK and several Nordic countries (Sweden, Iceland, Finland) [18-21]. Even though not tested in randomised controlled trials, many of these programmes have proven to be effective in reducing both morbidity and mortality from cancer of the uterine cervix. A high level of participation and adequate follow-up examinations after initial cytological abnormalities are crucial for a population-based screening programme to be effective. In Europe only six countries have invitational programmes and nine countries only invite those women who had not had a smear recently [21]. Smear test coverage was above 75% of the target population during the recommended screening interval in the screening programmes of Finland, Sweden, United Kingdom, Denmark, Iceland and the Netherlands. These countries, except Denmark, are among the countries with the lowest incidence of and mortality from cervical cancer in Europe.

Screening in the Netherlands has been started in 1976 with a pilot study in 3 regions (Nijmegen, Rotterdam and Utrecht), which covered 24% of the Dutch female population. Women aged 35 to 54 were invited centrally by one institution and smear-taking took place in mobile screening units by specially trained nurses. Soon afterwards, further cervical screening projects were developed and opportunistic screening (screening offered outside the organized screening programme, initiated by the woman involved or her physician) by General Practitioners (GPs), gynaecologists and midwives was also performed.

A nationwide screening programme started in 1989 for women aged 35 to 54, who were screened at three-year intervals, with GPs taking the smear [22]. Organization was primarily community-based, because experiences in the Nordic countries indicated that screening works best under community-based organizations, with individual invitations to each woman [18;23]. If a smear was abnormal, the laboratory notified the GP to arrange the follow-up.

In the early 1990s in the Netherlands, evaluation of the screening programme pointed evidently towards a suboptimal performing program, in terms of both the organization and the cost of screening of the target population. Therefore screening activities were restructured in 1996 and from then on women between 30 and 60 years old were screened at five year intervals, leaving the number of seven invitations during a lifetime unchanged [24;25]. In the last decades there have been many studies on improvements of the mass screening programme for cervical cancer, including extending the age interval to be screened, adding an HPV test to conventional cytology, the development of other screening tests which claim to have higher sensitivity and/or specificity for detecting high grade

lesions and so on [26-29]. In the long run, the discussion about screening may change with the introduction of HPV vaccines (Gardasil and Cervarix) [30].

1.3 Treatment

Until the 1980's, radiotherapy was the standard treatment of choice for all stages of cervical cancer. In the last few decades, many different approaches to the improvement of clinical practice have been tried with mainly the emerging of surgery in the smaller tumours.

Guidelines for the treatment of cervical cancer have been made and provide clinicians with evidence-based recommendations for every day practice and aim for increasing the efficiency of care and decreasing the variation in performance between professionals.

Cervical cancer is clinically staged according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification. According to the national guidelines of 1990, the primary treatment of choice for FIGO stage IB and IIA, radical hysterectomy or primary radiotherapy, should be based on age and contra-indications for surgery.

Table 1 Treatment of cervical cancer in the Netherlands per FIGO stage, according to the national guidelines of 2004

FIGO stage	Treatment
IA1	Conisation in case of wish for children or simple hysterectomy in case of no wish for children
IA2	Conisation of simple hysterectomy in the absence of unfavourable prognostic factors. Pelvic lymphadenectomy after conisation or radical hysterectomy in case of wish for children and pelvic lymphadenectomy in case of no wish for children
IB1 and IIA	Radical hysterectomy and pelvic lymphadencetomy or primary radiotherapy
IB2, IIB-IVA	Chemoradiation or radiotherapy and hyperthermia
IVB	Individualisation

Radiotherapy was the primary treatment of choice for FIGO stages IIB-IVA [31]. In 1999 the National Cancer Institute (NCI) released an announcement which stated that strong consideration should be given to adding chemotherapy to radiation therapy in the treatment of invasive cervical cancer. This statement

was based on five clinical trials which demonstrated superiority of combined platinum-based chemoradiation over radiotherapy alone for patients with high risk and/or locally advanced cervical cancer [32-36]. Furthermore, in 2002, a 3-year overall improvement of 27-51% was found for the survival of patients with FIGO stages IIB-IVA receiving radiotherapy combined with hyperthermia in a Dutch trial [37]. According to the national guidelines, which were implemented in 2004, patients with FIGO stages IB2 and IIB-IVA should now be given chemoradiation or radiotherapy combined with hyperthermia (table 1) [38].

1.4 Scope and outline: major study questions

The objectives which form the starting point of this thesis are to provide insight into:

Geographical differences in incidence and mortality of cervical cancer within the Netherlands and another, comparable, industrialised country

Differences in incidence and mortality from cervical cancer in relation to SES and other sociodemographic factors are described in chapter 3.1. Differences and trends in incidence and mortality from cervical cancer in relation to the mass screening programmes between Finland and the Netherlands are described in chapter 3.2.

The effectiveness and changing of screening programmes

The national mass screening programme is the main subject in chapter 4.1 which examines the effectiveness of the programme at regional level and also in chapter 4.2 which concerns a discussion about the age range to be screened, i.e. should the screening age for cervical cancer be lowered in the Netherlands?

Trends in treatment and survival in two regions in the Netherlands and the relationship with comorbidity and adherence to treatment guidelines

Changes and variation in stage, treatment and survival in cervical cancer of patients diagnosed in the period 1989 to 2004 in the regions of the Comprehensive Cancer Centre Stedendriehoek Twente (CCCST) and the Comprehensive Cancer Centre South (CCCS) in the Netherlands are described in chapter 5.1. The age-specific prevalence of co-morbid conditions in cervical cancer and the effects of co-morbidity on treatment modalities chosen are described in chapter 5.2.

Incidence of and mortality from uncommon tumours in the cervix and vagina

Little is known about the incidence of uncommon tumours in the vagina and cervix and therefore chapter 6.1 is a study on these rare cancers.

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Chapter 2

Populations, patients and methods

2.1 Populations

The Netherlands has 16.3 million inhabitants, of which 50.5% are female and 49.5% are male [1]. The territory of the Netherlands covers 41,574 km^2, 7,636 of which are water. Population density in the Netherlands is very high and among the highest in Europe: 483 per km^2 of land. The population is not evenly distributed throughout the country. The western part of the country with the three major cities Amsterdam, The Hague and Rotterdam has the highest population density. In 2006, the percentage inhabitants aged 65 or older was 14.3 and this percentage is growing rapidly. Immigration has changed the structure of the population during the last decades, especially in the larger cities. In 2006, immigrants constituted 19.3% of the total population. There are 104 hospitals in the Netherlands: 86 general hospitals, eight academic hospitals and ten specialised centres (e.g. cancer hospitals and rehabilitation centres). Radiotherapy is provided by the university and cancer hospitals as well as 12 regional institutes that serve combinations of community hospitals. The pathologists work in about 65 laboratories, which enter all diagnoses into a nationwide computer system (PALGA) that also notifies the regional cancer registries.

The region of the Comprehensive Cancer Centre Stedendriehoek Twente has 1.2 million inhabitants. In 2006, the percentage inhabitants aged 65 or older was 15.2 and immigrants constituted 14.7% of the total population. The region is served by seven general hospitals and two large radiotherapy institutes. The area does not enclose university or specialized cancer hospitals. There are three pathology laboratories.

The region of the Comprehensive Cancer Centre South, the Eindhoven Cancer Registry, has 2.3 million inhabitants and 14.2% is 65 years or older. The constitution of immigrants is 15.3% of the total population. The area of the Eindhoven Cancer Registry is now served by ten general hospitals at sixteen locations and two large radiotherapy institutes. The area does not enclose university or specialized cancer hospitals. There are six pathology laboratories.

Finland has 5.2 million inhabitants, of which 51.0% are female and 49.0% are male. Finland covers 338.145 km^2, of which 9.4% is water resulting in only 15.5 inhabitants per km^2, Finland is one of the less urbanised countries in Europe, with most of the people living in the southern part of the country. In 2004, 15.3% of inhabitants were aged 65 years or older [2]. Immigrants constituted 0.4% of the total population in 2006 [3]. Finland has five university hospitals, fifteen central hospitals and for about 40 smaller ‘district’ hospitals. The pathologists work in 70 laboratories from which cancer notifications are received. All university hospitals and seven central hospitals have radiotherapy units.

2.2 Patients

Cancer registries

In the Netherlands, nine regional cancer registries yearly submit their data to the Netherlands Cancer Registry (NCR), which is a population-based nationwide cancer registry since 1989 (figure 1). The registration in the Netherlands began in the region of the Eindhoven Cancer Registry in 1955 and was followed by the other regions during the 1980s. The nine regional cancer registries receive lists of newly diagnosed cases on a regular basis from PALGA and haematology departments in their region. Another source is the national registry of hospital discharge diagnosis (LMR), which accounts for up to 8 percent of new cases [4].

Figure 1 Regions of the Comprehensive Cancer Centres

Solely patients diagnosed and treated by the general practitioner only, outpatients without pathological diagnosis and patients diagnosed and treated abroad will generally be missed. Therefore, completeness of the registry is high: more than 95% of all malignancies are recorded [5]. Death certificates are not available to the cancer registries because of privacy regulations. A minimum data set which includes patient identification information and tumour and treatment information is collected by specially trained registration clerks. Some regional cancer registries collect optional items like co-morbidity. Coding of the items is based on international coding rules to facilitate international comparisons of cancer data. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICDO) [6]. For the staging of tumours the TNM classification is used [7].

The Finnish Cancer Registry (FCR) is a population-based nationwide cancer registry established in 1952, registration began in 1953. The FCR receives data on cancer cases from hospitals, health centres, medical practitioners, and pathological and cytological laboratories. It also receives information about all death certificates which mention cancer. The file of all deaths occurring in Finland is checked annually against the files of the FCR.

2.3 Methods

Population-based registry data

Clinical studies or randomized clinical trials (RCTs) are accepted as the most valid method for determining the efficacy of a therapeutic intervention, because the biases associated with other study designs can be avoided. However, it has been suggested that the usefulness of RCTs is often limited because of a lack of generalisability of the results, the difficulty of performing RCTs, the length of follow-up which is sometimes required and selection bias which cannot be excluded due to referral policies. This problem can be avoided by using data from a population-based registry, i.e. a systematic collection of data on all malignant neoplasms occurring in a geographically defined population. Other advantages of population-based studies are 1) they allow the estimation of distributions and prevalence rates of relevant variables in the reference population, 2) risk factor distributions measured at baseline can be compared with distributions in future cross-sectional samples to assess risk factor trends over time and 3) they are ideal to carry out unbiased evaluations of relations, not only of confounders to exposures and outcomes, but also among any other variables of interest. The most important disadvantage is that selection bias can not completely be ruled out because a cohort still is a defined population and generalisability to other populations may therefore be difficult sometimes. All the studies presented in this thesis are based on data collected by population based cancer registries.

Staging of the tumours

FIGO stage is not registered in the cancer registry as a separate item. Since FIGO stage for cervical cancer is a clinical stage it can be derived from the clinical TNM stage (cTNM) (table 1) [7]. In case of an unknown cTNM, FIGO stage was derived from the pathological TNM stage (pTNM). Clinical staging of cervical cancer has the disadvantage that tumour size and lymph node involvement can not be assessed adequately. Next to this, gynaecologists as well as registration clerks have to code according to available data which can be hard. For example: a woman who is clinically staged being diagnosed with FIGO IB1, may after surgery be staged as having stage IIA. Registration clerks, and of course also the gynaecologists, have to code this as IB1 although they know that this is not the ‘real’ stage.

Lymph node status is not included in the FIGO classification for cervical carcinoma, and therefore it was described separately. National coding rules allow registration clerks to give only a positive or negative clinical lymph node status when a CT-scan of the pelvis has been performed. When there is no

information about a CT-scan in the patient file, registration clerks have to code clinical lymph node status as unknown. In case of an unknown cN, the pN was taken. More information on the registration procedures can be found on www.ikcnet.nl.

Table 1 Description of cTNM and FIGO stage

cTNM	FIGO	Description
Tis	0	Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy
T1a1	IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4 cm in greatest dimension
T2	II	Tumour invaded beyond uterus but not to pelvic wall or to lower third of the vagina
T2a	IIA	Without parametrial invasion
T2b	IIB	With parametrial invasion
T3	III	Tumour extends to pelvic wall and/or involves the lower third of vagina and/or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumour involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumour extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumour invades mucosa of bladder or rectum and/or extends beyond true pelvis
M1	IVB	Distant metastasis

Co-morbidity

To explore the increasing complexity of oncological care in a greying population, serious co-morbidity with prognostic impact at time of diagnosis has been recorded for all patients since 1993 in the region of the CCCS, according to a slightly modified version of the Charlson index (table 2) [8]. Information on co-morbidity is obtained by previous admissions, letters from and to other specialists, the medical history and preoperative screening. Co-morbidity was

defined as diseases that were present at the time of cancer diagnosis and could affect prognosis independently of the cancer.

Table 2 Classification of co-morbidity, according to an adapted list of Charlson et al. [8]
Previous malignancies (except basal cell skin carcinoma and cervix carcinoma in situ)
Chronic obstructive pulmonary diseases
Cardiovascular diseases - Myocardial infarction - Heart failure - Angina pectoris - Intermittent claudication - Abdominal aneurysm - Cardiomyopathy - Valve prothesis (aorta or mitralis)
Cerebrovascular diseases - Cerebrovascular accident - Hemiplegia
Hypertension
Digestive tract diseases - Ulcerative disease (only registered since 1997) - Patients who underwent major surgery for ulcerative disease (Billroth I or II) - Chronic inflammatory diseases (Crohn's disease, ulcerative colitis except polyposis coli)
Liver disease (cirrhosis, hepatitis)
Diabetes mellitus
Other - Urinary tract diseases - Connective tissue diseases (rheumatoid arthritis) - Dementia - Chronic infections (HIV, TBC)

Socioeconomic status

The socioeconomic status (SES) scores for each six- and four-digit postal code area, provided by the "Sociaal Cultureel Planbureau" (a governmental organization), are based on the following items which were collected per six-digit postal code: 1) mean income per household, 2) the percentage of households with a low income, 3) the percentage of households with a low education [9]. The SES scores at the six-digit postal code level were used as follows: in three collective SES-codes which were based on deciles: 1=1st-3rd decile, 2=4th-7th decile and 3=8th-10th decile. The variables at the six-digit level were aggregated

to the four-digit level. After aggregation, the variables were merged into one score by means of factor analysis (principal components analysis). A rank number (1-9) given to each postal code region was used as the SES. SES at the four-digit level was divided into three groups based on the delivered rank numbers: 1=rank number 1-5 (SES score lower than mean SES score in the Netherlands), 2=rank number 6 (mean SES score of the Netherlands) and 3=7-9 (SES score higher than mean SES score in the Netherlands).

Data-analysis

Incidence and mortality trends

Incidence and mortality rates per 100,000 person-years were calculated age-adjusted to the World Standard Population (Word Standardized Rates, WSR). The Estimated Annual Percentage Change (EAPC) was used as an estimate of the trend. Using calendar year as a regression variable, a regression line is fitted to the natural logarithm of the incidence rates, i.e. y=mx+b, where y=ln(rate) and x=calendar year. Then EAPC=100*(e m-1). Testing the hypothesis that the EAPC is equal to zero is equivalent to testing the hypothesis that the slope of the regression line is zero, using the t-distribution of m/SEm. The number of degrees of freedom equals the number of calendar years minus 2. The standard error of m, i.e. SEm, is obtained from the fit of the regression line. This calculation assumes that the rates increased/decreased at a constant rate over the entire period. Additionally joinpoint regression analysis was used to identify points which indicate a statistically significant change over time in linear slope of the trend. In joinpoint analyses, the best-fitting points where the rate changes significantly (increase of decrease) are chosen [10]. The analysis starts with the minimum number of joinpoints, and tests whether one or more joinpoints are statistically significant and should be added to the model (up to three joinpoints). In the final model, each joinpoint indicates a statistically significant change in trend. Significant changes include changes in direction or in the rate of increase or decrease. Joinpoint analyses were performed using the 'Joinpoint' software from the Surveillance Research Program of the US National Cancer Institute [11].

Mapping

To visualize geographical patterns in incidence of cervical cancer, WSRs were calculated for each of the 458 municipalities in the Netherlands and presented as maps. For cities with more than 100,000 inhabitants the rates were presented as such as circles on the maps. The radius of the circle indicates the size of the

population and the colour the WSR. On the colour scale each step between the categories corresponds to a 10% increase in the WSR.

The rates for the remaining municipalities were smoothed to prevent disturbing chance variations [12]. For each grid (size 2 by 2 km) a weighted average of the WSRs for the neighbouring areas within a 150 km radius was calculated to define the colour of that grid. The weights were associated directly with the population of the municipality and inversely with the distance. The weight for distance was halved at 25 km and reached zero at 150 km.

Survival

Vital status was available up to January 1st 2006 in the regions of the CCCS and CCCST. In addition to follow-up via the hospitals, this information was also obtained via the Municipality Administration Database (GBA), where all deceased and emigrated persons in the Netherlands are registered via the civil municipal registries.

Cox regression was used to model crude survival analyses. In Cox regression, variables were considered confounders and included in the model when the regression coefficient of the variable of interest changed by more than 10%.

Relative survival was calculated as a measure of disease-specific survival using the Ederer II method in STATA version 9.2 [13]. The relative survival is the ratio between crude and expected survival and is close to disease-specific survival. Relative excess risks (RER) and 95% confidence intervals (CI) were calculated. The relative excess risk (RER) describes the difference between the hazard of death in a given group and in the reference group, taking into account the risk of death in the Dutch population. In modeling relative survival using Poisson regression, variables were considered confounders and included in the model when the regression coefficient of the variable of interest changed by more than 10%.

Relative survival has the disadvantage that if not all of the excess mortality is due to the cancer then the relative survival ratio will underestimate survival. For example, relative survival of people with low SES with co-morbidity will be underestimated [14;15].

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Chapter 3

Distribution of cervical cancer

Chapter 3.1

Geographical relationships between sociodemographic factors and incidence of cervical cancer in the Netherlands 1989-2003

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Abstract

Background. In many industrialized countries with some degree of screening, cervical cancer nowadays is most frequent among women of lower socioeconomic status (SES), partly due to their lower participation in screening. This study aims to provide support for specification of mass screening policy for cervical cancer by describing relationships between sociodemographic factors and the incidence of cervical cancer in the Netherlands based on geographical differences and by analysing the relationship between SES of neighbourhood and individual tumour characteristics.

Methods. Municipality-specific age-adjusted incidence rates for cervical cancer were calculated from the Netherlands Cancer Registry, and data on sociodemographic factors obtained from Statistics Netherlands. Logistic regression analysis was performed to investigate determinants of variations in incidence at the ecological level. An additional analysis linked individual tumour characteristics to SES estimates at the postal code level by calculating relative risks.

Results. Incidence was higher in municipalities with a high prevalence of immigrants (OR 7.9, 1.4-47 95% CI) and with more individuals on welfare (OR 8.6, 1.7-43 95% CI). Patients residing in neighbourhoods with lower SES had higher FIGO stages (RR 1.4, 1.2-1.6 95% CI) and fewer adenocarcinomas (RR 0.7, 0.6-0.9 95% CI) and were younger at diagnosis ($p<0.001$).

Discussion. Cervical cancer is more common among women of lower SES and immigrant women. This, together with the finding that lower SES is associated with more advanced cancer and consequently worse survival, emphasizes the importance of future cervical cancer prevention programmes targeted at women of lower SES who do not participate in opportunistic screening.

Introduction

Cervical cancer is the most common cancer among women in developing countries. Of the at least 350,000 new cases of cervical cancer diagnosed worldwide, 80% occur in developing countries [1]. In the Netherlands (population 16.3 million), about 700 invasive cases are diagnosed annually and about 250 women die from it; these numbers are slowly declining. Cervical cancer predominantly affects women of lower socioeconomic status (SES) in industrialized and developing countries [1-6]. A consistent and inverse trend in cervical cancer incidence was found for various indicators of social class, such as low level of education, small income or low-ranked occupation [7].

The main explanations for the excess risk among lower socioeconomic groups are sexual behaviour and the greater chance to acquire and/or become chronic carriers of human papillomavirus (HPV), the most significant risk factor for cervical cancer. Currently, 13 HPV types, including 16, 18, 31 and 33 are considered to be oncogenic [8]. Since development of cervical cancer involves transitions from dysplasia to carcinoma in situ to invasive cancer, early detection and treatment of precancerous lesions is known to prevent the development of invasive cancer.

Cervical cancer screening was started in parts of the Netherlands in the mid 1970's, both opportunistic and pilot studies of screening programmes. In 1988 a national screening programme was implemented, which was revised in 1996 [9]. At the end of 1996, together with opportunistic screening, 80% of women 30-60 years old had had at least one smear taken in the previous five years. However, participation in each separate round of the population-based screening programme is lower and varies between 60% and 70% [10]. Ethnic group and urbanisation negatively influenced cervical cancer screening attendance rates in the USA, resulting in a higher incidence of advanced stage disease and consequently higher mortality among non-white women and women living in larger cities than for the average population [11-15].

This study aims to provide support for intensification and specification of the current mass screening policy for cervical cancer by revealing relationships between sociodemographic factors and the incidence of cervical cancer in the Netherlands on the basis of geographical differences. Analysis of the relationship between socio-economic status (SES) of the neighbourhood of residence and stage at the time of diagnosis, histological type and age at diagnosis also contributes to our understanding.

Methods

Cancer registration

All cervical cancer cases diagnosed between 1 January 1989 and 31 December 2003 were selected from the nationwide population-based Netherlands Cancer Registry (NCR). Notifications are obtained from the Pathology Automated Archive (PALGA) and Haematology Departments in the region. Other sources are the Radiotherapy Departments of the hospitals, as well as the National Registry of Hospital Discharge Diagnoses, which accounts for up to 8% of new cases [16]. Death certificates are not available in an identifiable form to the cancer registry due to privacy regulations. All data are obtained from patient files in the hospital and include identifying information (e.g. first letters of the name, date of birth, sex, postal code) and tumour characteristics (e.g. date of diagnosis, topography, morphology, stage). Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O) [17]. The TNM classification is used for the staging of the tumours [18]. FIGO stage was derived from the clinical TNM stage.

Although carcinoma in situ is registered in PALGA, it is not included in the NCR and consequently only cases of invasive cervical cancer were included in this study.

Mapping

World Standardized Incidence Rates (WSR) for cervical cancer were calculated for each of the 458 municipalities in the Netherlands. Maps showing cancer incidence were then made. For cities with more than 100,000 inhabitants the rates were presented as such as circles on the maps. The radius of the circle indicates the size of the population and the colour the WSR. On the colour scale each step between the categories corresponds to a 10% increase in the WSR.

The rates for the remaining municipalities were smoothed to prevent disturbing chance variations [19]. For each grid (size 2 by 2 km) a weighted average of the WSRs for the neighbouring areas within a 150 km radius was calculated to define the colour of that grid. The weights were associated directly with the population of the municipality and inversely with the distance. The weight for distance was halved at 25 km and reached zero at 150 km.

Municipality-specific data about population density, as well as proportions of immigrants and living on welfare were obtained from Statistics Netherlands and transformed into similar map format as the cancer incidence data [20].

Ecological analysis of sociodemographic factors and cancer incidence

Multivariate logistic regression analysis was performed to investigate which factors are associated with high incidence rates in municipalities, using Statistical Package for Social Sciences (SPSS) version 12.0. The average incidence rates per municipality over the whole period were determined and divided into quartiles. In the analysis, municipalities with the lowest incidence (first quartile) were compared to municipalities with the highest incidence (fourth quartile), using the lowest incidence as reference category. Data on population density, percentage of legal immigrants and use of social security at the municipality level were derived from Statistics Netherlands, divided into quintiles and entered into the model as dummy variables, using the lowest category as reference. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Analysis of the influence of ecological SES on individual tumour characteristics

In the analyses of SES versus individual tumour characteristics, postal code at time of diagnosis was used to determine ecological SES. SES scores are available for each of the 411,303 six-digit and 3,876 four-digit postal code areas in the Netherlands. SES scores for (the total) six-digit postal code areas are more precise because these areas are smaller (streets). The six-digit postal code was only registered for 2,600 patients out of 10,547 and analyses were performed with both six-digit and four-digit postal codes to reflect the effects of using larger areas. The mean number of inhabitants was 39 per six-digit postal code area and 4907 per four-digit postal code area in 2001. The SES score for each six- and four-digit postal code area, provided by the “Sociaal Cultureel Planbureau” (a governmental organisation), is based on the following items which were collected per six-digit postal code: 1) mean income per household, 2) the percentage of households with a low income, 3) the percentage of households with a low education. The SES scores at the six-digit postal code level were used as follows: in three collective SES-codes which were based on deciles: 1=1st-3rd decile, 2=4th-7th decile and 3=8th-10th decile. The variables at the six-digit level were aggregated to the four-digit level. After aggregation, the variables were merged into one score by means of factor analysis (principal components analysis). A rank number (1-9) given to each postal code region was used as the SES [21]. SES at the four-digit level was divided into three groups based on the delivered rank numbers: 1=rank number 1-5 (SES score lower than mean SES score in the Netherlands), 2=rank number 6 (mean SES score of the Netherlands) and 3=7-9 (SES score higher than mean SES score in the Netherlands). Associations between SES and age at diagnosis were assessed by performing a t-test, because age at diagnosis was used as a continuous variable. Associations between SES of neighbourhood and stage of disease or

histological type of each cancer were analysed by calculating relative risks. Stage of disease was coded into low (FIGO IA-IIA) and high (IIB-IVB) and histological type into squamous cell carcinoma and adenocarcinoma. Patients with unknown FIGO stage (n=109, 1%) and 'other' or unknown histological type (n=200, 2%) were excluded from the analyses.

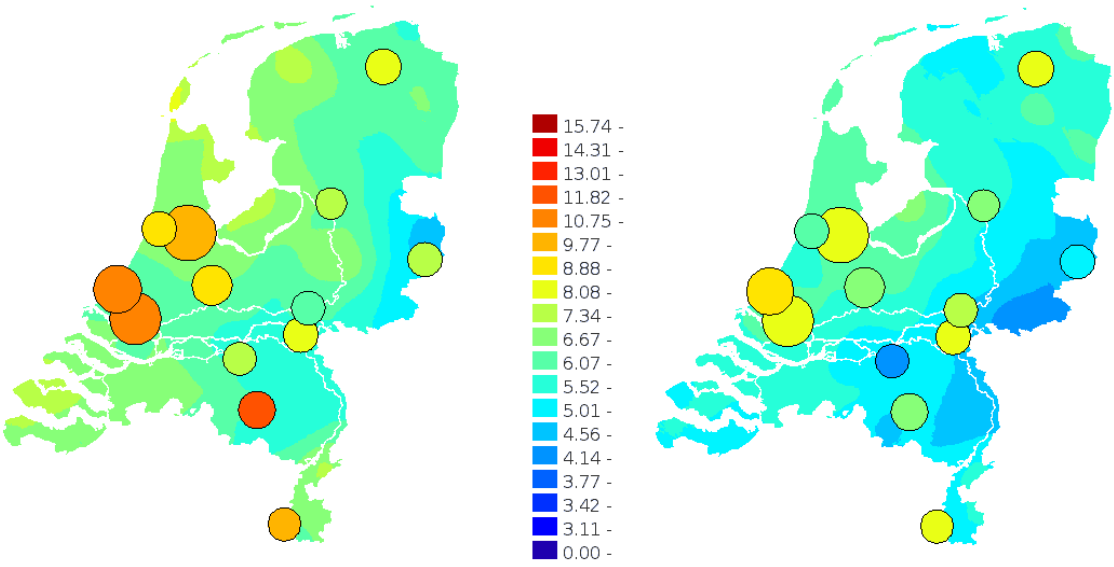

Figure 1 Spatial pattern of age-adjusted (World Standard) incidence rates of cervical cancer per 100,000 women in the Netherlands, period 1989-1993 (left) and 1998-2003 (right)

Results

In the period 1989-2003 10,574 women were diagnosed with invasive cervical cancer in the Netherlands. Two-thirds of the patients (67%) were younger than 60 years at diagnosis. The mean age at diagnosis was 52 years (range 12 to 100 years). Squamous cell carcinoma was the most frequently found histological type (74%), and 37% of the patients were diagnosed with FIGO stages IB-IIA.

Figures 1, 2, 3 and 4 show the maps of cervical cancer incidence, population density, and proportions of immigrants and people living on welfare. The decrease in the incidence of cervical cancer over time is also visualised in an animated map on the internet [22]. Visually, areas with the highest population density, highest percentage of immigrants and highest percentage of persons living on welfare showed the highest incidence of cervical cancer.

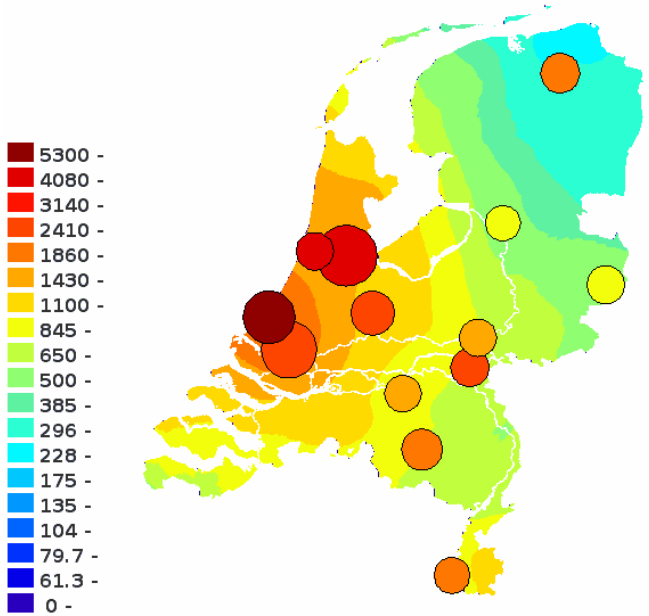

Figure 2 Population density in the Netherlands 2003 (inhabitants per km2)

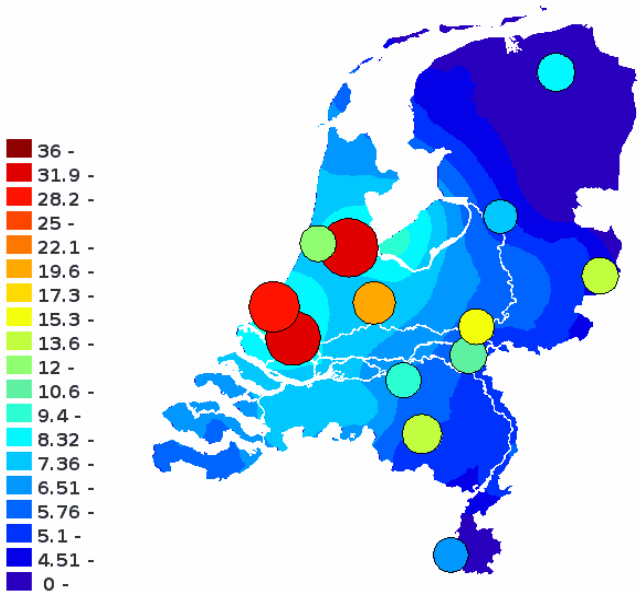

Figure 3 Distribution of immigrants in the Netherlands 2003 (%)

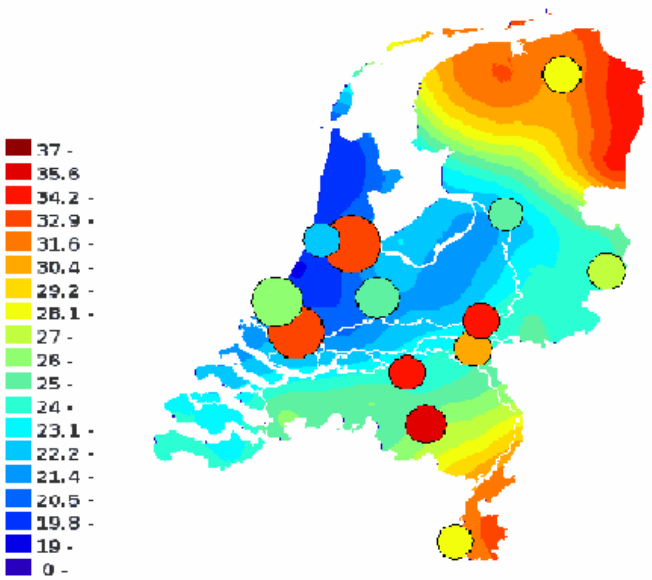

Figure 4 Persons living on welfare 2003 (%)

Multivariate logistic regression analysis at the ecological level revealed that women living in municipalities with a high population density did not have an independent increased risk of cervical cancer, whereas the proportion of immigrants (OR 7.9, 1.4-47 95% CI) and of persons living on welfare (OR 8.6, 1.7-43 95% CI) certainly mattered (table 1).

Patients from neighbourhoods with the lowest SES scores also had higher FIGO stages (RR 1.4, 1.2-1.6 95% CI), a lower proportion of adenocarcinomas (RR 0.7, 0.6-0.9 95% CI) and older age at diagnosis (p<0.001) compared with neighbourhoods with the highest SES scores.

Table 1 Sociodemographic determinants of high incidence municipalities of cervical cancer in the Netherlands in the period 1989-2003

Covariate	Univariate		Multivariate [a]	
	OR	95% CI	OR	95% CI
Population density (persons per km2)				
<184	1	reference	1	reference
184-299	0.5	0.2- 1.3	0.4	0.2- 1.2
300-518	1.3	0.6- 3.0	1.0	0.4- 2.7
519-1175	2.0	0.9- 4.5	0.7	0.2- 2.4
> 1175	9.8*	3.7- 26.2	1.6	0.4- 6.4
Percentage of immigrants				
<1.7	1	reference	1	reference
1.7-2.4	0.9	0.4- 2.3	0.9	0.4- 2.4
2.5-3.8	22.0	0.8- 4.7	1.6	0.6- 4.4
3.9-6.8	42.3	0.9- 5.6	31.3	0.4- 4.7
> 6.8	39.2*	10.6-145.6	7.9*	1.4-46.7
Percentage of persons living on welfare				
<15	1	reference	1	reference
15-19	1.5	0.6- 3.6	1.4	0.6- 3.7
20-26	1.6	0.6- 4.1	1.2	0.4- 3.2
27-40	4.0*	1.6- 10.2	2.3	0.8- 6.5
> 40	45.6*	11.8-176.4	8.6*	1.7-43.0

*p<=0.001 CI=confidence interval [a]Adjusted for all other factors in the table.

Same trends, with lower relative risks, were found for SES at the level of the four-digit postal code: patients from neighbourhoods with the lowest SES scores had higher FIGO stages than patients residing in neighbourhoods with the highest SES scores (RR 1.2, 1.1-1.2 95% CI). The proportion of adenocarcinomas was also lower (RR 0.8, 0.7-0.9 95% CI) while the age at diagnosis was older (p=0.003).

Discussion

Cervical cancer incidence was higher in densely populated municipalities; the excess was attributable to higher percentages of immigrants and people living on welfare. Low neighbourhood SES was a predictor for older age and more advanced stage at diagnosis and fewer adenocarcinomas. Analyses at the ecological and individual level do not necessarily yield similar results, e.g. the risk of cervical cancer may be highest in areas with the highest average income or SES, but at the same time also among individuals with the lowest SES. In the Netherlands the proportions of the lowest social strata tend to be largest in areas where the average SES is lowest – well-to-do people generally prefer living outside of the cities – and therefore the conclusions of the present paper based on ecological analyses would also have been obtained if an analysis at the level of individuals had been possible.

Women who live in an urban setting were at higher risk for developing cervical carcinoma. Relatively high cancer incidence rates for urban populations have been observed for many decades [23-27]. In the Netherlands, life-style differences between urban and rural areas have become less pronounced compared with the differences found 20 years ago, partly due to increased mobility of the population. This may have influenced the incidence of cervical carcinoma, which is known to be highly dependent on life-style aspects, such as age at first intercourse, the number of sexual partners and smoking [28]. In this study, population density was associated with cervical cancer risk, but it was no longer significant after adjustment for immigrants and living on welfare, suggesting that any urban-rural difference reflected differences in these two factors. Furthermore, the latency time of cervical cancer and effects of migration might have influenced the risks which were found in this study.

In accordance with three other studies performed in the Netherlands which found higher incidence rates for some, but not all, immigrant women, higher incidence rates for cervical cancer were derived for areas with a high percentage of immigrant women in the present study [29-31]. Several reasons can be suggested to explain this relationship. Attendance at screening is known to be low among immigrant women [13;14;32]. Thereby, these women mostly originate from countries with high cervical cancer incidence rates, the WSR per 100,000 being 12 for Morocco, 27 for Suriname, 16 for Indonesia and 13 for Caribbean women, also reflecting differences in the prevalence of carcinogenic subtypes of HPV between different population groups [33;34]. Furthermore, it is well-known that the major cause of cervical cancer is persistence of certain types of HPV infections [35]. Clinical and subclinical HPV infections have become the most common sexually transmitted diseases today: asymptomatic cervical HPV

infection can be detected in 5%-40% of women of reproductive age [36]. Unfortunately, there is no data from the Netherlands which makes a comparison of the prevalence of high risk HPV infection between immigrant and native women possible. However, a study in Utrecht in the Netherlands showed an increase in the incidence of sexually transmitted diseases, mainly among immigrants [37]. Another study from the Netherlands showed an increased rate of teenage pregnancies among immigrant women [38].

It is likely that HPV prevalence is higher among the socially less privileged, because of a higher number of sexual partners and earlier age at first sexual intercourse [28;39]. Also, previous studies have proven that the sexual behaviour of their partners is a risk factor [6;39]. Thereby, these women living in socioeconomically disadvantaged neighbourhoods appear to be less motivated to undergo screening and might have poorer health consciousness, both of which may contribute to later stage at diagnosis [40;41]. Consistent condom use by their partners should lead to a decreased risk of HPV infection in newly sexually active women [42].

In conclusion, sociodemographic factors contributed to the differences in incidence of cervical cancer. This, together with the finding that lower SES scores are associated with higher stage at diagnosis, emphasizes the importance of focusing on cervical cancer prevention programmes in the future. These prevention programmes, including vaccination and screening, need more emphasis on low socioeconomic and minority groups, in order to ensure that those most at risk benefit. It is known from other countries that attendance of high-risk groups depends predominantly on practicalities of the screening programme; if it fails to attain high attendance it mainly covers women with a low risk of cervical cancer and becomes then quite useless. Offering certain immigrant women information in their native tongue and opportunities to have their smear taken by a female general practitioner or assistant might increase attendance rates.

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3.2

Mass screening programmes and trends in cervical cancer in Finland and the Netherlands

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Abstract

Background. With respect to cervical cancer management, Finland and the Netherlands are comparable in relevant characteristics, e.g., fertility rate, age-of-mother at first birth and a national screening programme for several years. The aim of this study is to compare trends in incidence of and mortality from cervical cancer in Finland and the Netherlands in relation to the introduction and intensity of the screening programmes.

Methods. Therefore, incidence and mortality rates were calculated using the Cancer Registries of Finland and the Netherlands. Data on screening intensity were obtained from the Finnish Cancer Registry and the Dutch evaluation centre at ErasmusMC-Rotterdam. Women aged 30-60 have been screened every 5 years, in Finland since 1992 and in the Netherlands since 1996. Screening protocols for smear taking and referral to the gynaecologist are comparable. Incidence and mortality rates have declined more in Finland.

Results. In 2003, age-adjusted incidence and mortality in Finland were 4.0 and 0.9 and in the Netherlands 4.9 and 1.4 per 100,000 woman-years, respectively. Excess smear use in the Netherlands was estimated to be 24 per 1,000 women during a 5-year interval compared to 121 in Finland.

Conclusion. The decline in mortality in Finland seems to be almost completely related to the screening programme whereas in the Netherlands it was initially considered to be a natural decline. Differences in risk factors might also play a role: the Netherlands has higher population density and higher percentages of immigrants and (female) smokers. The greater excess smear use in Finland might also have affected incidence.

Introduction

Mass screening for cervical cancer has been performed in several countries with varying success, depending on the coverage and intensity of screening such as intervals between screens, age groups covered, attendance rate, quality of follow-up after a positive smear, coordination of organized and opportunistic screening (screening outside the screening programme) and other characteristics [1-3]. Actual proof of the effectiveness of cervical cancer screening was never obtained from randomized cervical cancer screening trials; instead, the evidence of the efficacy and effectiveness is based on cohort follow-up studies and also on geographical correlation studies [4,5]. Consequently, debate has arisen on the contribution of screening to the decrease in cervical cancer mortality that was found in some areas as well as to the prevention of an increase in other areas where cervical cancer mortality did not change significantly despite extensive screening [1,6,7]. The objective of cervical cancer screening is to prevent the occurrence of invasive cancer and thus death by detecting and treating high-grade intraepithelial lesions, being precursors of invasive cancer. The most widely used screening approach to detect lesions has been cervical cytology, followed by investigation of ‘’positive’’ women with colposcopy and directed biopsy [4,8]. Addition of an HPV test to the screening programme or substitution of the cytological test by the HPV-DNA test and even the inclusion of HPV vaccination in the national vaccination programmes are now under consideration in several countries with mass screening programmes [9-14].

It is now well-established that HPV infection is the central causal factor in cervical cancer. HPV is a common sexually transmitted infection and both women and men are usually exposed to the virus after the onset of sexual intercourse. The risk of infection with HPV and also the risk of cervical cancer is increased by the number of sexual partners, age at first intercourse and sexual behaviour of the woman’s male partners [15,16]. Additional risk indicators for cervical cancer are the number of live births, long-term use of oral contraceptives, cigarette smoking and immuno-suppression 16. The incidence of cervical cancer varies across the world depending on the presence of the above-mentioned risk factors and the availability of a screening programme [17].

The aim of the present study was to compare trends in the incidence of cervical cancer in Finland and the Netherlands and to relate the trends to the extent and intensity of the screening programmes. Finland and the Netherlands are comparable in most other relevant characteristics, e.g. gross domestic product, fertility rate and age at first birth [18,19].

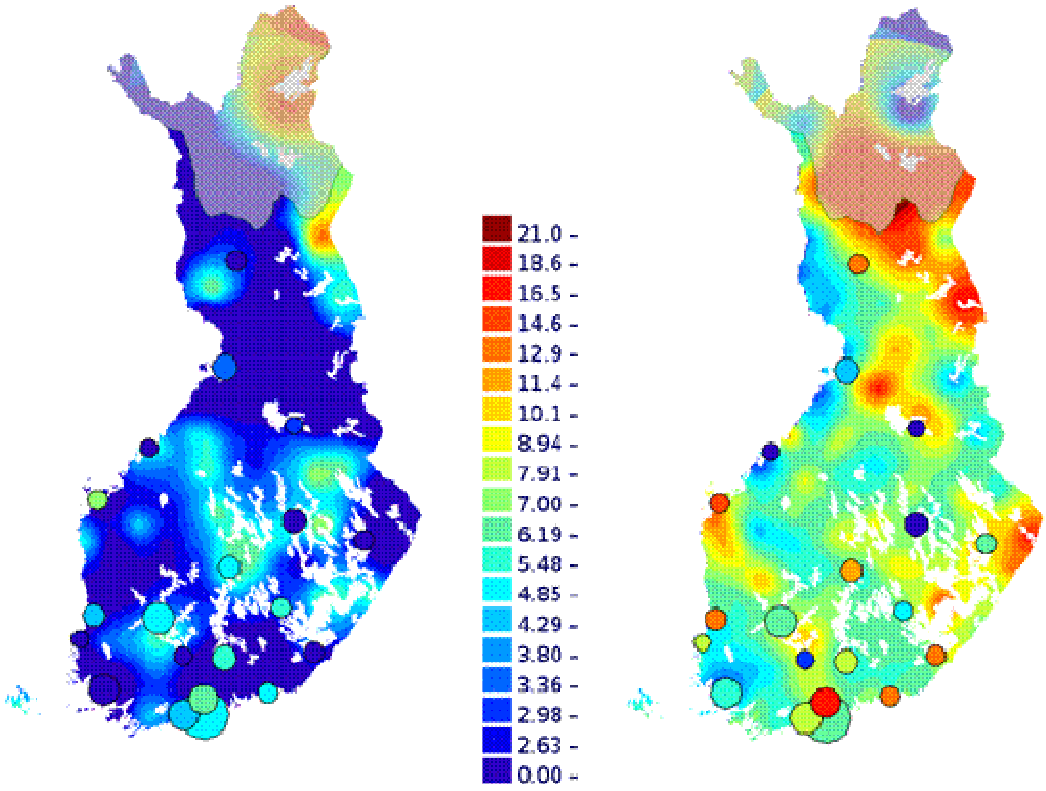

Figure 1a Truncated age-adjusted (World Standard) incidence rates per 100,000 women in Finland, age group 25-39 years, in the period 1989-1994 (left) and the period 1998-2003 (right)

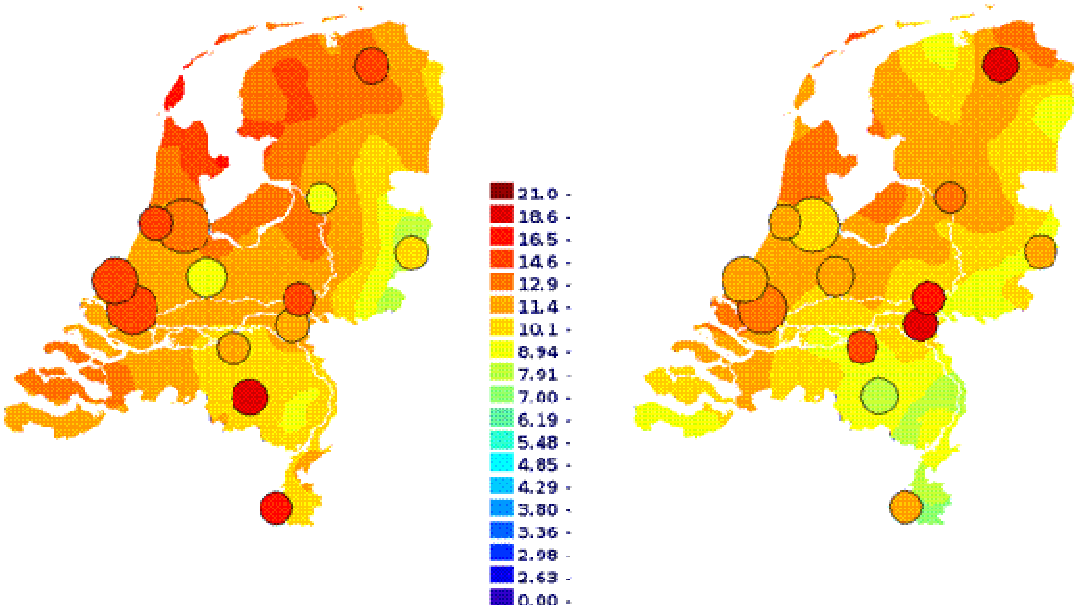

Figure 1b Truncated age-adjusted (World Standard) incidence rates per 100,000 women in the Netherlands, age group 25-39 years, in the period 1989-1994 (left) and the period 1998-2003 (right)

Methods

Study population

Age-specific and age-adjusted World Standardized Rates (WSR) for cervical cancer incidence and mortality were calculated from the Finnish Cancer Registry (FCR) and the Netherlands Cancer Registry (NCR).

The FCR is a population-based nationwide cancer registry established in 1952, registration began in 1953. The FCR receives data on cancer cases from hospitals, health centres, medical practitioners, and pathological and cytological laboratories. It also receives information about all death certificates which mention cancer. The file of all deaths occurring in Finland is checked annually against the files of the FCR.

Nine regional cancer registries submit their data to the NCR, which has been a population-based nationwide cancer registry since 1989. Registration in the Netherlands began in the region of the Eindhoven Cancer Registry in 1955 and was followed by the other regions during the 1980s. Notification is obtained from the Pathology Departments, the Dutch Network and National database for Pathology (PALGA), and Hematology Departments. Other sources are the Radiotherapy Departments of the hospitals, as well as the National Registry of Hospital Discharge Diagnosis, which accounts for up to 8% of new cases apparently without pathological notification [20]. Death certificates are not available in an identifiable form to the regional cancer registries and the NCR. Data on deaths from cervical cancer were therefore derived from Statistics Netherlands [21].

In the NCR, carcinoma in situ of the cervix is not registered; accordingly, also for Finland only cases of invasive cervical cancer were included in this study.

Mapping

Maps were made based on truncated age-adjusted (World Standard) incidence rates per 100,000 women (figure 1a and 1b). For cities with >100,000 inhabitants the rates were shown as such as circles on the maps. The radius of the circle indicates the size of the population and the colour the WSR. The remaining rates were smoothed to prevent disturbing chance variation [22]. Smoothing was done by calculating a weighted average of the age-adjusted incidence rates of the neighbouring areas for each grid (size 2 km by 2 km) to define the colour of that grid. The weights were inversely associated with the distance and reached 50% at a distance of 25 km and zero at 150 km. Every step between the categories represents a 1.13-fold increase in the rate.

History of screening programmes

In 1963 an organised cervical screening programme with five-year intervals was introduced as a pilot project in three municipalities in Finland, extending to most parts of the country within a few years. By 1970, the coverage of the invitational programme already exceeded 80% of women in the target age group of 30-50 years. Later, in 1992 30-60 years became the national target age. Some municipalities also invited women 25-30 and/or 60-65 years old. Furthermore, from the early 1970s onwards, registered coverage has become almost complete. According to a bylaw drawn up in 1992 the municipalities had to offer cervical cancer screening to 30-60 year old women with a five-year screening interval [23].

In the Netherlands, cytological screening has been available to women in some regions of the Netherlands since the mid 1970s within a combination of opportunistic screening and local and regional invitational programmes, with three-year intervals [24]. In 1988, a nationwide screening programme was initiated aimed at women aged 35-54 years screened at three-year intervals [25]. In 1996 screening activities were restructured for a new national programme. From then on women between 30 and 60 years old were screened at five year intervals, leaving the number of seven invitations during a lifetime unchanged [26].

Table 1 Comparison of Pap smear classification and Bethesda system

WHO terminology	Pap score [27*]	Bethesda [28]
Atypical cells	Pap II	ASCUS/AGUS
Mild/moderate dysplasia	Pap IIIA	LSIL
Severe dysplasia	Pap IIIB	HSIL
Carcinoma-in-situ	Pap IV	HSIL/AIS
Squamous cell carcinoma/Adenocarcinoma	Pap V	Squamous cell carcinoma/ adenocarcinoma

* Pap I = normal smear

Screening practices

In the Finnish screening programme, smears are taken out by trained nurses (midwives) in local health care centres and the smears are screened by cytotechnicians. Smear quality is under continuous control and assessed by the cytology laboratories. The cytologist checks every abnormal smear and a proportion of normal smears [23]. Referral to the gynaecologist for colposcopy and biopsy takes place after a clear finding of dysplasia (Pap III-V) or after several borderline findings (Pap II), based on the recommendation of the cytologist (table 1).

In the Netherlands, most of the programme smears are taken in general practice, by general practitioners or their practice assistants. Investigation of the smears is performed by specially trained cytotechnicians. The non-negative cases are evaluated by a head-cytotechnician. A cytopathologist has the final supervision and writes the final report on the non-negative cases. Screening results are filed at the laboratories and in PALGA. Comparable to Finland, referral to the gynaecologist takes place after repeated borderline findings (Pap II or IIIA) or after finding positive cytology (Pap IIIB-V).

Participation

In Finland the participation rate exceeded 70% (72% in 2004) but in addition to the organised screening programme, opportunistic smears are also more common. It has been estimated that the coverage of smears during a five-year period was about 90% (i.e. at least one smear made per female) and the coverage of women with a pap-smear at least once in their lifetime was estimated to be 98% [23]. Opportunistic screening is estimated to be more than 100% of the total screening activity (i.e. the use of smears is two times higher than recommended by the programme) and the excess use of Pap smears (all smears taken in a certain period that do not contribute to the observed coverage of the target population) was 121 per 1,000 women in a 5-year period [2,23].

In the Netherlands the participation rate was about 65% [29]. At the end of 1996, together with opportunistic screening, the percentage of women 30-60 years old with at least one smear in the previous five years was approximately 80% and coverage of women with a Pap-smear at least once in their lifetime was 90% [26]. However, participation in each following round of the population-based screening programme became lower; furthermore and with increasing age, attendance declined, being 10-15% lower for the age group 50-59 than the age group 30-49 [30,31]. The excess use of Pap smears was very low: 24 per 1,000 women in a 5-year period with opportunistic screening being <2% of the total screening activity in 2003 [2,32].

Results

During the period 1955-1964, the incidence of invasive cervical cancer in Finland was 15 per 100,000 woman-years, age-adjusted to the world standard population, with a slightly increasing trend within that period (figure 2). From 1965 to 1990 incidence rapidly decreased to 2.8 per 100,000 woman-years in 1991, which gives an overall decrease of approximately 70-80%. After 1991, the

incidence increased to 4.0 per 100,000 woman-years in 2003. The mean age-specific incidence rate for the age group 25-39 increased from 2.1 in 1989-1994 to 4.6 in 1998-2003; it was higher in urbanized areas (figure 1a). Mortality from cervical cancer decreased continuously from 6.8 per 100,000 woman-years during 1958-1962 to 0.9 per 100,000 woman-years in 2003 (figure 3).

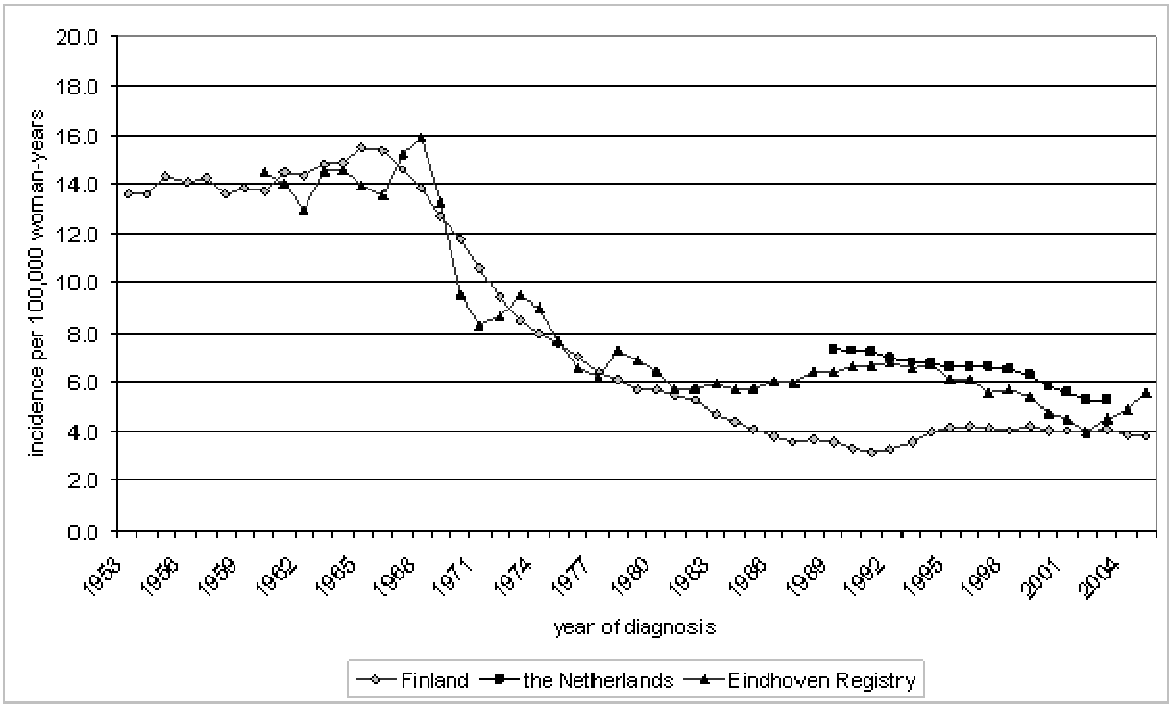

Figure 2 Age-adjusted (World Standard) incidence rates per 100,000 women in Finland and the Netherlands, according to year of diagnosis

In the Netherlands, the incidence of cervical cancer varied from 18 to 12 per 100,000 woman-years, age-adjusted to the world standard populaton, in the period 1960-1970 (Eindhoven registry) (figure 2). In 1970 incidence started to decrease from 12 per 100,000 woman-years (Eindhoven registry) to 3.6 per 100,000 woman-years in 2003 (national rates: 4.9 per 100,000). The mean age-specific incidence rate in the Netherlands for the age group 25-39 decreased from 11.6 in the period 1989-1994 to 9.8 in the period 1998-2003 with higher incidences in the cities and less urbanized areas (figure 1b). These differences were bigger than in Finland. Mortality from cervical cancer in the Netherlands decreased from 5.4 per 100,000 woman-years in 1970 to the lowest rate ever, 1.1 per 100,000 woman-years, in 2002 (figure 3).

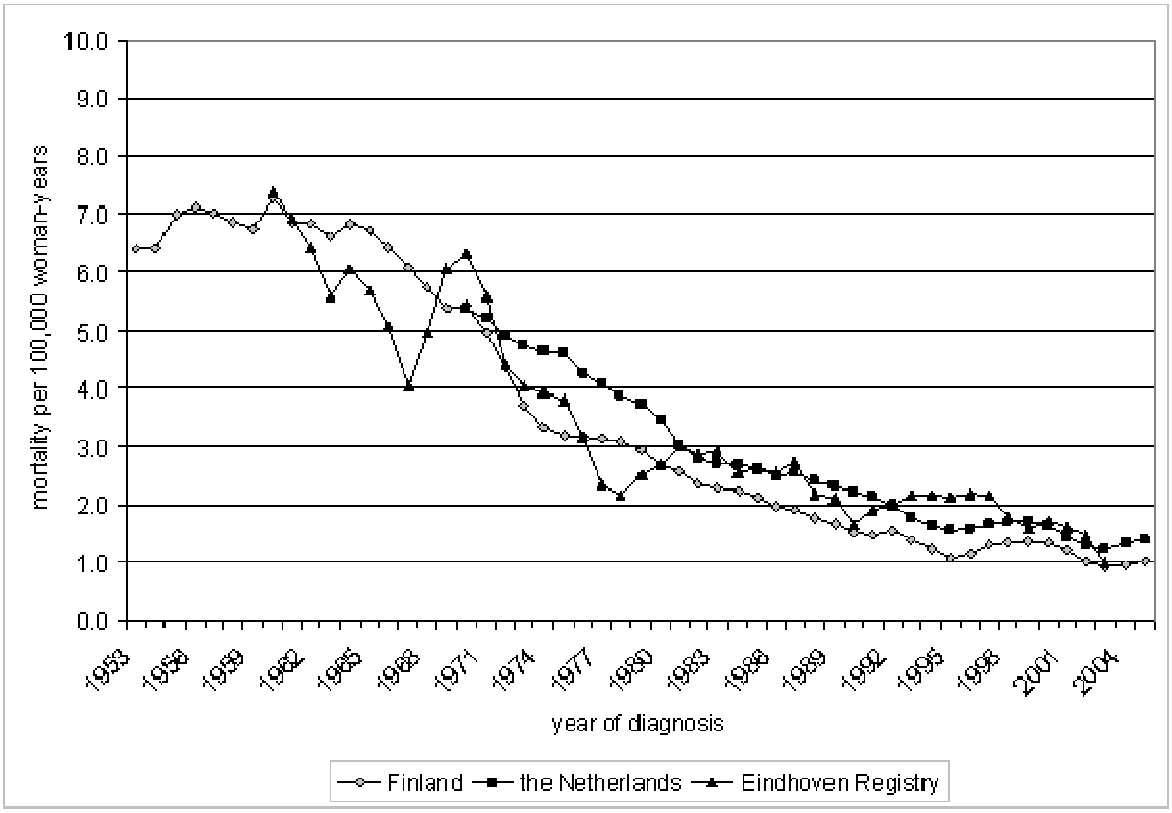

Figure 3 Age-adjusted (World Standard) mortality rates per 100,000 women in Finland and the Netherlands, according to year of death

Discussion

There is worldwide evidence of a considerable decline in incidence and mortality from cervical cancer in areas with active mass screening programmes. However, the effectiveness of these programmes varies, and initially the trends in the disease were hardly affected by screening in some countries such as the United Kingdom and Scotland [1]. This study has shown similarities, but also differences in the trends in incidence of and mortality from cervical cancer between Finland and the Netherlands. In Finland, the 80% decrease in the incidence and mortality rates has mainly resulted from the national screening programme, even though wide-spread opportunistic screening could also have affected these rates but in a clearly less degree [5,23,33,34]. Changes in sexual behaviour probably increased rather than decreased the background risk [35]. Mortality in the Netherlands started to decrease in 1970, earlier than an effect of mass screening could be expected, but definitely continued to drop after the introduction of screening, being currently 40% lower than around 1960. A drop in

the incidence of cervical cancer and a shift towards diagnosis of invasive cervical cancer in a less advanced stage seems the best explanation for the 'natural' decline [36,37]. In Finland, the death records have been continuously linked with the incidence records on an individual level. In the Netherlands, unfortunately there is no linkage of the cancer registry with the cause-of-death registry. However after 1970, there were very few uterus NOS cases of cancer in the Netherlands and therefore the trends in mortality were affected negligibly [21]. Differences in mortality rates may also partly be explained by a difference in background incidence between Finland and the Netherlands, the latter having more urbanized areas and more migration from abroad than Finland. These migrant women originate mainly from countries with higher cervical cancer incidence rates, the WSR per 100,000 women in 2002 being 12 for Morocco, 16 for Indonesia, 13 for women from the Caribbean islands to even 27 for Suriname [38,39]; 4% of all cervical cancer cases in the Netherlands are diagnosed in immigrant women [40].

Part of the difference in the decrease of incidence of cervical cancer could be explained by risk factors for cervical cancer. In contrast to Finland, the Netherlands does have a very high population density in most of the country and a higher percentage of (female) smokers, both of which are risk factors for cervical cancer [21]. Furthermore, the fertility rate was higher, especially in catholic parts of the Netherlands up until 1970 [21].

In Finland, a recent increase was observed in the incidence of cervical cancer in young women, possibly related to changes in sexual behaviour during the last few decades, suggesting an increasing role of some potentially oncogenic sexually transmitted infections, such as HPV [35]. Also among young Finnish women smoking increased during the 1980s. In the Netherlands, an increase in the incidence of cervical cancer could not yet be observed [41]. However, HIV and other sexually transmitted infections have been increasing, according to the latest surveillance data [42].

In both countries, discussion has started on a Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, which has been approved in the EU for prescription to women aged 9 years and older, to include it in the vaccination programmes in order to reduce further (and definitely) the incidence of cervical and other HPV-related cancers [9,12,43]. However, follow-up studies of the vaccines on the effect on cancer risk, i.e. the problems and limitations of the vaccine, are not available.

Furthermore, vaccination may create a false feeling of complete protection. The screening programme therefore may need to be continued in addition to the vaccination for several decades more.

The percentages of hysterectomy found for both countries might also explain the difference in incidence rates. Hysterectomy has been under discussion since the 1970s because of regional and international variations in frequency, indications and surgical methods [44]. In some countries, the increasing frequency of hysterectomy has led to an underestimation of the actual risk for cervical cancer. A study from Finland calculated 11% higher hysterectomy-corrected rates than the uncorrected rates [44]. The prevalence of hysterectomy in Finland in 1987-1989 was approximately the same as in the Netherlands. However, from 1991 to 1999 the annual number of hysterectomies in Finland increased by 16% and decreased by 24% in the Netherlands in almost the same period [44,45]. Therefore, the adjustment for age-specific fractions of women with a hysterectomy may have had some influence on the cervical cancer rates in both countries: the corrected incidence rates for Finland being somewhat higher and for the Netherlands somewhat lower.

To conclude, incidence and mortality rates of cervical cancer rates became very low in both Finland and the Netherlands, in fact the lowest in Europe due to a large extent their mass screening programmes. In the Netherlands, there still seems to be some room for improvement, whereas Finland might need to pay more attention to young women and the high rate of excess smear use. As long as cervical cancer occurs in women who are screened, most attention must be directed toward minimizing false-negative smears. Furthermore, anxiety might be caused in women by repeated testing of low-grade cervical abnormalities and colposcopic evaluation of high-grade abnormalities [4,46]. Unfortunately, more intensive screening greatly increases the need for more interventions for lesions which would never have developed into tumours [47]. Attention to quality of life and potential adverse aspects should therefore be part of the evaluation of screening programmes.

Acknowledgements

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Chapter 4

Cervical cancer screening

4.1

Differences in screening history, tumour characteristics and survival between women with screen-detected versus not screen-detected cervical cancer in the east of the Netherlands, 1992-2001

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Abstract

Background. In the Netherlands, despite a national screening programme since 1996, invasive cervical cancers have been detected in screened and non-screened women. The aim of this study was to determine differences between Pap-smear history, tumour characteristics and survival of patients with a tumour detected by the screening programme (SP) or outside the screening programme (OSP) in the region of the Comprehensive Cancer Centre Stedendriehoek Twente in the period 1992-2001.

Methods. In this period, 263 cervical cancer cases in women aged 30-60 were selected from the regional cancer registry. Patient and tumour characteristics, treatment and follow-up data were extracted. Also, detection modality of the tumour and Pap score of the smear which led to the diagnosis (‘diagnostic smear’) and the ‘previous smear’ were registered.

Results. Thirty-five percent were SP tumours and 65% were OSP tumours. SP tumours had a lower stage (FIGO I) than OSP tumours: 84% versus 57%. The OSP group exhibited a twofold increase in risk of death ($p<.05$) compared to the SP group. Subsequently 61 women (23%) and 46 women had an abnormal Pap smear (Pap II or higher) five years and three years before the ‘diagnostic smear’, respectively. Furthermore, 37 women (14%) and 23 women (9%) had a normal smear five years and three years before diagnosis, respectively.

Conclusion. SP tumours have a lower stage and a better prognosis, probably due to the fact that the screening programme detects the slow growing tumours which in general have a better prognosis. Furthermore, detection and treatment of patients with suspicious smears have been suboptimal and attention should therefore be paid to prompt follow-up of suspicious smears.

Introduction

Cervical cancer is the second cancer among women worldwide and in Europe. The incidence varies within different age groups as a result of screening activities [1]. The age-specific incidence of cervical carcinoma in an unscreened population usually shows a peak at ages 45 to 50 and a plateau after these ages [2].

The Netherlands is among the countries with low incidence and almost the lowest mortality from cervical cancer, 1.0 per 100,000 person-years (European Standardized Rate) [3]. On the basis of recent trends the prognosis is that the incidence of cervical cancer as well as the absolute number of cases of cervical cancer will decline further until 2015 [4]. Mortality stabilised between 1950 and 1965 and started to decrease between 1965 and 1970. After some fluctuation in mortality rates between 1970 and 1990, the decreasing trend (2% decrease per year) continued [5].

Cytological screening has been available to women in some regions of the Netherlands since the 1970s through a combination of local and regional programmes whereas opportunistic screening also occurred on a large scale. In 1988, a nationwide screening programme was initiated aimed at women aged 35-54 years who were screened at three-year intervals. From 1996 on the screening recommendations were modified to expand the target age group to 30-60 years and to screen at 5-year intervals. Since the goal of the current national screening programme is detection of premalignant cervical lesions in women aged 30 to 60 years, thus preventing progression to invasive cancer, one would expect to find fewer invasive cancers at the second screening and subsequent rounds. However, many invasive carcinomas have been detected after the second invitational smear in women participating in the screening programme.

The aim of this study is to determine how many women had a negative smear 3 or 5 year before the cancer was diagnosed, to evaluate follow-up of suspicious smears and to determine whether tumour characteristics, screening history and survival of patients differed between tumours detected by the screening programme (SP) and those diagnosed outside the screening programme (OSP).

Methods

Data collection

The cancer registry of the Comprehensive Cancer Centre Stedendriehoek Twente (CCCST) is a population-based cancer registry established in 1989 and is part of the population-based (nationwide) Netherlands Cancer Registry. Notification is obtained from the Pathology Departments, the Pathologisch Anatomisch Landelijk Geautomatiseerd Archief ("PALGA"; the automated national pathology archive), and Haematology Departments in the region. Other sources are the Radiotherapy Departments of the hospitals, as well as the National Registry of Hospital Discharge Diagnoses, which accounts for up to 8% of new cases [6]. Death certificates are not available in an identifiable form to the cancer registry because of privacy regulations. All malignant tumours are registered by the 7 (general) hospitals in the region. The region of the CCCST has approximately 600,000 female inhabitants and the attendance rate for the screening programme is usually very high: between 75% and 80% in the period 1996-2001 [7;8].

From the medical records in the hospitals identifying information (e.g. date of birth, postal code), tumour characteristics (e.g. date of incidence, topography, morphology, stage), treatment and follow-up data were collected and coded according to the national manual. This manual describes inclusion and exclusion criteria as well as definitions and coding of items. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICDO) [9]. The TNM classification is used for the staging of the tumours [10]. FIGO stage was derived from TNM stage. Lymph node status is not included in the FIGO classification for cervical carcinoma, and therefore it was described separately. National coding rules allow registration clerks to report only a positive or negative clinical lymph node status when a CT-scan of the pelvis is made. When there is no information about a CT-scan in the patient file, registration clerks have to code the clinical lymph node status as unknown. All women with cervical cancer in the region of the CCCST, in the target age group of the Dutch national screening programme, were included in this study; women diagnosed between 1 January 1992 and 31 December 1995 aged 35 to 55 years, and women diagnosed between 1 January 1996 and 31 December 2001 aged 30 to 60 years. The tumour detection modality, i.e. detected by means of the screening programme (SP) or outside the screening programme (OSP), and the Pap scores of the smear which led to the diagnosis ('diagnostic smear') and the smear before this smear ('previous smear') were derived from PALGA [11]. All pathology laboratories store the results of Pap smears in PALGA, according to a standardized cervix information system (table 1).

Table 1 Comparison of Pap smear classification and Bethesda system

WHO terminology	*Pap score*[11*]	*Bethesda* [12]
Atypical cells	Pap II	ASCUS/AGUS
Mild/moderate dysplasia	Pap IIIA	LSIL
Severe dysplasia	Pap IIIB	HSIL
Carcinoma-in-situ	Pap IV	HSIL/AIS
Squamous cell carcinoma/ Adenocarcinoma	Pap V	Squamous cell carcinoma/ adenocarcinoma

* Pap I = normal smear

The terminology of detection modality (SP or OSP) does not have any relationship with the screening history of the patient. SP tumours are tumours found as the result of a smear made in the screening programme. Women with SP tumours might or might not have been screened before, during or outside the screening programme. OSP tumours occur in women who went to see a specialist outside the screening programme with complaints such as vaginal discharge, vaginal bleeding or metrorrhagia as well as women whose mothers used diethylstilbestrol, the so-called DES-daughters. These women might or might not have been screened before, during or outside the screening programme. Because the aim of this study was to compare the characteristics of SP tumours and OSP tumours, women who underwent opportunistic screening (screening offered outside the organized screening programme, at the initiative of either the woman involved or her physician) were included in the OSP group. However, this is a very small group, because the number of excess smears is very low in the Netherlands (24 per 1,000 women in 1998) [13].

Information on the vital status of all patients was collected in the hospitals and from general practitioners. All patients had a minimal follow-up time of 5 years and a median follow-up time of 5.5 years.

Statistical analysis

The Statistical Package for Social Sciences (SPSS version 12.0) was used to perform the analyses. Age was divided into 5-year categories. Differences in distribution over stage and age categories between SP and OSP tumours were assessed with Chi-square analysis. Five-year relative survival was calculated as a measure of disease-specific survival using the Ederer II method with STATA version 9.2 [14]. The relative survival is the ratio between crude and expected survival and is close to disease-specific survival. Follow-up time was defined as time since diagnosis with death or the end of the study as endpoint (5-year survival). Associations were examined by multivariate analyses using Poisson regression, with the detection modality as variable of interest [15]. In modelling

relative survival variables were considered confounders and included in the model when the regression coefficient of the variable of interest changed by more than 10%. Relative excess risks (RERs) and 95% confidence intervals (CI) were calculated. The relative excess risk (RER) describes the difference between the hazard of death in a given group and the hazard in the reference group, taking into account the risk of death in the Dutch population. P-values of less than 0.05 were considered statistically significant.

Table 2 Characteristics of patients detected through the screening programme (SP) or outside the screening programme (OSP) in the region of the Comprehensive Cancer Centre Stedendriehoek Twente in the Netherlands, period 1992-2001 (%)

	SP (n=91)	OSP (n=172)	p-value
Mean age at diagnosis (years)	42	42	0.6
FIGO stage			
I	82	62	
II	10	20	
III	3	10	0.02
IV	5	6	
X	0	1	
Histology			
Adeno	17	17	
Squamous	75	73	0.9
Other	9	10	
Lymph node status			
Negative	50	54	
Positive	14	15	0.7
Unknown	36	31	

Results

On the basis of selection criteria, 263 patients were selected in the period from 1992 to 2001; 91 women (35%) were diagnosed by means of the screening programme (SP) and 172 women (65%) were diagnosed outside the screening programme (OSP) (table 2).

Age

The mean age did not differ between SP and OSP groups. The mean age of the SP group was 42 years (40-44 95% CI), the mean age of the OSP group was 42

years (41-44 95% CI). In both groups most cases were found in the age group 35-39 years, 26% of the SP group and 30% of the OSP group.

Tumour characteristics

The SP tumours had a lower stage than the OSP tumours; 82% (75-90 95% CI) of SP tumours versus 62% (55-69 95% CI) of OSP tumours were FIGO stage I when diagnosed. Also, 10% (4-16 95% CI) of SP tumours versus 20% (14-26 95% CI) of OSP tumours were FIGO stage II when diagnosed. So, significantly more tumours with FIGO stage I were found in the SP group and significantly more tumours with FIGO stage II were found in the OSP group (p=0.02).

No differences were found in morphology between SP and OSP tumours; 75% (66-84 85% CI) of SP tumours and 73% (66-79 95% CI) of OSP tumours were squamous cell carcinomas (p=0.9). Also, no differences were found in grade of histological differentiation between SP and OSP tumours (p=0.7).

Table 3 Pap smear history: outcome of 'diagnostic smear' and 'previous smear' of tumours detected through the screening programme (SP) or outside the screening programme (OSP) in the region of the Comprehensive Cancer Centre Stedendriehoek Twente in the Netherlands, period 1992-2001

	Diagnostic smear N(%)		Previous smear N (%)	
Pap score	SP	OSP	SP	OSP
0*	2 (2)	5 (3)	1 (1)	6 (5)
I	8 (9)	11 (9)	22 (47)	26 (34)
II, IIA	8 (9)	17 (13)	18 (38)	30 (39)
IIIB, IV, V	73 (80)	94 (74)	6 (13)	15 (19)
Total	91 (100)	127 (100)	47 (100)	77 (100)

* Pap 0 = smear could not be judged because of insufficient number of cells

Pap smear history

By definition, all women in the SP group had a smear with a direct connection to the diagnosis ('diagnostic smear'): 73 women with a SP tumour (80%) were diagnosed as Pap IIIB or higher. In the OSP group, 127 patients (66%) had a 'diagnostic smear': 94 (74%) of these women were diagnosed as Pap IIIB or higher (table 3). Most patients with Pap 1 had had indefinite complaints and therefore the gynaecologiist performed colposcopy, which revealed cervical cancer.

In the SP group, 47 patients (52%) had a 'previous smear', while in the OSP group 77 patients (61%) had had a 'previous smear'. In total, 61 women (23%) had an abnormal Pap smear (Pap II or higher) within the five years before the

'diagnostic smear', whereas 46 women (17%) had an abnormal smear within the three years before the 'diagnostic smear'. Furthermore, 37 women (14%) and 23 women (9%) had a normal smear five years and three years before diagnosis, respectively. Pap score IIIB or higher was found in the previous smears of 6 patients in the SP group (7%) and 15 patients in the OSP group (12%). Fifteen of these patients (SP+OSP) had this 'previous smear' in the 6 months before the 'diagnostic smear'. After this smear the diagnostic path was initiated and the 'diagnostic smear' was taken. The medical records of the other 6 cases were checked to find out why the carcinoma was not detected directly after finding the Pap IIIB or higher. Two patients had been treated for an abnormal Pap smear three years before the diagnosis, the Pap smears of two other patients turned out to be Pap V after revision of Pap I, one patient was treated for Trichomonas infection and the medical record of one patient was destroyed because of privacy regulations.

Table 4 Risk of death for patients in the region of the Comprehensive Cancer Centre Stedendriehoek Twente in The Netherlands, with cervical carcinoma diagnosed in 1992-2001 (n=263)

Factor		Univariate		Multivariate [a]	
	Cases	RER	95% CI	RER	95% CI
Detection modality					
SP	53	1	reference	1	reference
OSP	125	3.1*	1.6- 6.0	2.2*	1.1- 4.3
Age	263	1.1*	1.0- 1.1	1.0	0.9- 1.0
FIGO stage					
I	182	1	reference	1	reference
II	44	9.5*	4.7- 19	8.2*	4.0- 17
III	20	24*	11 - 51	19*	8.1- 42
IV	15	75*	33 - 169	73*	32 - 167
X	2	-	-	-	-

* $p<0.05$ CI=confidence interval [a] Adjusted for all other factors in the table

Survival

During the period 1992-2001 71 patients (27%) died within five years of diagnosis. The 5-year overall relative survival rate was 73% (67-78 95% CI). Relative survival was 87% (78-93 95% CI) for patients with SP tumours and 65% (57-72 95% CI) for patients with OSP tumours. The median follow-up time was 5.6 years for SP tumours (range 0-12.6) and 5.4 years (range 0-12.9 years) for OSP tumours.

Table 4 shows the results of the multivariate relative survival analysis whereby detection modality was investigated with SP tumours as reference category. The risk for OSP tumours according to the multivariate analysis was lower than that found with the univariate analysis (RER 2.2), meaning that the higher risk for women with an OSP tumour was caused by differences in tumour stage and age at diagnosis between the two groups. FIGO stage was investigated with stage I as reference category. The HRs for stages II and III and IV were increased significantly. Nodal involvement and histology were not included in the model because the regression coefficient of the variable 'detection modality' did not change by more than 10% when these variables were introduced into the model.

Discussion

The aim of this study was to determine the percentage patients who had a negative smear 3 or 5 years before the diagnosis, to evaluate the follow-up of suspicious smears and to determine whether tumour characteristics, screening history and survival of patients differed between tumours detected by the screening programme (SP) and those detected outside the screening programme (OSP). The main conclusions which can be drawn from this study are that SP tumours have a lower stage and a better prognosis and that treatment of patients with suspicious smears and prompt follow-up of both SP and OSP tumours had been suboptimal.

The 73% overall 5-year survival rate which was found in this study is high, since in Europe only the Nordic countries have comparable survival rates [16]. Some attribute these findings to the nationwide screening programme, since similar effects on incidence have been described in other countries with a screening programme [1]. But, the decline in mortality rates began before the start of the nationwide screening programme, because of a drop in incidence due to improvements in social circumstances or a shift towards diagnosis of invasive cervical cancer in a less advanced stage [5]. One of the most important findings in this study is that SP tumours have a lower stage and a better prognosis than OSP tumours. This is in accordance with former studies which support the notion that cytology screening contributes to earlier discovery of the carcinomas, leading to a better prognosis [1;16]. In addition, some studies found that screening changed stage distribution such that the proportion in stage I increased significantly [1;17]. Furthermore, a truly effective screening programme detects at least most of the slow-growing cancers, which in general have a better prognosis, leaving the rapidly growing cancers, with a worse prognosis, still to be detected. In other words, high survival rates for patients with screen-detected

cervical cancers may also indicate that the screening programme misses severe rapidly progressive cervical cancer precursors that eventually turn into cancer. Other potential explanations of the difference in survival are the broad FIGO stages used (FIGO I instead of FIGO IA1, IA2 etc.) and not taking into account differential treatment or follow-up after-treatment. This is a potential for residual confounding because there should, for example be, no deaths from cervical cancer after FIGO stage IA.

The proportion adenocarcinomas found did not differ between the two groups. This suggests that cytological screening is not a highly efficient approach to detect adenocarcinomas, as reported by other studies which found lower detection rates for adenocarcinomas [18;19]. With respect to the rising incidence of adenocarcinomas relative to squamous cell carcinomas as reported in several studies it may be important to focus screening methods on cytological changes in the endocervical gland in order to detect preinvasive and early invasive adenocarcinoma more effectively [18-21].

In this study, carcinomas developed in women with suspicious smears in their history, which suggests that prompt follow-up and adequate treatment after a suspicious smear (Pap IIIB or higher) are important and it stresses the need for studies of clinical factors that may be predictors for patients [22]. Also, it can be concluded that more attention has to be directed toward preventing false negative smears, because in this study 9% had a normal smear three years before the 'diagnostic smear'. This is lower than the results of another study in The Netherlands which found negative smears for 20% of all women in the three years before cancer was diagnosed. This was caused by suboptimal sampling and reporting errors because, except for very aggressive, rapidly growing cancers, invasive cervical cancer is unlikely to develop within 3 years [23]. The difference with our study may be explained by the period of the study (1992-1994), when there was excessive opportunistic screening and the fact that after 1996, financing and coordination of the screening programme were managed centrally, which might have improved the quality of the laboratories. Also, the mean age in our study was lower (42 years). Two American cohort studies found that 37% and 25% of women who developed cervical carcinoma had a normal Pap smear three years before diagnosis and almost half of them had had their latest normal test within the year before diagnosis [24;25]. Liquid-based cytology has been developed to decrease the number of false-positive and false-negative smear results and therefore it has replaced conventional cytological in the USA almost completely [26;27]. In the Netherlands, the agency which pays for the screening programme did not provide extra funding for liquid-based cytology [28]. Therefore, in the Netherlands the pathologist has to decide which method to use, with the same fee for both methods, and this is why the smears in our study have all been prepared by the cheaper conventional method. Education about

smears may be necessary because a study in The Netherlands on Pap smears made by physician's assistants showed that these smears are of lesser quality than smears taken by the physician himself [29].

Thirty-seven women (14%) and 23 women (9%) had a normal smear five years and three years before diagnosis, respectively. Therefore, it appears that if the screening interval had been three years, 9% would have been detected earlier. However, in 1996, the screening interval was increased from 3 to 5 years in a broader age group. With the same number of 7 smears per lifetime within a broader age range, the 5-year coverage in the new target age groups (30-34, 55-59) rose substantially to 70% or more, with a loss of a few percent in the old target age group (35-54) where the coverage remained around 80% [30]. Therefore, although 9% would have been detected earlier and exhibited a better prognosis, shortening the screening interval back to 3 years is not considered to be a cost-efficient way to improve the screening programme.

Younger women, who developed cervical carcinoma, were not all included in the screening programme as indicated by the peak in incidence of OSP tumours in the lower age categories. This finding, which has been confirmed by earlier reports, again stresses the need to encourage women who are at high risk, e.g. the younger women and women with a low socioeconomic status, to participate in the screening programme [31;32]. Furthermore, because of the limited sensitivity of one single Pap smear it is likely that not all cancers will be found with the screening programme, especially not in the relatively young age cohorts with few previous smears.

One of the drawbacks of this study is that women who underwent opportunistic screening have been included in the OSP group. They might have been for example on oral contraceptives and therefore received a Pap samear every year at their GP, while they also had been covered by the screening programme. However, the use of opportunistic screening decreased dramatically since the restructuring of the national screening programme in 1996 and we therefore think that this problem has little influence on the outcome of this study. Another drawback is that carcinoma in-situ is not registered in the cancer registry and therefore has not been included in this study. Comparing the rates of cervix carcinomas in-situ with the rates of the invasive carcinomas could have told us more about the effectiveness of the screening programme.

To conclude, cervical cancer happened to be found within the screening programme that thus did not yet work optimally. Although many cervical cancers have probably been prevented because of diagnosis and treatment of patients with suspicious smears, invasive cervical cancers were still being detected in women who have been screened. Efforts must therefore be made by laboratories to optimize the detection of all suspicious smears and by the

(family) doctors to reach more women for timely follow-up and to treat them adequately.

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4.2

Does lowering the screening age for cervical cancer in the Netherlands make sense?

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submitted for publication

Abstract

Background. Recommendations for the age to initiate cervical cancer screening should be directed toward maximum detection of early cervical cancer. The aim of this analysis is to determine whether the target age for cervical cancer screening should be lowered in view of apparent increases in new cases of invasive cancer below age 30 and in age group 30-44 years in the Netherlands.

Methods. All cervical cancer cases diagnosed between 1 January 1989 and 31 December 2003 were selected from the nationwide population-based Netherlands Cancer Registry (NCR). For age group 25-39 years, incidence data were also available for 2004 and 2005. To describe trends, the estimated annual percentage of change and joinpoint analysis were used.

Results. Between ages 25 and 28 years, the absolute number of new cases of cervical cancer annually has varied between 0 and 9 per age. Significantly decreasing trends in incidence were observed for age groups 35-39 and 45-49 ($p<0.0001$ and $p=0.01$, respectively). The annual number of deaths fluctuated with a decreasing trend for age groups 30-34 and 35-39 years ($p=0.01$ and $p=0.03$, respectively).

Conclusion. Because an increase in both incidence and mortality rates for cervical cancer was not found in this study, lowering the age for cervical cancer screening is not useful at this time. Although the number of years of life gained is high for every case of cervical cancer prevented, the disadvantages of lowering the screening age, i.e. overdiagnosis would be very large and even become disproportionate compared to the advantages of lowering the screening age.

Introduction

Mass screening for cervical cancer has been performed in several countries with varying success. This success depends on the coverage and intensity of the screening such as intervals between smears, age groups covered, attendance rate, quality of laboratories, quality of follow-up after a positive smear and coordination of organized and opportunistic screening [1-3]. The objective of cervical cancer screening is to prevent the occurrence of and death from cervical cancer by detecting intraepithelial lesions (CIN) and treating high-grade preinvasive lesions (HSIL).

It is now well-established that human papillomavirus (HPV) infection is the central causal factor in cervical cancer [4]. HPV is a common sexually transmitted infection and both women and men are usually exposed to the virus after the onset of sexual intercourse. The risk of infection with HPV and also the risk of cervical cancer increase with the number of sexual partners, lower age at first intercourse and promiscuity of male partners [4]. Additional risk indicators for cervical cancer are the number of live births, long-term use of oral contraceptives, cigarette smoking and immuno-suppression [5].

The prevalence of HPV infections and, as a result, cytological abnormalities in sexually active young women is high: 80% of all women eventually has an HPV infection with peak prevalence between ages 25 and 29 [6]. The fact that younger women have a higher risk of acquiring an HPV infection than older women might be due to acquired immunity against HPV from past exposure in the course of time in the latter group [7]. However, although 10% to 20% of HPV infections develop into CIN most cases of CIN will clear spontaneously: the likelihood of regression of CIN 1 is 60% while the risk of progression to invasion is 1%. The corresponding approximations for CIN 2 are 40% and 5%, respectively. The likelihood that CIN 3 will regress is 33% while progression to invasion is seen in more than 12% of cases [8]. In the Netherlands, referral to a gynaecologist takes place after repeated borderline findings (atypical squamous cells of undetermined significance (ASCUS) or low-grade CIN) or after clearly positive cytology (>= CIN 3).

Currently in the Netherlands, incidence and mortality rates are low and decreasing (World Standardized Rates 4.9 and 1.2 per 100,000 woman-years in 2003, respectively [9]). Screening for cervical cancer was started in the mid 1970's within a combination of regional programmes and opportunistic screening. In 1976, an official pilot study for cervical cancer screening was started in three regions, covering 24% of the Dutch female population. However, under political pressure the screening programme was soon extended to other regions, reaching almost nationwide coverage around 1980. In 1988, a national

screening programme was initiated for women 35-54 years, who were screened seven times at 3-year intervals [10]. In the early 1990s, evaluation of the screening programme in the Netherlands evidently indicated a suboptimal programme, in terms of both the organization and the cost of screening the target population. In 1996, this programme was therefore revised on the basis of extensive MISCAN model calculations. Since then women aged 30 to 60 years have been screened cytologically at six 5-year intervals [11]. The call-up schedule is based on birth years and therefore a woman born in 1969, for example, will be called up in 1999 as a probable, but not certain, 30-year-old at the time of the Pap smear.

Recently, it has been suggested that the age to initiate cervical cancer screening should be even lower in the Netherlands, for two reasons. First, due to the increased risk of HPV-infection because of earlier sex, the incidence of cervical cancer might be rising in age group 25-29 years. Secondly, some believe that there is an increase in the incidence of cervical cancer in age group 30-44 years and therefore the screening age should be lowered to detect preinvasive cervical lesions earlier.

Recommendations for the age to initiate cervical cancer screening should be directed toward maximum detection of early cervical cancer while avoiding the bulk of transient HPV infections. Since there is no database available on the incidence of HPV infections in the Netherlands, the aim of this study was to answer the question of whether the target age for cervical cancer screening should be lowered by determining (age-specific) incidence and mortality rates for cervical cancer in the Netherlands.

Methods

Study population

All cervical cancer cases diagnosed between 1 January 1989 and 31 December 2003 were selected from the nationwide population-based Netherlands Cancer Registry (NCR). For the age group 25-39 years, incidence data were also available for 2004 and 2005. The NCR obtains notifications come from the Pathology Automated Archive (PALGA), Haematology Departments and Radiotherapy Departments of the hospitals, as well as the National Registry of Hospital Discharge Diagnoses. Death certificates are not available in an identifiable form to the cancer registry due to privacy regulations. All data are obtained from patient files in the hospital and include identifying information (e.g. first letters of the name, date of birth, sex, postal code) and tumour characteristics (e.g. date of diagnosis, topography, morphology, stage).

Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification is used for staging the tumours [12;13].

Although carcinoma in situ is registered in PALGA, it is not included in the NCR, and consequently, only newly diagnosed cases of invasive cervical cancer were included in this study.

Data on mortality from cervical cancer were derived from Statistics Netherlands and only available per five-year age group [14].

Incidence and mortality rates per 100,000 person-years were calculated. The Estimated Annual Percentage Change (EAPC) was used as an estimate of the trend. Using calendar year as a regression variable, a regression line was fitted to the natural logarithm of the incidence rates, i.e. y=mx+b, where y=ln(rate) and x=calendar year. Then EAPC=100*(e m-1). Testing the hypothesis that the EAPC is equal to zero is equivalent to testing the hypothesis that the slope of the regression line is zero, using the t-distribution of m/SEm. The number of degrees of freedom equals the number of calendar years minus 2. The standard error of m, i.e. SEm, is obtained from the fit of the regression line. This calculation assumes that the rates increased/decreased at a constant rate over the entire period. Therefore, joinpoint regression analysis was also used to identify points which indicate a statistically significant change over time in the linear slope of the trend. In joinpoint analyses, the best-fit points where the rate changes significantly (increase or decrease) are chosen. The analysis starts with the minimum number of joinpoints, and tests whether one or more joinpoints are statistically significant and should be added to the model (up to three joinpoints). In the final model, each joinpoint indicates a statistically significant change in trend. Significant changes include changes in direction or in the rate of increase or decrease. Joinpoint analyses were performed using 'Joinpoint' software from the Surveillance Research Program of the US National Cancer Institute [15].

Results

Incidence

The incidence of cervical cancer appeared to increase from age 29 on (table 1). Before age 29, the absolute number of cases of cervical cancer varied annually between 0 and 9 per age year. Due to the small numbers, incidence varied markedly between different years of diagnosis, with potential decreases for ages 25, 26 and 28 years. In age group 25-29 the small increase was mainly based

Table 1 Number and incidence rates per 100,000 person-years of cervical cancer according to age in the Netherlands, 1989-2005

Year of diagnosis	Age at diagnosis N (per 100,000)					Incidence in 5 year age groups N (per 100,000)				
	25	26	27	28	29*	25-29	30-34	35-39	40-44**	45-49**
1989	1 (0.8)	4 (3.2)	6 (4.8)	5 (4.0)	11 (8.9)	27 (4.3)	78 (13.2)	105 (18.7)	77 (13.6)	64 (14.9)
1990	6 (4.7)	6 (4.7)	8 (6.3)	7 (5.5)	8 (6.4)	35 (5.5)	71 (11.9)	109 (19.3)	102 (17.5)	55 (12.5)
1991	4 (3.2)	8 (6.2)	3 (2.3)	8 (6.3)	11 (8.7)	34 (5.3)	84 (13.8)	110 (19.3)	81 (13.9)	63 (13.4)
1992	2 (1.6)	3 (2.4)	7 (5.4)	7 (5.4)	4 (3.1)	23 (3.6)	87 (14.0)	120 (20.8)	80 (14.0)	76 (14.9)
1993	1 (0.8)	7 (5.6)	3 (2.4)	8 (6.2)	12 (9.2)	31 (4.9)	93 (14.8)	118 (20.2)	77 (13.7)	70 (12.9)
1994	3 (2.3)	2 (1.6)	2 (1.6)	7 (5.5)	5 (3.9)	19 (3.0)	72 (11.3)	110 (18.5)	75 (13.3)	89 (15.8)
1995	2 (1.6)	9 (7.0)	5 (4.0)	9 (7.2)	12 (9.4)	37 (5.8)	91 (14.1)	124 (20.5)	78 (13.8)	74 (12.8)
1996	3 (2.4)	6 (4.6)	5 (3.9)	3 (2.4)	11 (8.8)	28 (4.4)	97 (15.0)	116 (18.9)	73 (12.8)	62 (10.7)
1997	0 (0.0)	6 (4.8)	2 (1.5)	8 (6.2)	15 (11.9)	31 (4.9)	90 (14.0)	103 (16.5)	86 (14.9)	84 (14.8)
1998	3 (2.7)	6 (5.0)	5 (4.0)	6 (4.6)	20 (15.5)	40 (6.5)	89 (13.9)	96 (15.2)	93 (15.9)	77 (13.8)
1999	3 (2.9)	7 (6.2)	3 (2.5)	5 (4.0)	15 (11.5)	33 (5.5)	92 (14.6)	105 (16.5)	93 (15.6)	73 (13.1)
2000	1 (1.0)	0 (0.0)	2 (1.8)	4 (3.3)	6 (4.7)	12 (2.3)	93 (15.4)	100 (15.7)	72 (11.9)	64 (11.4)
2001	0 (0.0)	2 (2.0)	9 (8.4)	3 (2.6)	11 (9.0)	24 (4.6)	74 (11.8)	101 (15.2)	69 (11.2)	58 (10.2)
2002	3 (3.1)	1 (1.0)	6 (5.8)	5 (4.6)	12 (10.4)	26 (5.2)	70 (11.2)	79 (12.3)	85 (13.6)	66 (11.5)
2003	0 (0.0)	1 (1.0)	3 (3.0)	3 (2.9)	12 (11.1)	16 (3.7)	66 (11.0)	71 (11.1)	86 (13.6)	61 (10.5)
2004	3 (3.1)	4 (4.1)	6 (6.1)	5 (5.0)	9 (8.7)	27 (5.4)	75 (12.4)	96 (14.8)	-	-
2005	1 (1.0)	6 (6.1)	4 (4.1)	4 (4.1)	13 (13.0)	28 (5.7)	71 (12.3)	88 (13.6)	-	-
EAPC	-1.4%	-3.8%	1.2%	-2.7%	3.6%	2.0%	-0.7%	-3.1%	-0.9%	-2.0%
p-value	0.635	0.260	0.658	0.072	0.102	0.862	0.226	<0.001	0.195	0.012

* the column of age 29 is grey because the incidence rates may be biased by women who were diagnosed by participation in the screening programme

** 2004 and 2005 data not available for this age category

on the incidence among 29-year-old women. Significantly decreasing trends were seen for age groups 35-39 and 45-49 ($p<0.0001$ and $p=0.01$, respectively).With joinpoint analyses we were not able to find any significant changes in trends over time.

Table 2 Mortality from cervical cancer according to age group per 100,000 person-years in the Netherlands, period 1989-2005

Year of diagnosis	Age (group) per 100,000				
	25-29	30-34	35-39	40-44	45-49
1989	3 (0.5)	12 (2.0)	18 (3.2)	16 (2,8)	13 (3.0)
1990	4 (0.6)	10 (1.7)	17 (3.0)	15 (2.6)	16 (3.6)
1991	5 (0.8)	15 (2.5)	15 (2.6)	22 (3.8)	16 (3.4)
1992	4 (0.6)	6 (1.0)	18 (3.1)	15 (2.6)	17 (3.3)
1993	4 (0.6)	10 (1.6)	9 (1.5)	16 (2.8)	15 (2.8)
1994	1 (0.2)	7 (1.1)	17 (2.9)	15 (2.7)	12 (2.1)
1995	1 (0.2)	4 (0.6)	13 (2.2)	15 (2.7)	17 (2.9)
1996	2 (0.3)	7 (1.1)	14 (2.3)	9 (1.6)	19 (3.3)
1997	4 (0.6)	8 (1.2)	13 (2.1)	16 (2.8)	17 (3.0)
1998	0 (0.0)	6 (0.9)	14 (2.2)	14 (2.4)	21 (3.8)
1999	1 (0.2)	7 (1.1)	19 (3.0)	14 (2.4)	21 (3.8)
2000	4 (0.7)	9 (1.4)	11 (1.7)	21 (3.5)	28 (5.0)
2001	3 (0.6)	12 (1.9)	23 (3.5)	10 (1.6)	18 (3.2)
2002	4 (0.8)	5 (0.8)	11 (1.7)	9 (1.4)	16 (2.8)
2003	4 (0.8)	3 (0.5)	10 (1.5)	16 (2.5)	14 (2.4)
2004	0 (0.0)	4 (0.7)	17 (2.6)	17 (2.6)	11 (1.9)
2005	3 (0.6)	8 (1.4)	12 (1.9)	15 (2.3)	14 (2.3)
2006	2 (0.4)	3 (0.5)	10 (15)	13 (2.0)	16 (2.6)
EAPC	1.9%	-5.1%	-2.6%	-2.1%	-1.5%
p-value	p=0.495	p=0.010	p=0.032	p=0.075	p=0.163

Mortality

The annual numbers fluctuated across the years with a decreasing trend for age groups 30-34 and 35-39 years ($p=0.01$ and $p=0.04$, respectively) (table 2). Compared to all other age groups, age group 25-29 was the only group with a (non-significant) increasing trend. Trends in the other age groups were not significant. We were not able to detect any significant joinpoints.

Discussion

Incidence of and mortality from cervical cancer in younger age groups excluded from the screening programme were very low and became lower compared to the rates for the target age group of the screening programme (30 to 60 years). The incidence among women 29-year-old, which is higher than the incidence for ages 25 to 28 separately, can be explained by the call-up schedule and the reorganization of the screening programme. The incidence for women 29-year-old started to rise in 1996, together with the lowering of the screening age from 35 to 30 years. It is known that the incidence of cancer increases after first onset of screening activities, because prevalent cases will be detected then. Also, because the call-up schedule is based on birth years a woman will be called up as a probable, but not certain, 30-year-old at the time of the Pap smear. If we adjust for this phenomenon by considering all women who were actually 29 years old at the time of diagnosis but were going to be 30 years old in the year of diagnosis as 30 at diagnosis, the increase in 29-year-old women becomes a non-significant decrease (EAPC -4.2%, p=0.1).

In the Netherlands, the decrease in age at first intercourse stopped about 10 years ago [16]. However, the incidence of HIV and other sexually transmitted infections has been increasing, according to the latest surveillance data, and an increase in the incidence of HPV infections may therefore also be expected. Tobacco smoking, which is also a risk factor for cervical cancer [17], increased among women in the Netherlands during the 1950s and 1960s and started to decrease around 1970 [18]. In Finland, a recent increase in the incidence of cervical cancer was revealed among young women [19]. There have been no changes in organised screening or diagnostics as such. However, the average number of sexual partners for Finnish women increased and the average age at first intercourse of these women decreased [20]. Also tobacco smoking has increased substantially among young Finnish women during the 1980s [21].

Lowering the screening age will have both psychological and financial effects. In 2004 there were 97,000 25-year-old women in the Netherlands. The mean attendance rate in the Netherlands was 68% for age group 30-34 years (2003) [22]. Projecting this attendance rate to 25-year-old women means that 64,000 25-year-old women would have been screened if the target age of the screening programme was 25-60 years. In the Netherlands, the frequency of abnormal smears among 30-year-old women was 3.9% ≥ CIN 1 in 2003 [23]. A study from the USA found that 4% of women aged 25-29 years have HSIL or higher or to have repeated borderline findings, which means that about 2560 women (4% of 64,000) will be referred to a gynaecologist for colposcopic evaluation in the Netherlands [24]. In addition to the anxiety associated with undergoing a

colposcopic examination, false positive results may cause persistent anxiety for many years. On the other hand, a negative screening test result may reinforce an unhealthy lifestyle [25]. Another problem is 'overtreatment'; many women undergo conisation or loop electrosurgical excision procedure (LEEP) for a CIN which may otherwise go into regression due to its transient nature, especially in young women. Another potential adverse effect of false-positive results is the expenses of follow-up diagnostic procedures.

Although lowering the screening age for the whole population does not seem to improve the result of the screening programme in the Netherlands, there might be specific risk groups for cervical cancer at young age. Several studies have found more cervical abnormalities among young women in certain immigrant populations who are also known for their lower screening attendance rates [26;27]. Increasing their knowledge about HPV infection might result in higher screening attendance rates. Another risk group are prostitutes who run a higher risk of HPV infections and cervical intraepithelial lesions [28]. Finally, according to some studies, genital HPV infections and cervical intraepithelial lesions are more common among sexually abused than nonsexually abused girls [29]. However, since other studies indicate that the majority of anogenital HPV infections among children are probably the result of nonsexual horizontal transmission [30] and because it is so difficult to prove whether HPV infections are the result of involuntary sexual activity, it is almost impossible to classify these women as a risk group and to treat them differently in terms of offering them smears more frequently.

Unfortunately, CIN lesions and carcinoma in-situ are not included in the Netherlands Cancer Registry. Although CIN 1 and CIN 2 have very low progression rates, CIN 3 (severe dysplasia) rates or rates of cervix carcinoma in-situ could have been good predictors for a (future) rise in the incidence of cervical cancer. Furhtermore, these rates could have been used in the evaluation of the screening programme. Because the number of cervical cancer cases per age year was very small, it hampered the finding of statistically relevant changes in trends in incidence and mortality rates.

In conclusion, because increases in incidence and mortality rates for cervical cancer could not be found in this study or could just be attributed to earlier screening activity at age 29 since 1996, further lowering the age for cervical cancer screening does not seem useful at this time. Although mortality from cervical cancer is very low, the number of life-years gained is high per woman who is prevented from developing cervical cancer. However, the disadvantages of lowering the screening age in terms of 'overtreatment' and anxiety are very high and seem therefore to be disproportionate. It seems better to focus on improving the attendance rates among high risk groups, improving the quality of

the smear and the validity of the cytological diagnosis with possibly adding the HPV test. The potential introduction of an HPV vaccine might make this problem superfluous in the long run, even though some sort of mass screening programme might need to remain in place.

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Chapter 5

Determinants of survival

5.1

Management and survival of cervical cancer in the east and the south of the Netherlands, 1989-2004

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Abstract

Background. This study aims to describe trends and variation in treatment and survival of cervical cancer in two regions in The Netherlands and to relate this to adherence to the treatment recommendations.

Methods. Patient characteristics, tumor characteristics, treatment and follow-up data were collected for 1954 cervical cancer cases diagnosed in the period 1989-2004.

Results. In FIGO IB-IIA 93% of patients were treated according to the recommendations of the working group. No survival benefit was found for patients receiving radical hysterectomy+radiotherapy. In FIGO IIB-IVA 76% of patients were treated according to the recommendations of the working group. Chemoradiation was given to older patients less often than to younger patients: 2% (0.5-5 95% CI) versus 23% (16-29 95% CI). No survival disadvantages were found for patients who received radical hysterectomy+radiotherapy, which is in contrast to the recommendations. A decreased risk of death was found for patients receiving chemoradiation (RER 0.6, 0.3-0.9 95% CI) compared to those receiving “radiotherapy only”.

Discussion. Far from being always followed, the treatment recommendations were better implemented for treatment of patients with FIGO IB-IIA. Attention has to be paid to the role of adjuvant radiotherapy in FIGO IB-IIA. Within the broad spectrum of patients with FIGO IIB-IVA, individual patient and tumor characteristics remain of major importance for adequate treatment. Elderly patients with FIGO IIB-IVA were more likely to have received suboptimal treatment in this study and showed an independent increased risk of death, which confirms that the need becomes stronger for paying attention to treatment of elderly patients.

Introduction

According to the treatment recommendations which were described by the Netherlands Working Group Gynecologic Oncology in 1990 and which were altered into national guidelines in 2004, conisation or simple hysterectomy is the treatment of choice for FIGO stage IA1 cervical cancer. In case of unfavorable prognostic factors, a pelvic lymphadenectomy is advised. For FIGO stage IA2 with presence of unfavorable prognostic factors, pelvic lymphadenectomy after conisation is advised in case of a wish for children and radical hysterectomy when there is no wish for children. Conisation or simple hysterectomy may only be offered in the absence of unfavorable prognostic factors [1;2]. For FIGO stages IB-IIA the primary treatment of choice, radical hysterectomy or primary radiotherapy, will be based on age and contra-indications for surgery and not on tumor characteristics [3]. For FIGO stages IB-IIA radiotherapy is just as effective as radical hysterectomy, 5-year survival rates after radiotherapy being 74-91%, which is comparable to 83-91% reported for radical surgery [4]. In the present national guidelines which were firstly established in 2004, and which were only recommendations until that time, radical hysterectomy and primary radiotherapy are both advised for patients with FIGO stages IB-IIA 2. A primary surgical approach gives insight into the depth of invasion of cervix and lymphovascular space, occult extrauterine disease such as nodal involvement, parametrial extension or intraperitoneal spread can be identified, lymphatic disease can be debulked and the ovarian function can often be preserved [5]. Adjuvant radiotherapy for high-risk patients (parametrial invasion, large lesion size, positive surgical margin) after surgery for stage I cervical cancer is often used to improve local control rates but has no effect on survival [6].

In the recommendations of 1990, radiotherapy was the primary treatment of choice for FIGO stages IIB-IVA 1. However, in 1999 a clinical advisory committee of the National Cancer Institute (NCI) announced that five clinical trials demonstrated superiority of combined platinum-based chemoradiation over radiotherapy only [7-11]. In advanced cervical cancer concurrent chemoradiation improved 5-year survival rates from 38% to 42% 6. In 2002 a three-year overall improvement of 27-51% was found for the survival of patients with FIGO stages IIB-IVA after radiotherapy combined with hyperthermia in a Dutch trial [12]. According to the present national guidelines, these patients should now be given chemoradiation or radiotherapy combined with hyperthermia [2].

Treatment of patients diagnosed with FIGO stage IVB depends increasingly on specific patient and tumor characteristics.

Since the 1970s cytological screening on an individual basis has been available for women in some regions of the Netherlands in a combination with local and

regional invitational programs and opportunistic screening. The nationwide screening program, which was started in 1988, resulted in the identification of lower stage tumors since they will be caught earlier [13]. In addition to the screening program, new diagnostic procedures, such as the CT-scan and MRI, were introduced in the 1980's and 1990's. This, together with the introduction of more advanced and specific treatment modalities based on the national guidelines should lead to increased survival rates.

The aim of this study is to describe changes and variation in stage, treatment and survival of patients with cervical cancer diagnosed in the period 1989 to 2004 in the regions of the Comprehensive Cancer Centre Stedendriehoek Twente (CCCST) and the Comprehensive Cancer Centre South (CCCS) in The Netherlands and to relate this to adherence to the recommendations of the Netherlands Working Group Gynecologic Oncology.

Methods

Patient selection

The cancer registries of the CCCST and the CCCS are population-based registries and form part of the nationwide Netherlands Cancer Registry as of 1989. Both serve community hospitals only. The cancer registry of the CCCST was started in 1989 and serves nowadays 1.1 million inhabitants. The cancer registry of the CCCS was started in 1955; this region nowadays covers 2.3 million inhabitants. The two registries together serve about 20% of the total population of the Netherlands. All malignant tumors are registered in the (community) hospitals in both regions. Notification is obtained from Pathology (the automated archive PALGA), and the Hematology Departments in the region. Other sources are Radiotherapy Departments, as well as the National Registry of Hospital Discharge Diagnoses (LMR), which accounts for up to 8% of new cases [14]. Death certificates are not available to the cancer registries because of privacy regulations.

Specially trained registration clerks routinely collect data from the medical records on identifying information (e.g. first letters of the name, date of birth, sex, postal code), tumor characteristics (e.g. date of diagnosis, topography, morphology, stage), treatment and follow-up data. A national manual describes inclusion and exclusion criteria as well as the definitions and coding of items. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICDO)[15]. FIGO stage and lymph node status were derived from the clinical TNM stage (cTNM). In case of an unknown

cTNM, FIGO stage and lymph nodes status were derived from the pathological TNM stage (pTNM) [16]. Lymph node status is not included in the FIGO classification for cervical carcinoma, and therefore it was described separately. National coding rules allow registration clerks to give only a positive or negative clinical lymph node status when a CT-scan of the pelvis has been performed. When there is no information about a CT-scan in the patient file, registration clerks have to code clinical lymph node status as unknown.

Information on the vital status of all patients was collected actively from the hospitals, general practitioners and municipality registries.

All cases of cervical cancer cases diagnosed between 1 January 1989 and 1 January 2005 were selected from the regional cancer registries of the CCCST and the CCCS. Cases diagnosed in 2003 and 2004 were not included in the survival analyses.

Statistical analysis

The Statistical Package for Social Sciences (SPSS version 12.0) was used to perform the analyses. FIGO stages were classified as IA, IB-IIA, IIB-IVA and IVB, because treatment is based on this classification [1;2]. Period of diagnosis was subdivided into 4 categories for analysis of treatment: 1989-1992, 1993-1996, 1997-2000 and 2001-2004. For survival analyses the period of diagnosis was divided into 3 categories: 1989-1993, 1994-1998 and 1999-2002. Age was also divided into 3 categories: younger than 50 (<50), between 50 and 70 (50-69) and 70 years and older (>=70). Differences in distribution over age, stage, nodal involvement, histological grade and morphology between tumors from the CCCS and CCCST were assessed by Chi-square analysis (p-values from two-sided tests). Differences between both regions were assessed because they were served by gynecologists practicing in community hospitals only. Relative survival was calculated as a measure of disease-specific survival using the Ederer II method in STATA version 9.2 [17]. The relative survival is the ratio between crude and expected survival and is close to disease-specific survival. Separate analyses were performed for survival of those with stages IB-IIA and stages IIB-IVA. In modeling relative survival, variables were considered confounders and included in the model when the regression coefficient of the variable of interest changed by more than 10%. Relative excess risks (RER) and 95% confidence intervals (CI) were calculated. The relative excess risk (RER) describes the difference between the hazard of death in a given group and in the reference group, taking into account the risk of death in the Dutch population. Nodal involvement and morphology were divided into categories and entered into the model as dummy variables. P-values of less than 0.05 were considered statistically significant (two-sided).

Table 1 Patient and tumour characteristics of patients with cervical cancer living in the east (CCCST) and south (CCCS) of the Netherlands and diagnosed in the period 1989-2004 (%)

		Overall (n=1954)	CCCST (n=698)	CCCS (n=1256)
Mean age at diagnosis		51.7 (50.9-52.4)	51.1 (49.8-52.4)	52.0 (51.0-52.9)
Age group	<50	52	54	51
	50-69	28	25	29
	≥70	20	20	20
FIGO stage	IA	28	30	27
	IB-IIA	37	33	40
	IIB-IVA	27	29	26
	IVB	5	6	4
	X	3	2	3
FIGO stage/ lymph node	IA/negative	42	32	48
	IA/positive	2	1	2
	IA/unknown*	56	66	50
	IB-IIA/negative	70	60	75
	IB-IIA/positive	13	16	11
	IB-IIA/unknown*	17	24	14
	IIB-IVA/negative	33	24	36
	IIB-IVA/positive	15	18	13
	IIB-IVA/unknown*	52	57	49
	IVB/negative	13	14	12
	IVB/positive	40	43	38
	IVB/unknown*	47	43	50
	X/negative	11	0	15
	X/positive	4	6	3
	X/unknown*	86	94	83
Histology grade	good	7	7	7
	intermediate	30	28	32
	poor	28	27	28
	anaplastic	2	1	2
	unknown	34	37	31
Morphology	adeno	15	16	15
	squamous	73	73	74
	other	11	11	12

* according to registration practices

Results

From the cancer registries of the CCCS and the CCCST 1954 patients were selected. The mean age at diagnosis was 51.7 years, the youngest and oldest patients being 12 and 100 years, respectively (table 1). A trend in age at diagnosis could not be discovered (data not shown). Two girls younger than 20 at diagnosis had rhabdomyosarcomas: one girl of 12 years old lived in the CCCST region and another of 15 in the CCCS region. Most patients were younger than 50 (52%), and most patients were diagnosed with FIGO stages IB-IIA (37%). In the CCCST region the lymph node status per FIGO stage was unknown for more patients (data not shown: $p<0.05$). Histological grade was known in 66% of cases, and most frequent grades were intermediate (30%) or poor histological grade (28%). Squamous cell carcinoma was the most common morphological type (73%). A trend in time for morphological type was not found (data not shown).

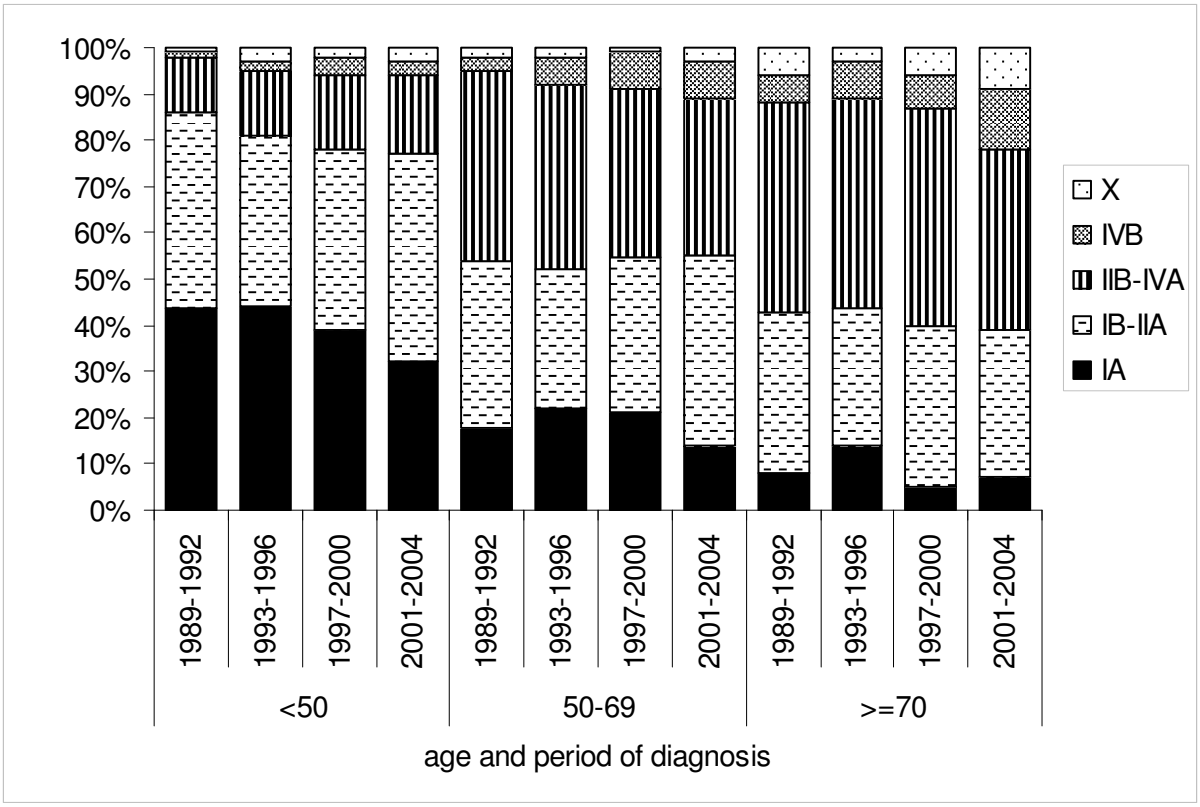

Figure 1 Trends in stage distribution of cervical cancer in the Netherlands in the period 1989-2004 (N= 1954).

Trends in stage distribution

Small changes in stage distribution were found across different time periods (figure 1). Differences in FIGO stages per age group were found: 15% FIGO stages IIB-IVA in age group <50 years (12-17 95% CI) compared to 38% (34-42 95% CI) in age group 50-69 years and 44% (39-49 95% CI) in age group >=70 years ($p<0.05$). Small differences in lymph node status were found across different periods (data not shown).

Trends in treatment according to FIGO classification

Patients with FIGO stages IA1 and IA2 (n=549) underwent mainly hysterectomy (34%), local treatment being conisation or loop excision (26%) or surgery "not otherwise specified" (nos) (35%). It was not possible to discover a trend in time because hysterectomy and local treatment were both coded as "surgery nos" until 1995.

Of patients with FIGO stages IB-IIA tumors (n=730), 93% were treated according to the recommendations of the working group (radical hysterectomy or radiotherapy only). The proportion of patients treated according to the recommendations of the working group decreased from 97% (95-99 95% CI) in 1989-1992 to 83% (77-88 95% CI) in 2001-2004 ($p<0.05$) (figure 2). Adjuvant radiotherapy was given to 72% of patients with positive lymph nodes who were treated with radical hysterectomy. Negative lymph node status was found for 47% of the patients who received adjuvant radiotherapy. The use of chemoradiation increased from 0.5% (0-1 95% CI) in 1989-1992 to 10.5% (6-15 95% CI) in 2001-2004 ($p<0.05$). No differences were found in treatment regimens between the specialists of the CCCS and CCCST regions (data not shown).

Considering the whole period, 76% of patients with FIGO stages IIB-IVA (n=527) were treated according to the recommendations of the working group (radiotherapy, eventually combined with hyperthermia and chemoradiation), without much variation over time (figure 3). In the CCCST region this proportion was 84% (79-89 95% CI) in contrast to 73% (68-77 95% CI) in the CCCS region ($p<0.05$), where 43 patients (13%) with FIGO stages IIB-IVA underwent radical hysterectomy followed by radiotherapy: 81% with FIGO stage IIB and 77% younger than 70. The proportion of patients receiving chemoradiation increased from 6% (2-10 95% CI) to 34% (25-43 95% CI) ($p<0.05$). Chemoradiation was given to older patients less often than to younger patients: 2% (0.5-5 95% CI) of patients older than 70 versus 23% (16-29 95% CI) and 17% (12-22 95% CI) of patients younger than 50 and 50-69 years old, respectively ($p<0.05$). Of patients

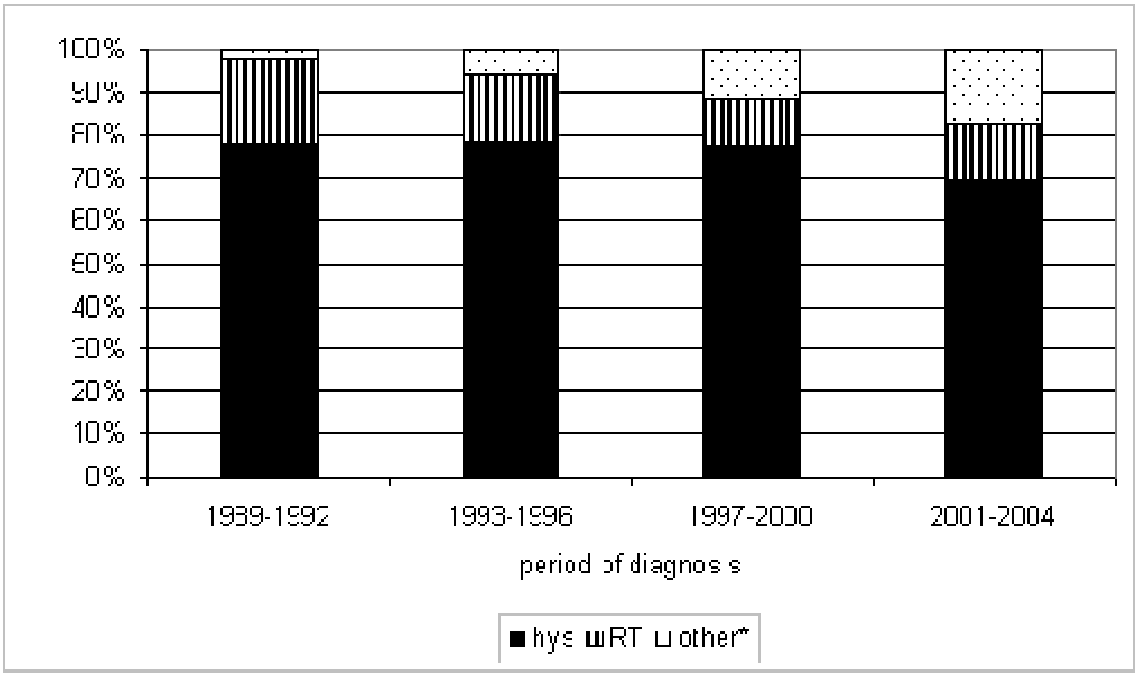

Figure 2 Percentage of patients with cervical cancer who underwent radical hysterectomy (HYS) or radiotherapy (RT) per period of diagnosis FIGO IB-IIA (N=730) in the Netherlands in the period 1989-2004 (N= 1954)

* surgery nos, vaginal hysterectomy, primary chemotherapy, hormonal therapy, metastasectomy, unknown therapy, no therapy

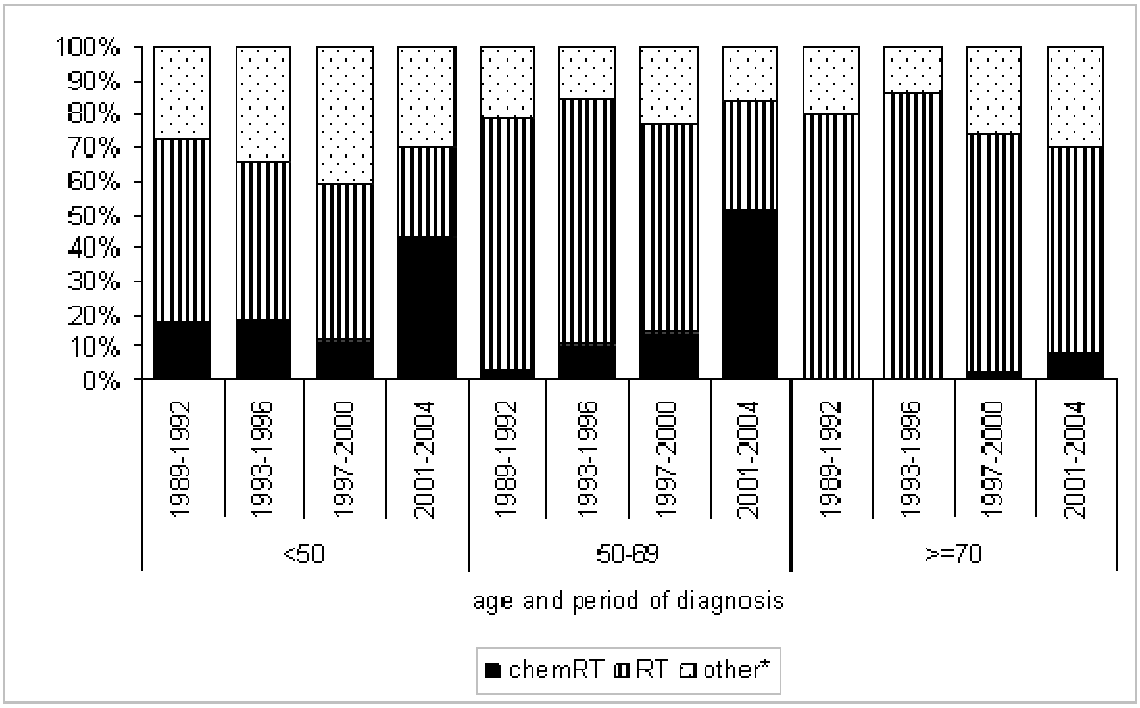

Figure 3 Percentage of patients with cervical cancer who underwent radiotherapy (RT) or chemoradiation (chemRT) per year of incidence FIGO IIB-IVA (N=527) in the Netherlands in the period 1989-2004 (N= 1954)

* surgery nos, vaginal hysterectomy, primary chemotherapy, hormonal therapy, metastasectomy, unknown therapy, no therapy

receiving radiotherapy, 6% received both radiotherapy and hyperthermia. Patients diagnosed with FIGO stage IVB (n=92) received mainly radiotherapy (36%) or no therapy (33%). However the proportion of patients receiving radiotherapy decreased from 60% (35-85 95% CI) in the period 1989-1992 to 18% (15-49 95% CI) in the period 2001-2004 (p>0.05). Other therapies included treatment of metastases (10%), chemotherapy (8%) or chemoradiation (8%).

Survival

During the period 1989-2002, the crude 5-year overall relative survival rate was 68%. Patients with FIGO stage IA exhibited a relative 5-year survival of 90% compared to 2% for patients diagnosed with FIGO stage IVB. Both regions exhibited 5-year relative survival rates of 68%.

Table 2 Relative excess risk of death (RER) for patients diagnosed with cervical cancer in the east (CCCST) and south (CCCS) of the Netherlands in the period 1989-2002, FIGO stages IB-IIA (N=624)

		Univariate		Multivariate [a]	
Factor	Cases	RER	95% CI	RER	95% CI
Age group					
<50	349	0.6*	0.4-0.9	0.6*	0.4-0.9
50-69	160	1	reference	1	reference
≥70	115	1.4	1.4-3.5	1.1	0.7-1.8
Lymph nodes					
negative	426	1	reference	1	reference
positive	84	2.2*	1.4-3.4	2.1*	1.1- 3.3
unknown	114	2.2*	1.4-3.5	1.1	0.6- 1.8
Treatment					
radical hysterectomy	486	1	reference	1	reference
radiotherapy	96	3.0*	2.0-4.5	2.3*	1.4- 3.9
other	42	2.8*	1.5-5.5	3.0*	1.6- 5.8

* p<0.05 CI=confidence interval [a] Adjusted for all other factors in the table

Table 2 shows the results of the univariate and multivariate analyses of relative survival for FIGO stages IB-IIA. In univariate analysis, the relative excess risk of death decreased with younger age (RER 0.6, 0.4-0.9 95% CI) and increased with positive and unknown lymph node status (RER 2.2, 1.4-3.4 and RER 2.2, 1.4-3.5 95% CI). Furthermore, an increased excess risk was found for patients who received radiotherapy only or other therapies (RER 3.0, 2.0-4.5 and RER 2.8, 1.5-5.5 95% CI), compared to those who just underwent radical

hysterectomy (figure 4). Survival for patients who received adjuvant radiotherapy after radical hysterectomy had equal survival compared to patients who received radical hysterectomy only, after correction for age and lymph node status (data not shown). Within the group of patients with FIGO stages IB-IIA and positive lymph node status relative survival for patients who underwent radical hysterectomy only was 51% (12-81 95% CI) compared to 63% (47-75 95% CI) for patients receiving adjuvant radiotherapy after radical hysterectomy. Period of

Table 3 Relative excess risk of death (RER) for patients diagnosed with cervical cancer in the east (CCCST) and south (CCCS) of the Netherlands in the period 1989-2002, FIGO stages IIB-IVA (N=475)

		Univariate		Multivariate	
Factor	Cases	RER	95% CI	RER	95% CI
Age group					
<50	131	1.2	0.9-1.7	1.1	0.8-1.5
50-69	189	1	reference	1	reference
≥70	155	1.3	0.9-1.7	1.7*	1.2-2.4
Lymph nodes					
negative	156	1	reference	1	reference
positive	59	1.7*	1.1-2.5	1.5*	1.0-2.2
unknown	260	1.0	0.8-1.4	1.2	0.9-1.7
Treatment					
RT	314	1	reference	1	reference
radical hysterectomy+RT	51	0.7	0.4-1.1	0.6	0.4-1.0
chemRT	50	0.6	0.4-1.0	0.6*	0.3-0.9
other	60	2.6*	1.8-3.7	2.4*	1.6-3.4

* p<0.05 CI=confidence interval [a] Adjusted for all other factors in the table

diagnosis was not associated with risk of death (figure 5). In multivariate analysis, a decreased excess risk was still found for younger patients (RER 0.6, 0.4-0.9 95% CI) and an increased excess risk was still found for patients with positive lymph node status (RER 2.1, 1.1-3.3 95% CI) and for patients who received radiotherapy only or other therapies (RER 2.3, 1.4-3.9 and RER 3.0, 1.6-5.8 95% CI).

Table 3 shows the results of the univariate and multivariate analyses of relative survival for FIGO stages IIB-IVA. Univariately, an increased relative excess risk of death was found for patients diagnosed with positive lymph node status (RER 1.7, 1.1-2.5 95% CI) and other therapies (RER 2.6 1.8-3.7 95% CI). Period of diagnosis was not associated with risk of death. Multivariately, women in the oldest age group had an increased excess risk compared to those 50-69 years

(RER 1.7, 1.2-2.4 95% CI). Furthermore, increased excess risks were found for positive lymph node status (RER 1.5, 1.0-2.2 95% CI) and other therapies (RER 2.4, 1.6-3.4 95% CI). A decreased excess risk was found for patients who received chemoradiation (RER 0.6, 0.3-0.9 95% CI) compared to those receiving radiotherapy only.

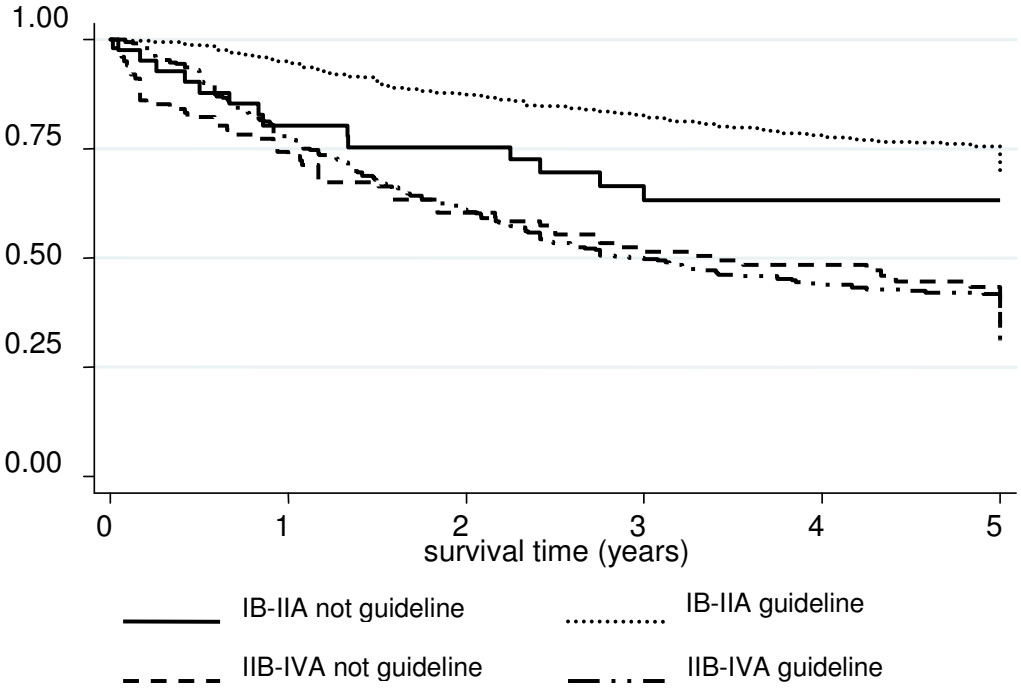

Figure 4 Kaplan-Meier survival estimates, by guideline adherence

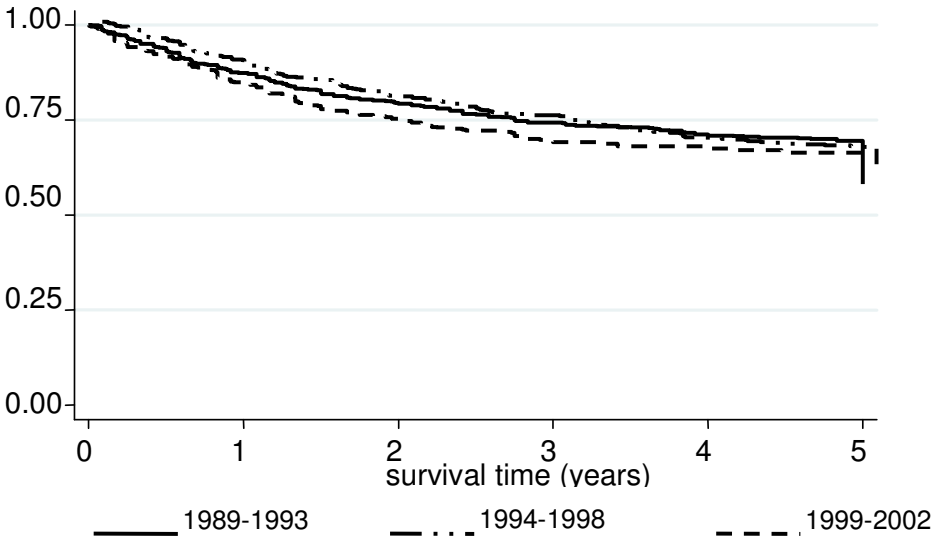

Figure 5 Kaplan-Meier survival estimates, by period of diagnosis

Discussion

The recommendations for treatment of cervical carcinoma were implemented for the treatment of FIGO stages IB-IIA better than for FIGO stages IIB-IVA but they certainly were not always followed.

Treatment of FIGO stages IB-IIA tumors was usually radical hysterectomy and no differences were found in survival between patients undergoing radical hysterectomy and patients undergoing radical hysterectomy and adjuvant radiotherapy. Partly, this could be explained by the fact that 47% of these patients had a negative lymph node status. However, lymph node status on the basis of CT scanning is unreliable and data concerning risk factors like infiltration depth and parametrial invasion were not available in this study. Patients who received adjuvant radiotherapy sufficed the criteria of the Gynecologic Oncology Group which are taken up in the Dutch recommendations: radiotherapy is recommended for patients with risk factors such as pelvic lymph node metastasis, parametrial invasion and positive resection margins or in the presence of two out of three unfavourable prognostic factors (vascular space invasion, deep stromal invasion and tumor diameter >4 cm) [1;2]. The effect of postoperative radiotherapy in improving local control has been demonstrated extensively, but without any improvements in survival, yet [18-21]. Since some studies have already concluded that radiotherapy (whether or not after hysterectomy) for cervical cancer reduces quality of life, quality of life measurements should be included more often in future clinical trials, for example in terms of psychological and sexual functioning [22-24]. In the present study, patients with FIGO stage IB-IIA receiving radiotherapy only exhibited worse survival than those after radical hysterectomy after correction for risk factors such as age and lymph node status. This would contrast a study from Japan which suggested that radiotherapy only may be as effective for the lower stages of cervical carcinoma as radical hysterectomy [4]. The results of our study will mainly be due to selection bias because patients who have been offered radiotherapy only instead of surgery in general have poorer general condition. However, this study does not have enough details to get insight into causes for this difference.

At the FIGO Congress in Montreal in 1994, the Gynecologic Oncology Committee made some changes in the staging for cervical cancer, concerning FIGO stage IA and FIGO stage IB [25]. Because of the classification used in this study, the results of this study should not be affected by the changes in FIGO staging. However, this broad classification of FIGO stages could be a source for residual confounding, just like not taking into account differential treatment or after-treatment follow-up.

For 43 patients with FIGO stages IIB-IVA, treatment did not follow the recommendations in the region of the CCCS. One gynecologist working in one hospital in the CCCS region refused to give young patients with FIGO stage IIB (chemo)radiation, when he could also offer them radical hysterectomy followed by radiotherapy. A study of the validity of stage in the south of the Netherlands revealed 12% major and 23% minor disagreements when staging of the specialist was compared to staging information in the Maastricht cancer registry, so misclassification can also explain the discrepancy [26]. However, the prognosis for patients diagnosed with FIGO IIB-IVA was not worse after treatment with radical hysterectomy and adjuvant radiotherapy than for patients treated according to the recommendations. From 2000 onwards, both the CCCST and CCCS regions followed the clinical alerts published by the NCI concerning chemoradiation for patients with FIGO stage IIB-IVA while these alerts were not incorporated into the national guidelines until 2004. In accordance with a meta-analysis in 2001, a significant survival benefit could be seen in the present study for chemoradiation compared to radiotherapy only [27].

In conclusion, changes in survival were expected in different time periods related to the introduction of new staging strategies such as CT-scans and MRI, and new treatment strategies such as chemoradiation, but no improvements in survival have been seen yet. However, the influence of small improvements in diagnosis and treatment on survival is sometimes overestimated, definitely when taking into account that slow growing tumors are detected within the cervical cancer screening program leaving the more aggressive tumors to be treated. In the next revision of the national guidelines, attention has to be paid to the role of adjuvant radiotherapy because survival benefits could not be proven so far. Furthermore, although we did not have detailed information about prognostic factors, it can be concluded that elderly patients with FIGO stages IIB-IVA in this study were likely to have received suboptimal treatment. Combined with the independently increased risk of death for these patients the need becomes stronger for paying attention to treatment of elderly patients.

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5.2

Co-morbidity and age affect treatment policy and prognosis for cervical cancer: a population-based study in the south of the Netherlands, 1995- 2004

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Abstract

Background. Treatment of elderly patients with cervical cancer as well as patients with co-morbidity is often not based on standard recommendations, therefore survival of such patients may be poorer.

Aim. To estimate the effects of age and co-morbidity on the choice of treatment modalities and prognosis for patients with cervical cancer.

Methods. All patients with cervical cancer newly diagnosed between 1995 and 2004 (n= 775) were selected from the population-based Eindhoven Cancer Registry. Time trends in treatment modalities and differences in treatment between patients with and without co-morbidity were assessed by Chi-square analysis and a multivariate Cox regression model was used to evaluate the independent prognostic effects of age and co-morbidity.

Results. For patients with FIGO stages IB-IIA (excluding IB2), both age and co-morbidity significantly affected the choice of treatment. In multivariate survival analysis, age had an independent prognostic value: the risk of dying increased by 2% for every additional year in age. For patients with FIGO stages IB2, IIB-IVA, age especially affected the choice of chemoradiation significantly. According to multivariate survival analysis, co-morbidity and FIGO stage were independent prognostic factors: the risk of death for patients with 1 co-morbid condition was twice as that high as for patients without co-morbidity. Furthermore, the risk of death of patients with FIGO IIIA, IIIB, and IVA was 2.0, 3.5 and 7.7 respectively, times higher compared to patients diagnosed with FIGO IIB.

Conclusion. Treatment of elderly patients with cervical cancer and those with co-morbidity was quite different. Furthermore, co-morbidity had an independent prognostic value for patients with FIGO stages IB2, IIB-IVA. Because of its ever increasing role in clinical decision-making for increasingly older patients in the near future, development of age-specific guidelines incorporating levels and management of specific co-morbidity seems warranted.

Introduction

As in most northwestern European populations, the incidence of and mortality from cervical cancer have been decreasing in the Netherlands [1]. The main risk factor for cervical cancer, Human Papillomavirus (HPV), is found in almost all patients with cervical cancer, being strongly related to sexual behaviour, especially with multiple partners and early age at first intercourse [2]. Smoking markedly affects risk while a large number of live births and oral contraceptive use are also risk indicators [3;4].

According to the national recommendations in 1990 for FIGO stage IB and IIA cervical cancer, primary surgery and radiotherapy were equal therapeutic options, the choice depending mainly on patient characteristics such as age and co-morbidity. Radiotherapy was the treatment of first choice for FIGO stages IIB-IVA [5]. In 1999 the American National Cancer Institute (NCI) announced that adding chemotherapy to radiation therapy was highly recommended. This statement was based on five clinical trials which demonstrated superiority of combined platinum-based chemoradiation over radiotherapy alone for patients with high risk and/or locally advanced cervical cancer [6-10]. A Dutch trial combining radiotherapy with hyperthermia also resulted in a significant improvement in the 3-year overall survival for patients with FIGO stages IIB-IVA [11]. Therefore, from 2004 on the revised national guideline recommends primary chemoradiation or radiotherapy combined with hyperthermia for patients with FIGO stage IB2, IIB and higher [12].

In general, treatment guidelines are based on the results of clinical trials from which patients with co-morbidity and/or older age are often excluded. However, treatment of individual patients will be affected by age and co-morbidity [13]. Therefore, we studied the influence of age and co-morbidity on the treatment modalities chosen and the ultimate survival of unselected patients with cervical cancer.

Methods

Data collection

All patients with cervical cancer diagnosed between 1st January 1995 and 31st December 2004 (n=775) were selected from the Eindhoven Cancer Registry, that records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants that is served by the Comprehensive Cancer Centre South (IKZ). It consists of 10 community

hospitals at 16 sites and two large radiotherapy institutes in Tilburg and Eindhoven.

After notification from the pathological laboratories, trained registration clerks collect information from the medical records on diagnosis, tumour stage and treatment. To explore the increasing complexity of oncological care in a greying population, serious co-morbidity with prognostic impact at the time of cancer diagnosis has been recorded for all patients since 1993, according to a slightly modified version of the Charlson index (table 1) [14].

Table 1 Classification of co-morbidity, according to an adapted list of Charlson et al. [14]

Previous malignancies (except basal cell skin carcinoma and cervix carcinoma in situ)
Chronic obstructive pulmonary diseases
Cardiovascular diseases - Myocardial infarction - Heart failure - Angina pectoris - Intermittent claudication - Abdominal aneurysm - Cardiomyopathy - Valve prothesis (aorta or mitralis)
Cerebrovascular diseases - Cerebrovascular accident - Hemiplegia
Hypertension
Digestive tract diseases - Ulcerative disease (only registered since 1997) - Patients who underwent major surgery for ulcerative disease (Billroth I or II) - Chronic inflammatory diseases (Crohn's disease, ulcerative colitis except polyposis coli)
Liver disease (cirrhosis, hepatitis)
Diabetes mellitus
Other - Urinary tract diseases - Connective tissue diseases - Dementia - Chronic infections

Information on co-morbidity is obtained from reports on previous admissions, letters from and to other specialists, the medical history and preoperative screening. In the absence of information on co-morbidity in the patient files, the

registrars have to code this as 'unknown'. Patients for whom co-morbidity was unknown were excluded from the survival analyses (n=37 with FIGO IB-IIA and n=37 with FIGO IB2, IIB-IVA).

Tumour stage was defined according to the FIGO staging system, based on pre-operative clinical information. Only patients with FIGO Stage IB – IVA were included for further analysis of treatment and survival. Because of the different treatment recommendations, the patients were divided into two groups: FIGO stages IB(excluding IB2)-IIA and FIGO stages IB2, IIB-IVA. FIGO stage IB2 was included in stage group IIB-IVA because treatment of FIGO IB2 is considered to be chemoradiation since the publication of the National Cancer Institute in 1999 [15]. Although FIGO stage IB was divided into stages IB1 and IB2 in 1997, this modification has been included in the cancer registry only since 1999 [16].

Treatment of patients with FIGO stages IB-IIA was classified as surgery (+/- radiotherapy, +/- chemotherapy), radiotherapy (+/- chemotherapy) and other/none (palliative, lymph node dissection only, chemotherapy only, metastasectomy and unknown therapy). Treatment for FIGO stages IB2, IIB-IVA was classified as radiotherapy, chemoradiation (including radiotherapy combined with hyperthermia, n=2), surgery (+/- radiotherapy, +/- chemotherapy) and other/none (palliative, lymph node dissection only, chemotherapy only, metastasectomy and unknown therapy).

Socioeconomic status (SES) was considered to be a possible confounder. The SES of each patient was defined at the neighbourhood level (based on postal code of residence, 17 households on average) combining mean household income and mean value of the house, derived from individual fiscal data made available at an aggregated level. Postal codes were assigned to three SES categories: low (1st-3rd decile), intermediate (4th-7th decile) and high (8th-10th decile). Postal codes of institutions, such as nursing homes, were assigned to a separate category and excluded from the analyses of SES (n=39).

Vital status was available up to January 1st 2006. In addition to passive follow-up via the hospitals, this information was also obtained through the national Genealogical Office and the Municipality Administration Database, where all deceased and emigrated persons in the Netherlands are registered via the civil municipal registries.

Statistical analysis

The prevalence of co-morbidity was analysed according to age (<70 and >= 70 years). Time trends in treatment modalities and differences in treatment between patients with and without co-morbidity were assessed by Chi-square analysis, overall and by age group.

Crude 5-year survival rates were computed, survival time being the time from diagnosis to death or January 1st 2006. The log-rank test was performed to evaluate significant differences between survival curves in univariate analyses. A multivariate Cox regression model was constructed for evaluation of the independent prognostic effects of age and co-morbidity on survival. The independent prognostic effects of age and co-morbidity were first estimated using a model without treatment modality. Then treatment was included in the model in order to investigate whether the prognostic effects of age and co-morbidity could be fully explained by the treatment modality chosen. The prognostic effect of the number of co-morbid conditions was also evaluated. The prognostic impact of specific diseases and combinations of diseases could not be evaluated because the number of patients in each subgroup was too small. Hazard ratios (HR) and 90% confidence intervals (CI) were calculated. Due to the small number of patients in each subcategory, p-values of 0.10 were considered significant. Period of diagnosis, SES and FIGO stage were divided into categories and entered into the model as dummy variables using a stepwise approach. Variables were considered confounders and included in the model when the regression coefficient of the variable of interest (treatment) changed by more than 10%. Separate analyses were performed for survival of those with stages IB-IIA and stages IB2, IIB-IVA. Furthermore, relative survival was calculated to estimate differences between the two age groups as a measure of disease-specific survival using the Ederer II method in STATA version 9.2 [17]. Relative survival is the ratio between crude and expected survival and approaches disease-specific survival. Relative survival was used only to estimate differences between age groups since overcorrection would occur if patients without co-morbidity were compared with the general population.

Results

General

The median age of the patients in this study was 48 years (range 15-100), 81% being younger than 70 years at diagnosis. Most patients presented with FIGO stage IB(excluding IB2)-IIA (37%), followed by 28% of patients with FIGO IA and 26% of patients with FIGO stages IB2, IIB-IVA. Six percent of the patients presented with metastatic disease. FIGO stage was unknown in 3% of cases. The proportion of patients with one or more co-morbid conditions at the time of diagnosis was 18% for patients aged <70 and 59% for patients aged >=70 ($p<0.001$). The most frequent co-morbidity in both age categories was

hypertension. Cardiovascular diseases and diabetes were also very common among those aged >=70 (table 2).

Table 2 Number and type of co-morbid conditions present in newly diagnosed patients with cervical cancer in south-eastern Netherlands, 1995-2004, according to age group

	<70 yrs N (%)*	>=70 yrs N (%)*	Total N (%)*
Number of co-morbid conditions			
0	408 (65)	43 (29)	451 (58)
1	84 (13)	49 (33)	133 (17)
2 or more	27 (4)	40 (27)	67 (9)
Unknown	106 (17)	18 (12)	124 (16)
Type of co-morbid condition			
Previous cancer	20 (3)	15 (10)	35 (5)
Cardiovascular disease	22 (4)	38 (25)	60 (8)
Hypertension	36 (6)	42 (28)	78 (10)
COPD	23 (4)	9 (6)	32 (4)
Diabetes mellitus	24 (4)	28 (19)	52 (7)
Cerebrovascular	4 (1)	10 (7)	14 (2)
Dementia	0 (0)	3 (2)	3 (0.4)
Digestive tract	7 (1)	1 (1)	8 (1)
Other	14 (2)	6 (4)	20 (3)

* One patient may have more than one co-morbid condition, so the total of all co-morbid conditions can be more than 100% (more than the number of patients in the study)

FIGO IB(excluding IB2)-IIA

Median age of patients with FIGO stages IB-IIA was 47 years (range 24-88 years). Patients aged >=70 exhibited co-morbidity more frequently than patients aged <70 (76% versus 23%, p<0.001). Both age and presence of co-morbidity had a significant influence on the choice of treatment modality. Eighty-three percent of patients aged <70 underwent surgery as primary treatment, i.e. 92% of those without co-morbidity and 69% with at least one co-morbid condition (p<0.001). In contrast, only 46% of patients aged >=70 years underwent primary surgery: 73% of those without co-morbidity and 41% with at least one co-morbid condition (p=0.006) (table 3).

Five-year relative survival for patients aged >=70 was 61% versus 81% for patients aged <70 years (p=0.005). Crude five-year survival rates were significantly worse for patients aged >= 70 (50% versus 80%, respectively), for

Table 3 Treatment of cervical cancer in south-eastern Netherlands according to FIGO stage, age and co-morbidity, 1995-2004

Age	Co-morbid conditions	FIGO IB-IIA			FIGO IB2, IIB-IVA			
		Surgery N(%)	RT* N(%)	Other/none N(%)	RT* N (%)	CHEMRT* N (%)	Surgery N (%)	Other/none N (%)
<70	0	145 (92)	8 (5)	5 (3)	42 (44)	29 (30)	15 (16)	10 (10)
	1+	33 (69)	13 (27)	2 (4)	13 (50)	10 (38)	1 (4)	2 (8)
	Unknown	21 (62)	3 (9)	10 (29)	10 (37)	3 (11)	2 (7)	12 (44)
>= 70	0	8 (73)	3 (27)	0 (0)	13 (65)	1 (5)	3 (15)	3 (15)
	1+	14 (41)	18 (53)	2 (6)	29 (83)	0 (0)	1 (3)	5 (14)
	unknown	1 (33)	0 (0)	2 (67)	2 (20)	1 (10)	1 (10)	6 (60)

* RT=radiotherapy, CHEMRT=chemoradiation (including 2 patients who received radiotherapy + hyperthermia)

patients with FIGO stage IIA (65% versus 78% and 79% for FIGO IB and IB1, respectively), and for patients with co-morbidity (83% without, 66% with one and 48% with two or more co-morbid conditions) (table 4). Survival for patients with FIGO IB-IIA receiving primary radiotherapy was 47% versus 81% for those who underwent primary surgery. No effect on survival was found for period of diagnosis or SES. In multivariate survival analysis, age was the only independent prognostic indicator (table 4). The risk of dying increased with 2% per every additional year in age (p=0.04). The hazard ratios for age and co-morbidity did not change when primary treatment was introduced in the model.

FIGO IB2, IIB-IVA

Median age of patients with FIGO stages IB2, IIB-IVA was 57 years (range 28-94 years). Patients aged >=70 more frequently suffered from co-morbidity than patients aged <70 (64% versus 21%, p<0.001). Especially age had a significant influence on the choice of treatment modality: 28% of patients aged <70 received chemoradiation, 30% of those without co-morbidity and 38% of those with at least one co-morbid condition. Only 3% of patients aged >=70 received chemoradiation, 5% of those without co-morbidity and none of those with at least one co-morbid condition (p<0.001) (table 3). Differences in the use of chemoradiation according to the presence of co-morbidity, within both age categories, were not significant. A small group of patients with FIGO stages IB2, IIB-IVA without co-morbidity received surgery more often than patients with one or more co-morbid conditions (n=18 versus n=2, p<0.001). The use of chemoradiation increased from 9% in the period 1995-1997 to 32% in the period 2001-2004 (p=0.01), being 41% of patients aged <70 and 5% of patients aged >=70 (p=0.02) in the latter period. When analyzing the time trend per year it could be revealed that the use of chemoradiation already increased from 1999, the year of the clinical alerts of the NCI (p=0.02). The number of patients who received radiotherapy combined with hyperthermia was too small (n=2) to reveal a time trend.

Five-year relative survival for patients aged >=70 was poorer compared to patients aged <70 (32% versus 51%, p=0.05). In univariate analysis, five-year crude survival was significantly worse for patients aged >=70 (24%, compared to 48% for patients aged <70), for having one co-morbid condition (24%, compared to 42% without co-morbidity), for patients with FIGO IIIA (33%), IIIB (23%) and FIGO IVA (16%), compared to patients with FIGO IB2 or IIB (54% and 55%, respectively) and for receiving radiotherapy (38%, compared to 49% for patients receiving chemoradiation and 57% for surgery) (table 4). No effect was found for period of diagnosis and SES. In multivariate survival analysis, co-morbidity and FIGO were independent prognostic factors (table 4). The risk of dying for

Table 4 Overall survival of cervical cancer patients diagnosed in south-eastern Netherlands, 1995-2004

				Univariate		Multivariate		
			N	5 year (%)	P	HR	90% CI	P
FIGO	Age		288	-	-	1.02	1.00-1.04	0.04
IB-IIA	FIGO	IB	167	78				
		IB1	64	76				
		IIA	57	65	0.09			
	Period of	1995-1997	89	78				
	diagnosis	1998-2000	88	74				
		2001-2004	111	73	0.9			
	Co-morbidity	0	169	83		1	reference	reference
		1	48	66		1.2	0.6- 2.3	0.60
		2+	34	48	<0.001	1.5	0.7- 3.0	0.37
	Treatment	Surgery	222	81		1	reference	reference
		Radiotherapy	45	47		1.7	0.9- 3.2	0.14
		Other/none	21	64	<0.001	5.4	1.9-15.1	0.007
FIGO	Age		214	-		1.0	0.9-1.0	0.90
IB2,	FIGO	IIB	91	55		1	reference	reference
IIB-		IIIA	21	33		2.0	1.1- 3.6	0.05
IVA		IIIB	38	23		3.5	2.2- 5.5	<0.001
		IVA	31	16		7.7	4.7-12.7	<0.001
		IB2	13	54	<0.001	1.2	0.5- 2.9	0.68
	Period of	1995-1997	67	39				
	diagnosis	1998-2000	63	38				
		2001-2004	84	48	0.9			
	Co-morbidity	0	116	42		1	reference	reference
		1	42	24		2.0	1.3- 3.0	0.006
		2+	19	40	0.03	1.6	0.8- 2.9	0.25
	Treatment	Radiotherapy	109	38		1	reference	reference
		Chemoradiation*	23	57		0.8	0.5- 1.3	0.44
		Surgery	44	49		-	-	-
		Other/none	38	29	0.004	2.2	1.3- 3.7	0.009

* (including 2 patients who received radiotherapy + hyperthermia)

HR=Hazard Rate for death 90% CI=90% Confidence Interval

patients with 1 co-morbid condition was twice as high as for patients without co-morbidity (p=0.006). Furthermore, the death risks of patients diagnosed with FIGO IIIA, IIIB, and IVA were respectively, 2.0 (p=0.05), 3.5 (p<0.001) and 7.7

($p<0.001$) times higher compared to patients diagnosed with FIGO IIB. The hazard ratios for age and co-morbidity did not change when treatment was introduced in the model.

Discussion

Substantial variations were found in the treatment of and prognosis for women with cervical cancer if stratified by age and presence of co-morbidity in this retrospective population-based study.

In FIGO stage IB(excluding IB2)-IIA cervical cancer, both primary surgery and radiotherapy were equal therapeutic options, resulting in similar outcomes [18]. However, the present study showed that in the elderly patients, especially in the presence of co-morbidity, radiotherapy remained the main treatment of choice. Relative survival for patients aged older than 70 years was worse than for their younger counterparts, which may be explained by the higher proportion of FIGO IIA tumours in the older patients ($p<0.001$). However, in a multivariate analysis age was the only independent prognostic indicator. Although this population-based study has the advantage of avoiding selection bias, detailed and uniform information on the performance status of the patient, adherence to protocol (dose reduction, treatment delay) for radio- and/or chemotherapy and treatment-related complications were not available. These and other factors which determine frailty like cognitive disorders might also affect the prognosis of the patients. In patients with FIGO stages IB2, IIB-IVA cervical cancer, especially age influenced the therapy of choice: radiotherapy or chemoradiation. Only 5% of patients aged 70 years or older received chemoradiation versus 41% of patients aged younger than 70 years in the period 2001-2004. As a matter of fact, chemoradiation was proposed as superior alternative to radiotherapy alone since 1999 and only incorporated in the guideline since 2004. In multivariate analysis, prognosis was determined by the number of co-morbid conditions and FIGO stage. Patients with one co-morbid condition exhibited worse survival compared to patients without co-morbidity. By contrast, the increased risk of death for the rather small group of patients with multiple comorbid conditions did not reach statistical significance. Furthermore, no change was seen in the hazard ratio for age when treatment was included in the model, which may indicate that chemoradiation does not improve survival for the elderly.

Although no severity of co-morbidity was recorded, misclassification of co-morbidity seems limited, because the concomitant conditions are recorded routinely by trained registry personnel directly from the medical records of the

patients, thereby using a variety of sources. A validation study among breast cancer patients showed some underregistration, mainly for less severe cardiovascular conditions [19]. Furthermore, not all cases of non insulin-dependent diabetes are subclinical, implying that the prognosis of patients without diabetes might therefore be underestimated. The true effects of co-morbidity on treatment choice and survival may thus be stronger than described here.

It is known that elderly are less likely to be included in clinical trials and to receive aggressive therapy, because of considerations concerning patient safety [20;21]. In addition, older women are more likely than their younger counterparts to refuse aggressive treatment [22;23]. We found that older patients and patients with co-morbidity indeed were treated differently compared to younger patients and patients without co-morbidity in both lower and higher FIGO stages. However, treatment was not an independent prognostic factor in both stage groups, indicating that the right treatment modality was in general offered to the right patient.

Survival could have been affected by improvements in primary treatment, although these effects may have been attenuated by on the one hand relatively more rapidly growing tumours escaping screening practices or non-participants [24], and the at least relatively increased numbers of older women with cervical cancer. With respect to progress, treatment guidelines and recommendations have changed practice, leading to more regionalization based on numbers of patients per hospital.

In conclusion, in cervical cancer, treatment modalities chosen and prognosis differed between younger and older patients and between patients with and without co-morbidity. Attention should be paid to treatment with respect to ageing and co-morbidity. In an increasingly ageing population (on the basis of recent numbers of population growth it is estimated that the number of women older than 65 year will increase with 23 percent [25]), co-morbidity and other factors that determine frailty like performance status will probably play an increasing role in clinical decision-making and outcome. Development of age-specific guidelines, incorporating levels of co-morbidity and for example performance score, may therefore be warranted, leading to an increased awareness about co-morbidity among physicians.

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Chapter 6

Uncommon tumours

6.1

Vaginal and (uncommon) cervical cancer in the Netherlands, 1989-2003

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Abstract

Background. The clinical and prognostic evaluation of cervical and vaginal tumours other than squamous cell and adenocarcinomas is hampered by the low incidence, and clinical and epidemiological studies on these uncommon tumours are scarce. By its close affinity with pathology the Netherlands Cancer Registry (NCR) offers a great opportunity to study frequency, stage, treatment and survival of uncommon tumours in the cervix and vagina and separately the clear cell adenocarcinoma (CCAC) of the vagina and cervix.

Methods. All invasive cervical tumours (n=10,570) and all in-situ and invasive vaginal tumours (n=778) diagnosed in the Netherlands during 1989-2003 were selected from the NCR. Age, stage at diagnosis and treatment were described for each histological subgroup in order to find differences between common and uncommon tumours, including relative 5-year survival rates.

Results. A significantly worse prognosis was found for patients with small cell neuroendocrine cervical tumours and for patients with vaginal melanomas. Patients with CCAC of the vagina and cervix were found across all age categories.

Conclusion. The less common histological types of cervical and vaginal cancer were clearly different from squamous cell carcinomas, especially with respect to age at diagnosis and survival rates. Spreading population-based knowledge of effects of treatment of these uncommon tumours should improve prognosis. Furthermore, the diagnosis of patients with these tumours should be discussed in a multidisciplinary setting. If curative treatment is possible, these patients should be referred to specialised oncology centres.

Introduction

Regions where one type of epithelium replaces another (metaplasia) seem to be predilections for cancer formation and environmental factors are closely related to this metaplastic carcinogenesis. In particular, cancer of the cervix uteri and vagina are both hosts for the human papillomavirus (HPV) primarily at the transformation zone [1;2]. The transformation zone is a region, mostly situated at the (ecto)cervix but sometimes also partially at the vagina, where original columnar epithelium is replaced in squamous epithelium by the physiological process of metaplastic transformation. Squamous cell carcinomas and adenocarcinomas of the cervix uteri and vagina both develop in the transformation zone and these two tumour sites therefore presumably share etiologic features [3]. Moreover, on both localisations clear cell adenocarcinoma (CCAC) can develop.

Cervical cancer and its precursors follow basically two histological lineages depending on whether they originate in squamous or in glandular cervical epithelium. Most cases are squamous cell carcinomas, but adenocarcinomas also represent a major group [4]. The latter are in general associated with lower relative survival rates as compared with squamous cell carcinomas [5]. Other tumours in the cervix are for example melanomas, lymphomas and sarcomas.

Cancer of the vagina is frequently found as either a synchronous or a metachronous neoplasm with cervical cancer [6] and accounts for about 1-2% of all gynaecological malignancies [7]. Little is known about the risk factors for vaginal cancer, the majority of which occurs at older ages.

In 1971, diethylstilbestrol (DES), formerly used to prevent adverse outcomes of pregnancy, was first linked to CCAC of the vagina in young women exposed in utero [8]. Later, this strong association between intra-uterine DES exposure and risk of CCAC of the vagina and also of the cervix was confirmed by others [9;10]. Nonetheless, the absolute risk remained small: one per thousand DES daughters will eventually develop a CCAC [11;12].

The clinical and prognostic evaluation of cervical and vaginal tumours other than squamous cell and adenocarcinomas is hampered by the low incidence, and clinical and epidemiological studies on these uncommon tumours are scarce. The Netherlands Cancer Registry (NCR) offers a great opportunity to study frequency, stage, treatment and survival of uncommon cervical and vaginal tumours and separately the CCAC of the vagina and cervix.

Methods

The NCR consists of nine regional cancer registries and it includes all invasive and in situ malignancies diagnosed from 1989 onwards in the Netherlands. Notification is obtained from the national automated pathology archive (PALGA) and hematology departments in the region. Other sources are the radiotherapy departments of the hospitals, as well as the National Registry of Hospital Discharge Diagnosis, which accounts for up to 8% of new cases [13]. From the medical records data were collected concerning identifying information (e.g. first letters of the name, date of birth, sex, postal code), tumour characteristics (e.g. date of incidence, topography, morphology, stage), treatment and follow-up data. All data are collected from patient files in the hospital and are coded according to a national manual by trained registrars. This manual describes inclusion and exclusion criteria as well as definitions and coding of items. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICDO) [14]. The TNM classification is used for the staging of the tumours [15] and is the basis for FIGO staging. Stage 'X' means 'unknown stage', which is mostly due to insufficient information in the patient file to stage the tumour.

Treatment for patients with cervical cancer was classified as 'surgery' (+/- radiotherapy, +/- chemotherapy), 'radiotherapy' (+/- chemotherapy), 'other' (palliative, lymph node dissection only, chemotherapy only, metastasectomy and unknown therapy) or 'none' (no therapy). Treatment for patients with vaginal cancer and CCAC was classified as 'surgery' (+/- radiotherapy, +/- chemotherapy), 'radiotherapy' (+/- chemotherapy) or 'other/none' (palliative, lymph node dissection only, chemotherapy only, metastasectomy, unknown therapy and no therapy). In-situ tumours of the cervix are not registered in the NCR and we therefore selected all invasive cervical tumours (n=10,570) and all in situ and invasive vaginal tumours (n=778) diagnosed in the period 1989-2003 from the NCR.

Statistical analysis

The Statistical Package for Social Sciences (SPSS, version 15.0) was used to perform the analyses. Age, stage at diagnosis and treatment were described per histological subgroup in order to compare differences between common and uncommon tumours. Time trends in incidence were assessed by Chi square analysis. The histological subtypes were described conform the classification of Blaustein, which is based on the classification of the World Health Organization [16]. 'Neoplasms not otherwise specified' were in our study classified as 'other'.

Vital status was available up to January 1st 2006 for the patients from four of the nine regional cancer registries (n=6,258 cervical cancers, n=396 vaginal tumours and n=84 CCAC): Northwest, North, East and South. Relative five year survival rates were calculated separately for cervical tumours, vaginal tumours and CCAC. For both cervical and vaginal cancer, patients with "other" histological types and histological subgroups with less than 20 patients were excluded from the survival analyses (n=6,153 cervical cancers, n=330 vaginal cancers). Survival time was defined as the time from diagnosis to death or the end of the study (January 1st 2006). Relative survival was calculated as a measure of disease-specific survival using the Ederer II method in STATA version 9.2 [17]. The relative survival is the ratio between crude and expected survival and is close to disease-specific survival. Relative survival was modelled multivariately only for vaginal cancer, due to the small number of different histological subgroups of cervical cancer and CCAC. In modelling relative survival, variables were considered confounders and included in the model when the regression coefficient of the variable of interest changed by more than 10%. Relative excess risks (RER) and 95% confidence intervals (CI) were calculated. A p-value of 0.05 was considered to be significant. The relative excess risk (RER) describes the difference between the hazard of death in a given group and the hazard in the reference group, taking into account the risk of death in the Dutch population.

Results

Cervix

Nearly all tumours diagnosed during the period 1989-2003 were carcinomas, 74% being of squamous cell origin, 16% of glandular origin and 8% being classified as 'other epithelial tumours' including adenosquamous carcinoma and small cell neuroendocrine carcinomas. Furthermore, 0.2% were leiomyosarcomas, 0.3% mixed epithelial and mesenchymal tumours like malignant mullerian mixed tumours, 0.3% lymphomas and melanomas and 0.4% 'other' tumours (table 1). No time trends in incidence for the different histological subtypes were found.

Patients with papillary squamous cell carcinomas were older than patients with common tumours of squamous cell origin (73% were older than 50 years at diagnosis compared to 48%) and they most often received radiotherapy (73%).

Table 1 Number, age, stage and treatment of (uncommon) cervical tumours, diagnosed in the Netherlands in the period 1989-2003

Histology	Cases	%	% within group	Age				FIGO					Treatment*				
				<25	25-49	50-74	75+	IA	IB-IIA	IIB-IVA	IVB	X	local	surg	rt	other	none
Squamous cell carcinoma	7752	73	99	0.6	51	35	14	27	38	29	4.2	2.3	8.1	49	37	1.3	5.1
Verrucous carcinoma	15	0.1	0.2	6.7	33	60	0.0	40	27	27	6.7	0.0	6.7	40	40	6.7	6.7
Papillary squamous cell carcinoa	26	0.2	0.3	0.0	27	46	27	7.7	42	50	0.0	0.0	3.8	23	73	0.0	0.0
Lympho-epithelioma-like carcinoma	8	0.1	0.1	0.0	50	38	13	13	88	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0
Adenocarcinoma	1516	14	87	0.4	57	30	12	29	44	19	5.1	3.4	5.9	64	21	2.3	6.1
Mucinous adenocarcinoma	55	0.5	3.2	1.8	71	20	7.3	20	62	15	3.6	0.0	7.3	75	16	1.8	0.0
Endometrioid adenocarcinoma	34	0.3	1.9	0.0	35	50	15	15	47	24	15	0.0	2.9	62	32	0.0	2.9
Clear cell adenocarcinoma	121	1.1	6.9	5.8	33	40	22	11	51	28	9.1	0.8	2.5	61	30	0.8	5.8
Serous adenocarcinoma	4	0.0	0.2	0.0	25	50	25	25	25	25	0.0	25	0.0	50	50	0.0	0.0
Mesonephric carcinoma	4	0.0	0.2	0.0	50	0.0	50	0.0	0.0	0.0	0.0	100	0.0	100	0.0	0.0	0.0
Well-differentiated villoglandular carcinoma	11	0.1	0.6	0.0	100	0.0	0.0	18	73	9.1	0.0	0.0	36	64	0.0	0.0	0.0
Other epithelial tumours	485	4.6	55	1.2	65	24	9.9	61	12	13	7.6	6.4	16	56	15	2.7	12
Adenosquamous carcinoma	313	3.0	36	1.3	56	36	7.7	17	52	23	5.4	1.6	3.2	68	25	0.6	3.5
Glassy cell carcinoma	3	0.0	0.3	0.0	67	33	0.0	0.0	67	33	0.0	0.0	0.0	67	0.0	33	0.0
Mucoepidermoid carcinoma	5	0.0	0.6	0.0	60	40	0.0	0.0	60	0.0	40	0.0	0.0	60	20	20	0.0
Adenoid cystic carcinoma	2	0.0	0.2	0.0	0.0	100	0.0	50	0.0	50	0.0	0.0	0.0	50	50	0.0	0.0
Adenoid basal carcinoma	2	0.0	0.2	0.0	0.0	50	50	50	50	0.0	0.0	0.0	0.0	50	0.0	0.0	50
Small cell neuroendocrine carcinoma	67	0.6	7.6	0.0	43	37	19	6.0	30	28	30	6.0	1.5	30	36	24	9.0
Large cell neuroendocrine carcinoma	1	0.0	0.1	0.0	100	0.0	0.0	0.0	100	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0
Typical carcinoid tumor	3	0.0	0.3	0.0	100	0.0	0.0	33	33	0.0	0.0	33	0.0	100	0.0	0.0	0.0
Small (Oat) cell carcinoma	1	0.0	0.1	0.0	0.0	100	0.0	0.0	100	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0
Mesenchymal tumours	8	0.0	24	13	50	25	13	0.0	0.0	0.0	0.0	100	0.0	75	13	13	0.0
Leiomyosarcoma	25	0.2	76	8.0	32	56	4.0	0.0	0.0	0.0	0.0	100	0.0	84	4.0	8.0	4.0
Mixed epithelial and mesenchymal tumours	33	0.3	100	3.0	21	42	33	0.0	0.0	0.0	0.0	100	0.0	64	18	6.1	12
Miscellaneous tumours	-	0.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Melanoma	3	0.0	9.4	0.0	33	33	33	0.0	0.0	0.0	0.0	100	0.0	100	0.0	0.0	0.0
Lymphoma	29	0.3	91	3.4	17	52	28	0.0	0.0	0.0	0.0	100	0.0	21	41	35	3.4
Other	44	0.4	100	4.5	14	43	39	0.0	4.5	0.0	0.0	96	0.0	11	18	11	59

* surg=surgery, rt=radiotherapy

CCAC was the most frequent subtype within the adenocarcinoma group (1%). These tumours and endometrioid type adenocarcinomas were mainly found in patients older than 50 years (61% and 65%, older than 50 years, respectively). All patients diagnosed with well-differentiated villoglandular carcinoma were diagnosed in patients below 50 years and 91% was diagnosed in FIGO stages IA-IIB.

Adenosquamous tumours represented 3% of all cervical tumours and this subtype was the most frequent within the group of 'other epithelial tumours'. Patients diagnosed with small cell neuroendocrine carcinoma were older (19% diagnosed in patients aged 75 or older) and had a higher stage (30% diagnosed in FIGO IVB). Furthermore, this patient group was the only group showing a significantly worse prognosis compared to the patient group with squamous cell carcinomas (p<0.001, table 2).

Table 2 Five-year relative survival related to histological classification of patients with cervical cancer in the

Histology	Five year relative survival				Five year relative survival per			
	N	5- year	95% CI	P*	N	5-year	95%	P*
Squamous cell carcinoma	4608	77	76-79	ref	464	77	76-79	ref
Adenocarcinoma	870	76	72-79	0.4	100	76	72-79	0.3
Mucinous adenocarcinoma	35	81	60-93	0.4				
Endometrioid adenocarcinoma	20	73	44-91	0.9				
Clear cell adenocarcinoma	68	71	56-82	0.1				
Other epithelial tumours	256	83	77-88	0.04	519	78	73-82	0.9
Adenosquamous carcinoma	206	77	70-83	0.8				
Small cell neuroendocrine	49	52	35-68	<0.001				
Mixed epithelial and	41	73	52-87	0.3	41	73	52-87	0.3

* ref=reference category

Leiomyosarcoma was the most frequent malignant tumour of mesenchymal origin and most frequently diagnosed in age group 50-74 (56%).

Patients with lymphoma were relatively old: 79% was older than 50 years and they most often received chemotherapy (69%). Patients with melanoma most often received radiotherapy.

Of all cervical cancer patients, 25 patients (3%) subsequently developed a vaginal tumour (during 1989-2003) and 19 out of these patients underwent hysterectomy for their cervical cancer (19 out of 25).

Table 3 Number, age, stage and treatment of (uncommon) vaginal tumours, diagnosed in the period 1989-2003 in the Netherlands

Histology	Cases	%	Age				FIGO						Treatment*		
			<25	25-49	50-74	75+	In-situ	I	II	III	IVA	IVB	X	surg	rt	other/none
Squamous cell carcinoma	518	67	0.2	17	43	39	12	29	21	12	12	6.0	8.5	28	57	15
Adenocarcinoma	109	14	3.7	28	37	32	0.9	40	18	4.6	11	10	15	39	39	22
Other epithelial tumours	62	8.0	0.0	23	48	29	34	9.7	11	6.5	8.1	8.1	23	34	40	26
Mesenchymal	17	2.2	12	29	35	24	0.0	0.0	0.0	0.0	0.0	0.0	100	77	0.0	24
Mixed epithelial and mesenchymal tumours	5	0.6	0.0	0.0	20	80	0.0	0.0	0.0	0.0	0.0	0.0	100	20	40	40
Melanomas	59	7.6	0.0	8.5	41	51	0.0	0.0	0.0	1.7	5.1	0.0	93	76	12	12
Other	8	1.0	13	0.0	38	50	0.0	0.0	0.0	0.0	0.0	0.0	100	13	0.0	88

* surg=surgery, rt=radiotherapy

Table 4 Five-year relative survival of patients with vaginal cancer in the Netherlands, 1989-2003

			Five year relative survival			Multivariate survival analysis		
Factor		Cases	5-year %	95% CI**	P**	RER	95% CI**	P**
Age group	<25	16	72	9- 96	0.9	1.5	0.2-12	0.7
	25-49	76	76	62- 86	reference	1	reference	reference
	50-74	139	45	36- 54	0.001	2.6	1.3-5.2	0.006
	75+	99	27	17- 39	<0.001	3.8	1.9-7.5	<0.001
FIGO stage	In-situ	52	95	75-102	reference	1	reference	reference
	I-II	89	58	47- 68	0.03	55.8	-	0.4
	III-IVA	45	16	7- 29	0.002	145.5	-	0.3
	IVB	21	15	3- 42	<0.001	404.6	-	0.2
	X	65	26	14- 40	0.002	100.0	-	0.3
Histology	squamous	171	52	44- 60	reference	1	reference	reference
	adeno	80	38	23- 53	0.2	1.4	0.9-2.4	0.2
	epithelial NOS	50	47	25- 69	0.5	2.6	0.9-3.6	0.09
	melanoma	29	9	2- 24	<0.001	1.8	1.4-4.9	0.004
Treatment*	RT	152	39	30- 48	reference	1	reference	reference
	Surgery	123	61	49- 71	0.002	0.6	0.4-0.9	0.04
	Other/none	55	31	17- 48	<0.001	2.4	1.5-3.8	<0.001

* RT=radiotherapy **reference=reference category

Vagina

During the 15-year period 1989-2003, 778 vaginal tumours (52 in-situ carcinomas) were diagnosed, on average 50 annually. No specific time-trends in incidence were found, neither for age or stage at diagnosis. Most patients were elderly with 38% being older than 75 years (table 3). Squamous cell carcinoma was the most frequent histological subtype (67%). Patients who were diagnosed with carcinoma in-situ mostly received surgery (65%). Most women with FIGO stage I cancer received surgery (47%) or radiotherapy (48%). Women with FIGO stages II and higher most often received radiotherapy.

Few differences in age, stage and treatment were found between the different histological subtypes of vaginal cancer. Patients with melanomas were mostly older than 75 years (51%) and most often underwent surgery (76%) (table 3).

Five year survival was complete for 385 patients; relative five year survival was significantly worse for patients aged 50-74 and 75+ ($p=0.001$ and $p<0.001$ respectively), for patients with melanomas ($p<0.001$) and for those who underwent surgery ($p=0.002$) (table 4). Patients diagnosed with FIGO stages other than in-situ tumours had a worse prognosis, but the difference between patients diagnosed with FIGO stages I-II and III-IVA was also remarkable (58% and 16% respectively|). In multivariate analysis age, treatment and histological type were independent prognostic factors, with independent significant worse survival for patients with aged 50-74 and 75 or older ($p=0.006$ and $p<0.001$ respectively), patients who underwent surgery ($p=0.04$) and patients with melanoma ($p=0.004$).

CCAC

During the period 1989-2003, 121 patients with CCAC of the cervix and 38 patients with CCAC of the vagina were diagnosed. Patients with CCAC were diagnosed across all age categories with more than half of the patients being staged FIGO stage I (table 5).

Surgery was the most frequently used therapy (55%), especially in FIGO stages I and II (77% and 48%, respectively), while radiotherapy was the treatment of choice in 61% of patients with FIGO stages III+. Older women tended to receive surgery in FIGO stage I less often compared to younger women: 84% in age group younger than 45 years versus 55% in age group 75 years or older ($p=0.1$).

Although complete follow-up was only available for 69 patients, five year relative survival appeared significantly worse for patients aged 50-74 ($p=0.03$) and for patients diagnosed with FIGO stages III and higher ($p<0.001$) (table 5).

Table 5 Patient and tumour characteristics and relative survival of clear cell adenocarcinoma of the cervix and vagina 1989-2003

Patient and tumour characteristics (N=159)			Five-year relative survival (N=84)			
Factor	%	95% CI	Cases	5-year %	95% CI	P**
Localisation						
Cervix	76	17-31	62	58	42-72	reference
Vagina	24	70-83	22	58	30-79	0.3
Age group						
<25	6.3	2.5-10	6	80	20-97	0.9
25-49	38	30-45	35	72	52-86	reference
50-74	36	28-43	27	47	24-68	0.03
75+	20	14-26	16	34	8-70	0.07
FIGO stage						
I	51	43-59	46	73	53-86	reference
II	28	21-35	21	55	26-78	0.2
III+	18	12-24	12	11	1-38	<0.001
X	3.8	0.8-6.7	5	81	17-119	0.9
Treatment*						
Surgery	55	47-63	44	77	58-89	reference
RT	38	31-46	34	40	19-62	0.1
Other/none	6.9	3.0-11	6	18	1-55	0.002

* RT=radiotherapy **reference=reference category

Discussion

The less common histological types of cervical and vaginal cancer were clearly other entities than squamous cell carcinomas, which was reflected in differences in age at diagnosis and survival rates.

A good prognosis was exhibited for cervical cancer patients with 'other epithelial tumours' and particularly poor prognosis for patients with small cell neuroendocrine tumours. In contrast to the literature, small cell neuroendocrine carcinomas only accounted for 0.6% in our study [18], but with similar poor survival rates as indicated in the literature where small cell carcinomas are characterized by frequent and early nodal metastases and frequent vascular invasion [18;19]. Also, the percentage of lymphomas was lower in this study than in the literature [18]. As in the literature, the patients with lymphomas were mainly treated with combinations of radiotherapy and chemotherapy [18;20].

Furthermore, we showed that patients with vaginal melanomas had a worse prognosis compared to other histological groups, which was also confirmed by others [21;22]. It is clear that vaginal melanoma is mainly a disease of elderly women, who are often reluctant to see a doctor and are therefore often diagnosed in late stages [23;24].

Use of data from the population-based nationwide NCR allowed analysis of rare tumours, although many different pathologists are involved in diagnosing the tumours. There may be some problems with classifying and localizing the tumours. Firstly, it may sometimes be hard to discern where the cervix uteri ends and the vagina begins. The size of the cervix decreases in the senium due to atrophy and tumours which develop there might therefore occasionally incorrectly be regarded as vaginal tumours. Secondly, most of the carcinomas of the cervix uteri are squamous cell carcinomas, however many also have invasive components of adenocarcinoma and are therefore adenosquamous types. In the literature adenosquamous carcinomas account for 5-25% of all cervical cancers [18;25], while in this study only 3% of all cervical cancers were classified as adenosquamous. Pathologists usually classify tumours according to the histological type, most prominent in the tissue. It is therefore not clear which part of the cervical tumours are true adenosquamous carcinomas. In our study, 77% of patients with adenosquamous carcinomas were alive after five years, while in other studies worse survival was reported for patients with these tumours [26;27]. Thirdly, endometrioid type adenocarcinomas situated in the cervix uteri may in fact be endometrial carcinomas. A recent study concerning these endometrioid adenocarcinomas indicated that staining of vimenting and HPV determining may be helpful in distinguishing between true cervical carcinoma and endometrioid type adenocarcinoma developing in the uterus [28].

Patients treated for a (pre)malignancy of the cervix may develop a vaginal carcinoma later in life [29]. In our study, 25 patients (3%) with cervical cancer subsequently developed a vaginal tumour (during 1989-2003) and 19 out of these patients underwent hysterectomy for their cervical cancer (19 out of 25). When the uterus is removed by means of a hysterectomy, the vaginal top remains in situ and if the transformation zone is still present in the vaginal top, then this is the predelicted site for tumours induced by high risk HPV.

The treatment of vaginal carcinoma is a challenge as it is rare; seen in any hospital on average once every two years. In this study, younger patients underwent surgery more often than older patients (data not shown, $p<0.001$) and these patients showed significantly better survival compared to patients who received radiotherapy or other therapies who usually have a poorer general condition. Unfortunately, we did not have any data about co-morbid conditions or performance status and were therefore not able to adjust for that.

Cervical and vaginal carcinomas share some etiologic features as they are both associated with high-risk HPV and both develop at the transformation zone. However, vaginal cancers mainly develop in older patients while cervical cancers are most frequent in younger patients. This might indicate that mainly the vaginal tumours in younger patients, who are most likely to carry high risk HPV, are comparable to cervical cancer. In evaluating the mass screening programme for cervical cancer vaginal carcinomas, mainly in younger patients, should therefore also be taken into consideration.

Remarkably, in this study, patients with CCAC of the vagina and cervix were found across all age categories. It is known that DES-associated clear cell carcinomas mostly appear in young women, aged 15-29 [30]. Moreover, one should bear in mind that CCAC of the vagina has already been described before the onset of the so-called DES era and therefore most likely not all CCAC found in this study are due to intra-uterine DES exposure [31]. A study from the Netherlands found a bimodal age distribution of patients with CCAC at young age (mean of 26 years) and at older age (mean of 71 years). This bimodal age distribution still applied when the cases in whom DES exposure was reported had been excluded, suggesting a carcinogenesis-promoting role of menarche and menopause and/or the existence of a subpopulation with genetic risk factors or exogenous risk factors other than intra-uterine exposure to DES [32]. The absence of a rise in the incidence of CCAC in this study could partly be explained by the investigated period. The incidence of CCAC, already rising since 1980, may now have reached a plateau [11]. The guidelines for the follow-up of DES-daughters in the Netherlands recommend initial examination and yearly follow-up in case of vaginal adenosis or abnormal shape of the vagina or cervix [33]. From age 30 years onwards, follow-up takes place by means of the national screening programme in which DES-daughters are also expected to participate. Despite the relatively favourable prognosis for patients with CCAC, periodical checks are not proven to be (cost-)effective and rather increase anxiety among patients.

In conclusion, patients with small neuroendocrine tumours and vaginal melanomas showed a worse prognosis compared to patients with the most common histological subtypes. By obtaining and spreading knowledge of effects of treatment of these uncommon tumours, the prognosis for these patients might increase. Furthermore, the diagnosis of patients with these tumours should be discussed in a multidisciplinary setting. If curative treatment is possible, these patients should be referred to specialised oncology centres, given the clinical complexity.

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Chapter 7

Discussion

How to further lower mortality from cervical cancer effectively in industrialised countries with decreasing trends in incidence and mortality?

7.1 Introduction

In this thesis, descriptive studies on cancer of the cervix uteri are presented, which were performed using the population-based Netherlands Cancer Registry (NCR) and the regional cancer registries of the Comprehensive Cancer Centre Stedendriehoek Twente (CCCST) and the Comprehensive Cancer Centre South (CCCS), serving 590,000 and 1.1 million women respectively (together serving about 20% of the Netherlands). Both CCC's each hosted 2 regional radiotherapy institutes and 7 respectively 10 community hospitals. In both regions the attending gynaecologists increasingly subspecialized within the hospital staffs and 2 subregional collaborations. In the CCCS region these collaborations were merged into one in 2004.

Unfortunately, cervical intraepithelial lesions (CIN) and cervix carcinoma in-situ have not been included in the Netherlands Cancer Registry. Although CIN 1 and CIN 2 have very low progression rates, CIN 3 (severe dysplasia) rates or rates of cervix carcinoma in-situ could have been better predictors for a (future) rise in the incidence of cervical cancer. Furthermore, trends in the incidence of cervix carcinoma in-situ are a better indicator for the effectiveness of the national screening programme than the incidence of invasive cervical carcinoma.

Geographical differences in incidence and mortality from cervical cancer were explored within the Netherlands and by comparing Finland and the Netherlands. We concluded that within the Netherlands the risk of getting cervical cancer was eight or nine fold higher in municipalities with a high prevalence of immigrants and with more individuals on welfare respectively. Furthermore, patients residing in neighbourhoods with lower SES had a 40% higher risk for being diagnosed with higher FIGO stages, a 30% lower risk for being diagnosed with adenocarcinomas and they were younger at time of diagnosis. Comparing Finland and the Netherlands, incidence and mortality rates had declined more in Finland. In 2003, age-adjusted incidence and mortality in Finland were 4.0 and 0.9 and in the Netherlands 4.9 and 1.4 per 100,000 woman-years, respectively. However, excess smear use in the Netherlands was estimated 24 per 1,000 women during a five-year interval compared to 121 in Finland.

The mass screening programme for cervical cancer was studied in two ways in this thesis. Firstly, by comparing screen-detected tumours with symptomatic tumours in the CCCST region. In this study we concluded that screen-detected tumours have a lower stage and a better prognosis and that detection and treatment of patients with suspicious smears had been suboptimal. Second, according to our national study on trends in incidence and mortality in young women, the time may not yet have come to lower the screening age of 30 years for cervical cancer.

In the two studies on trends in treatment and survival in two regions in the Netherlands and the relationship with co-morbidity and adherence to treatment guidelines in the CCCS we noticed that age and co-morbidity affected the choice of radical effective treatment and thus the prognosis of patients with cervical cancer.

Finally, the national study on patients with uncommon tumours of the cervix and vagina showed a worse prognosis for some of the uncommon tumours compared to more regular tumours, which justifies more studies, also in European datasets, because by obtaining and spreading knowledge about effects of treatment of these uncommon tumours prognosis for these patients should increase.

In most industrialized countries, cervical cancer became less of the major clinical problem it was up till the 80's, in the presence of a mass screening programme which started in the Netherlands in 1988 and was perfected in 1996 [1]. The incidence of and mortality rates from cervical cancer in the Netherlands have now become among the lowest in the world: World Standardized Rates (WSR) for incidence and mortality 4.9 and 1.2 per 100,000 woman-years in 2003, respectively (figure 1) [2].

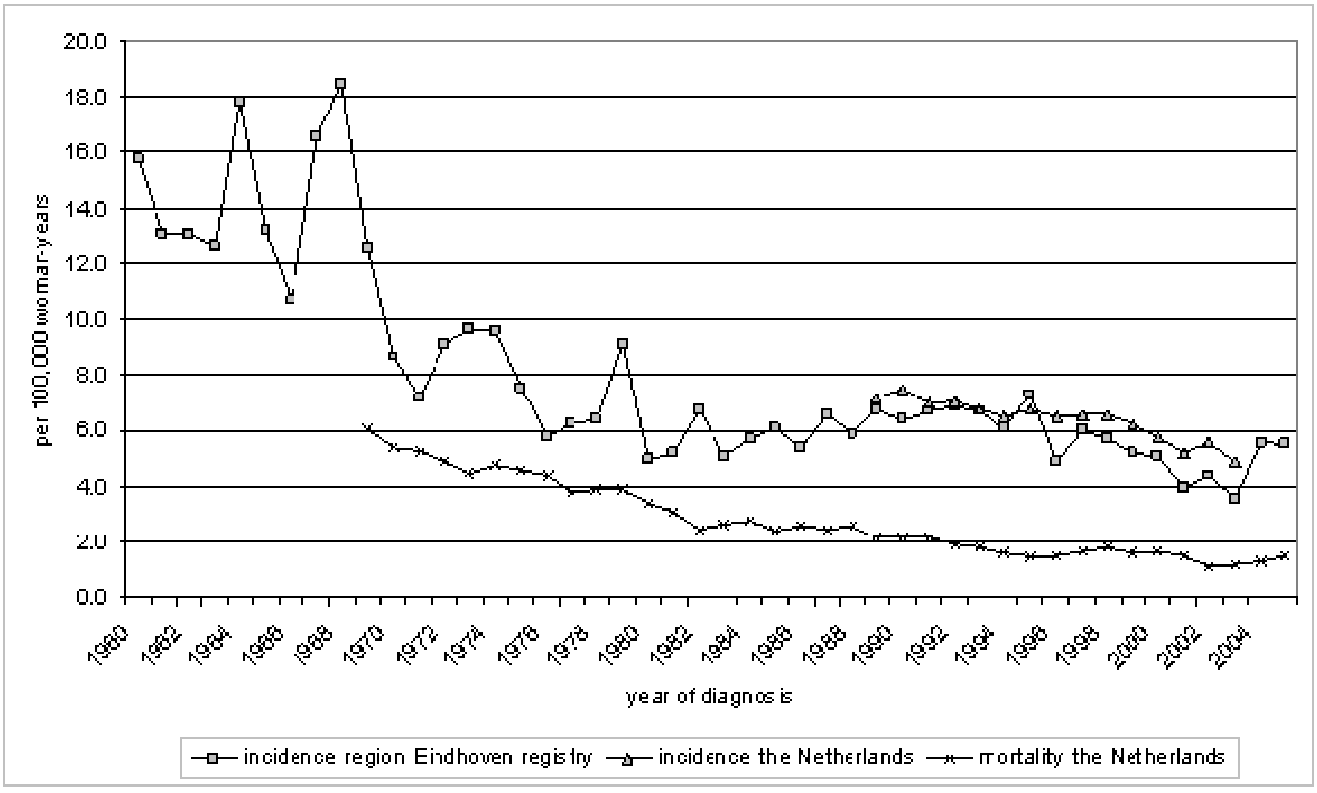

Figure 1 Age-adjusted (World Standard) incidence and mortality rates of cervical cancer per 100,000 women in the Netherlands and the region of the Eindhoven registry

Putting this in perspective, cervical cancer is not in the top ten of most frequent cancers in women in the Netherlands: the WSR for breast cancer being 46, for colon cancer 35 and lung cancer 35 per 100,000 woman-years in 2003. It is estimated that without many extra screening efforts the annual number of cervical carcinomas will decrease from 677 in 2000 to 527 in 2015. Mortality was 219 in 2005 and is expected to decrease to 181 in 2015 [3]. For example, an average general practitioner with a fixed practice of about 1300 women would encounter a new case of cervical cancer only once in 15 years. It is estimated that of 10,000 screened women three women are prevented from getting cervical cancer [4]. Of course it remains unknown how many of the precancerous lesions would really have developed into cervical cancer.

Because cervical cancer mainly affects young and middle-aged women, the emotional burden caused by cervical cancer is still high. These women are often diagnosed in their fertile period of life and the number of life years lost is relatively high if a young woman dies from cervical cancer.

In this discussion, the results of the studies presented in this thesis will be put into perspective and related to recent and future developments concerning primary prevention, screening and treatment in order to clarify how to further lower mortality from cervical cancer effectively, taking into account the current favourable trends in incidence and mortality.

7.2 Prevention

Risk factors

Recognition that HPV infection is the central cause of cervical neoplasia [5] has created new research fronts aiming at primary and secondary prevention of this disease. Epidemiological studies of the past decades have consistently indicated that infection with HPV and thus cervical cancer risk is strongly influenced by sexual activity: number of partners, age at first sexual intercourse and sexual activity of male partners [6]. However, the public is largely unaware of HPV or its role in cervical cancer, although there is increasing recognition of a link between cervical cancer and sexual behaviour. Ensuring that information on the risks of infection with HPV is accessible to people at all levels of health literacy will therefore be important, even though it will only have long term effects.

Furthermore, tobacco smoking has been a well-known risk factor for cervical cancer [7], so women have to be encouraged not to start smoking or have to be made aware of the importance to quit smoking.

HPV vaccination

A recent study in the Netherlands estimated that 80% of all women ever encounters an HPV infection during her lifetime [8]. Because of the transient nature of these infections with a spontaneous clearance of 90% by the immune system many women are temporarily infected with the virus and only very few women are diagnosed with cervical cancer [9].

Currently, 15 HPV types are considered to be oncogenic of which HPV16, HPV18, HPV31 and HPV33 are the most important types [10]. In phase III trials, two HPV virus-like particle vaccines have been shown effective in preventing incident and persistent HPV16 and HPV18 infections and associated precancerous lesions, with reported efficacies in the region of 90-100% [11;12]. The HPV vaccine is explicitly designed to prevent cancer induced by a virus and the vaccines could prevent around 70% of all cervical cancer [13]. Two vaccines, Gardasil en Cervarix, have been developed and the first has recently been licensed for individual use in the US and in Europe [14]. However, important questions about how a HPV vaccine should be used at a population level remain. At what age should the vaccination been given? Should the vaccine be given to females only or to both females and males? Should a catch-up vaccination campaign accompany the introduction of routine vaccination? A study in Finland demonstrated that more cervical cancer cases are prevented when 12-year-old girls are targeted and that the vaccine generates greater long-term benefits if delivered before the first sexual intercourse [15]. Furthermore, vaccinating males as well as females has more impact on the proportion of cases prevented when vaccinating at younger ages.

We have shown in one of our studies that cervical cancer is more likely to occur in patients with low socioeconomic status and in areas with high population density, more people living on welfare and more immigrants (chapter 3.1). Since HIV and other sexually transmitted infections have been increasing in the Netherlands according to the latest surveillance data [16], an increase in HPV-infections resulting in an increase in incidence of cervical cancer in young women should not be unexpected, although not yet observed (chapter 4.2). In Finland, a country comparable to the Netherlands in terms of mass screening programme and thus with relatively low incidence and mortality rates, a recent increase was observed in the incidence in young women (chapter 3.2). This increase is attributed to more extensive sexual behaviour during the last few decades, with an increasing role of some potentially oncogenic sexually transmitted infections, such as HPV [17]. Tobacco smoking has also increased among young Finnish women during the 1980s. It might be worthwhile to consider the trends in lung cancer in young women in the NCR which after steep

rises show a decrease in women born after 1965 since 2001, although the latency times still remain about 20 years [2].

The Dutch association for Obstetrics and Gynaecology has formed a working group on the implementation of the HPV-vaccine in the Dutch national vaccination programme. The coverage of the national vaccination programme of childhood infections in the Netherlands is very high, about 95% [18]. It is known that the groups who do not participate in the national vaccination programme (people living in 'the bible belt' and people with an anthroposophic philosophy) do not belong to the high risk groups for cervical cancer mentioned above (low socioeconomic status and immigrants). It might thus be expected that with the introduction of the HPV vaccine the high risk groups for cervical cancer will be covered. However, the HPV vaccine under consideration only protects against 4 types of the virus (HPV6, HPV11, HPV16, HPV18), which are responsible for 70% of all cervical cancers. Thereby, the durability of immune protection and risk of a change in the pattern of infections are unknown and thus the screening programme needs to exist for a few decades following the introduction of the vaccination programme. Uptake of the HPV vaccine in the Dutch vaccination programme is estimated to cost 36 million euros annually and it is estimated that vaccination of preadolescent girls in the Netherlands would require 24,000 euros per life year gained [4;19]. This ratio is near the limit for an acceptable cost-effective preventative intervention used in the Netherlands, which is 20,000 euros per quality-adjusted life years [20]. Together with the costs of the present mass screening programme, the prevention of cervical cancer will then cost about 62 million euros annually [4].

7.3 Detection

Cervical cancer screening

Early detection of cervical neoplasia provides an opportunity to prevent or delay progression to invasive cancer by performing clinical interventions such as colposcopy, conisation, laser vaporization, loop electrosurgical excision, and, when necessary, hysterectomy. There is evidence that early detection through routine Pap testing and treatment of precursor cervical intraepithelial lesions (CIN) can lower mortality from cervical cancer [21;22]. The findings from a study in the Netherlands indicate that women with negative Pap tests are at very low risk for cervical cancer for several years [23]. However, attendance to screening is known to be low among women from certain high risk groups: immigrant women and among women living in socioeconomically disadvantaged neighbourhoods [24-27]. Therefore, it is suggested that a better direction for cervical cancer

screening would be to save women at lower risk the inconvenience and expense of seven five-annual screenings by lowering the screening frequency after for example 45 years and focus on surveillance of women with higher risk.

In our study concerning lowering the screening age for cervical cancer we revealed no recent increases in incidence of and mortality from cervical cancer in ages 25 to 49 (chapter 4.2); we stated that although the incidence of cervical cancer among young women increased recently in Finland, lowering the screening age for cervical cancer in the Netherlands would not be useful at this time. The number of life-years gained is high per woman who is prevented from getting cervical cancer, but the disadvantages of lowering the screening age in terms of 'overtreatment'; and anxiety are very high and seem therefore disproportionate. Another study about screening in this thesis revealed that 61 out of 263 women (23%) and 46 out of 263 women (17%) had an abnormal Pap smear (Pap II or higher) five years and three years before the cancer was diagnosed in the period 1989-2001 (chapter 4.1). But, by contrast, 37 women (14%) and 23 women (9%) had a normal smear five years and three years before diagnosis, respectively. This may support the conclusion that the additional resources which would be needed for increasing the frequency of screening or lowering the screening age with the same frequency of smears should better be used for improving the attendance rates among high risk groups, improving the quality of the smear, the validity of the cytological diagnosis and the follow-up of suspicious smears.

Because cervical and vaginal cancers both develop on the transformation zone and are both associated with HPV they have shared etiologic features. However, vaginal cancers mainly develop in older patients while cervical cancers are most frequent in younger patients. This might indicate that mainly the vaginal tumours in younger patients, who are most likely to carry high risk HPV, are comparable to cervical cancer. In evaluating the mass screening programme for cervical cancer vaginal carcinomas, mainly in younger patients, should therefore also be taken into consideration.

A new screening modality for cervical cancer that may become important in the future is HPV testing. This can theoretically find the vast majority of women at-risk for developing cervical cancer and is described to be more sensitive than cytology [28]. With modern DNA analysis, we have the ability to tell which subtype, or strain, of HPV a person is infected with. The subtype of HPV predicts how likely it is to develop into a cervical cancer. Using HPV testing has several advantages. First, the sample collection can be done at home, in private, by a woman collecting a sample herself and sending it to a laboratory via the mail [29]. Second, if HPV testing is combined with the Pap test the sensitivity for detecting CIN 3 and invasive cancer increases by which CIN 3 is deteted earlier, which

may permit an extension of the screening interval [30-32]. Therefore it is also more woman-friendly because a reduction was seen in colposcopy referrals with outcome <CIN 2 of up to 56% and in repeat smears of 30-100% [33]. Although multiple large well-controlled screening trials have clearly demonstrated that HPV testing would be considerably more sensitive than conventional or liquid-based cytology, cervical cytology remains necessary to determine which HPV-positive women require additional follow-up or colposcopy, because of the lower specificity of the test (especially in women aged 30 years and younger) [34-36]. The HPV test is not perfect because the majority of women with HPV will not develop cervical cancer and, more important, HPV infection will be cleared by the immune system in >90% of the cases [37]. The decrease in mortality from cervical cancer is estimated to be 90% with a participation grade of screening of 100% and therefore the extra number of life years gained by adding an HPV test to the current screening programme will be modest. Furthermore, HPV testing is estimated to be up to 5 times more expensive compared to cytology, but these expenses may be compensated by the lower number of visits to the gynaecologist due to the higher sensitivity of the combination of routine cytology and HPV test result.

7.4 Management

In 1990, the Netherlands Working Group for Oncologic Gynaecology introduced treatment recommendations for the treatment of gynaecological cancers, such as cervical cancer [38]. They in fact implied more radical surgery and regionalization. The specific recommendations were changed after the clinical announcements of the American National Cancer Institute in 1999 which developed into national guidelines in 2004 [39]. These guidelines use the classification IA (IA1 and IA2), IB1+IIA, IB2+IIB-IVA and IVB. Therefore, the studies in this thesis concerning treatment of cervical cancer and this discussion also used this classification.

Diagnostics and staging

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are usually performed to determine lymph node involvement and parametrial spread, respectively. Previous studies have shown that MRI and CT have similar poor sensitivity (44%) for the detection of nodal metastasis [40-42]. Positron emission tomography (PET) had been shown to be significantly superior to CT/MRI in identifying metastatic lesions, although it lacks the precise anatomical

resolution of CT or MRI. PET/CT scanners combine function information from PET with anatomical information from CT, and the use of this imaging modality in cancer patients has increased very rapidly since its introduction in 2001. A study from Denmark demonstrated that whole-body PET/CT scanning for newly diagnosed patients with FIGO stage IB or higher cervical cancer has a high sensitivity and specificity, and can be a valuable supplement to the FIGO staging procedure and may therefore be better in planning treatment strategies [43]. MRI however, might be used for assessing tumour diameter and volume as an adjunct to clinical evaluation [44;45]

FIGO IA

Treatment of patients diagnosed with FIGO stage IA depends increasingly on specific patient and tumour characteristics. This stage with micro-invasive cervical carcinoma has limited metastatic potential and therefore is most likely curable by non-radical treatment. If distant spread is very unlikely, simple but complete excision of the lesion would suffice [39]. An extended operation should be performed in case it is likely that the cancer has spread. The treatment options for stage IA1 are conisation in women wishing to retain fertility and simple hysterectomy for women who do not wish to retain fertility. Lymphovascular invasion is generally considered to be a poor prognostic factor in cervical cancer, however, patients with FIGO stage IA1 with lymphovascular space invasion should be treated with modified radical hysterectomy with pelvic node dissection. Also, patients with FIGO stage IA2 should undergo radical hysterectomy with pelvic node dissection in the presence of unfavourable prognostic features.

Furthermore, because of recent changes in cervical cancer incidence in favour of a rise in the rate of adenocarcinoma in young women, more attention will be paid to fertility preserving surgery. In the late eighties, success was reported on the radical trachelectomy procedure, which has nowadays been proven to be an oncologically safe fertility preserving surgery for young women with early stage cervical cancer [46-49]. Radical trachelectomy with laparoscopic pelvic node dissection is therefore advised in women with FIGO IA1 or IA1 who want to retain fertility [50].

FIGO IB-IIA

In the present national guidelines radical hysterectomy and primary radiotherapy are both advised for patients with FIGO stages IB-IIA, with the exception of FIGO IB2 [51]. Adjuvant radiotherapy for high-risk patients (parametrial invasion, large lesion size, positive surgical margin) after surgery for stage I cervical cancer is often used to improve local control rates but has little effect on survival

[52]. Primary radiotherapy offers similar outcome compared to radical hysterectomy with five-year survival after this therapy ranging from 78% to 91% [53]. However, radiotherapy related complications like bladder dysfunction, bowel symptoms and lymphoedema are often permanent, while most surgical complications can be relatively easy corrected. By contrast, radiotherapy is easier to deliver for patients who are obese, are old or have severe co-morbidity which could be considered to be contraindications to the surgical approach. Radiotherapy also avoids the risks of anaesthesia and avoids the laparotomy scar.

In our study of the effects of age and co-morbidity on the application of treatment modalities and prognosis for patients with cervical cancer, we found that patients in FIGO stages IB-IIA without co-morbidity being younger than 70 years underwent surgery more often than patients older than 70 years (chapter 5.2). In another study concerning management of patients with cervical cancer in relation to guideline adherence in the east and south of the Netherlands, 93% of patients diagnosed with FIGO IB-IIA were treated according to the recommendations of the national Working Group for Oncologic Gynaecology (chapter 5.1).

Not unexpectedly, patients without co-morbid conditions received surgery more often than patients with one or more co-morbid conditions: 91% versus 57% respectively. In multivariate analysis age had independent prognostic value, which may have been due to a worse general condition of older patients. Furthermore, these patients are affected by other factors which determine frailty and therefore exhibit worse survival, for which we could just partly adjust by considering co-morbidity.

Because of the low incidence rates for cervical cancer in the Netherlands, centralisation of radical hysterectomy has become important in the optimalisation of the existing therapies. The centralisation of infrequent and complicated radical surgery has been widely advocated in publications addressing quality of care in oncology [54;55]. It has been stated that regionalization in moderate to high volume centres is essential to allow optimal treatment and that experienced surgical skills are essential when unexpected difficulties arise [52]. A study in the Netherlands showed an argument for centralisation of performing radical hysterectomies by demonstrating declining operating time and blood loss over 13 years of performing radical hysterectomies in the relatively ideal situation of a single institution with the same surgical procedure and clinical policies by the same surgical team [57].

Five year survival rates for patients with cervical cancer who are diagnosed in stage IB1 or IIA are very high (between 60% and 98%) and attention is focused on new therapeutic options with less morbidity and therefore higher quality of

life. Despite these high survival rates, the price in terms of surgery-related mortality and morbidity remained high for radical hysterectomy [58;59] and therefore several less invasive techniques have now been introduced. One of the new techniques to overcome serious morbidity related to the extent of radical hysterectomy are specific nerve-sparing [60;61]. Other studies reported that laparoscopic radical hysterectomy can be performed with reasonable operative outcomes in abdominal as well as vaginal procedures [62-65]. Also, there have been attempts to decrease the radicality of parametrial resection in an effort to decrease the postoperative morbidity, although the role of parametrial involvement in survival of cervical cancer remains controversial [66-69]. Finally, in the surgical management of cervical cancer, pelvic lymph nodes are dissected to remove and examine as many as possible. During the last few years several pilot studies on the feasibility of lymphatic mapping and/or sentinel node biopsy in cervical cancer have yielded

promising results [70;71].

FIGO IB2, IIB-IVA

Radiotherapy has long been the primary treatment of choice for FIGO stages IIB-IVA 33. However, in 1999 a clinical advisory committee of the National Cancer Institute (NCI) announced, based on five clinical trials, that combined platinum-based chemoradiation was superior over radiotherapy only [72-76]. In advanced cervical cancer concurrent chemoradiation improved 5-year survival rates from 38% to 42% [52]. Furthermore, in 2002 a 3-year overall improvement of 27-51% was found for the survival of patients with FIGO stages IIB-IVA after radiotherapy combined with hyperthermia in a Dutch trial [77]. According to the national guidelines, patients with FIGO stages IB2 and IIB-IVA should now be given chemoradiation or radiotherapy combined with hyperthermia [51].

In our study concerning management of patients with cervical cancer, in FIGO IIB-IVA 76% of patients were treated according to the recommendations of the working group (chapter 5.1). Furthermore, we have shown that chemoradiation was given to 2% of older patients compared to 23% of younger patients and that a 40% lower risk of death was found for patients receiving chemoradiation compared to those receiving “radiotherapy only”. This is in accordance with our study of co-morbidity in which patients with FIGO stages IB2, IIB-IVA younger than 70 years without co-morbid conditions received chemoradiation more often than patients older than 70 years without co-morbid conditions (chapter 5.2). Furthermore, patients without co-morbid conditions received chemoradiation more often than patients with co-morbid conditions and in multivariate analysis, co-morbidity and FIGO stage were independent prognostic factors.

With the aging of the population, increased attention has been focused on the treatment of geriatric patients with cancer. Age has been described as an important factor in the selection and allocation of treatment for a host of malignancies. Although patients with cervical cancer are relatively young, we found that the elderly are less likely to receive aggressive therapy and are less likely to be included in clinical trials, because of the presence and severity of co-morbidities and ethical considerations which concern patient safety [78;79]. Even though final proofs have not been delivered, but are also difficult to deliver in individual cases, it does not seem very illogical that older women are more likely than their younger counterparts to refuse aggressive treatment. This trend has been observed elsewhere for surgery, radiation, and chemotherapy [80;81]. Development of age-specific guidelines, incorporating levels of co-morbidity and for example performance score, may therefore be warranted and moreover, increase awareness about co-morbidity among physicians.

Nowadays, there is a renewed interest and need to re-evaluate the effects of common clinical and pathologic factors in cisplatin-based regimens. Other concurrent chemotherapy regimens are therefore being compared to radiation therapy alone in randomized trials in cervical cancer. In a meta-analysis evaluating randomized trials of chemoradiation, a statistically significant improvement in the hazard ratio was seen in platinum-containing chemoradiation regimens, but was not statistically significant for the non-platinum containing chemoradiation regimen subgroup [82]. Although cisplatin-based chemotherapy in combination with radiotherapy is considered to be the gold standard in management of patients diagnosed with FIGO stages IB2, IIB-IVA, controversy exists about the most appropriate chemotherapy schedule and whether similar results for tumour control and toxicity may be achieved with optimally delivered radiotherapy. While several studies demonstrate high survival rates for weekly cisplatin [83-86], a recent study reported shorter three years progression-free survival rates and more acute toxicities for patients treated with weekly cisplatin at a dose of 40 mg/m2 compared to a dose of 20 mg/m2 for five days [87]. Furthermore, multimodal investigational treatments including radical surgery after neo-adjuvant chemoradiation have also been explored, although no definitive conclusion on survival improvement has been reported [88-90]. A recent study evaluated pretherapeutic laparoscopic extraperitoneal lymph node staging of patients with locally advanced cervical carcinoma [91]. This approach turned out to offer valuable information for individualized treatment planning with minimal morbidity.

FIGO IVB

Treatment of patients with metastatic disease, FIGO IVB, is mainly individual [35],

with cisplatin-based combination chemotherapy sometimes considered being standard of care. This therapy gained acceptance after a Gynecologic Oncology Group (GOG) Phase II study demonstrated a 44% response rate among untreated patients [92]. Various studies have evaluated the use of cisplatin in combination with other cytotoxic agents. One study found found carboplatin and paclitaxel to be an active regimen, which because of its ease of administration and improved toxicity profile should be considered in the treatment of advanced, recurrent or progressive cervical cancer [93].

7.5 Conclusion

Cervical cancer has on the one hand become rare in the Netherlands but relatively often affects young and middle aged women and therefore many life years could be lost when a woman dies from cervical cancer. Next to this, the impact of the current treatment modalities in cervical cancer is enormous, especially for women with stage IB and higher (about 75% of all cervical cancer cases) who are likely to have become infertile or suffer from various other treatment-related complications. Avoidability of cervical cancer by decreasing the HPV infection rate and screening for premalignant lesions remains important for a long time and still brings a large role for clinical or epidemiological research. Despite the developments in cervical screening and the tendency to go for less radical treatment solutions, we must still consider the substantial anxiety (due to false-positive findings) and potential ‘overtreatment’ of women screened or treated for cervical cancer.

New cervical cancer prevention methods must also be introduced with consideration of added value and added cost [94], thereby avoiding overtreatment of women at low risk and neglect of women at higher risk. Upon the adoption of new technologies it can be helpful to calculate ‘numbers needed to screen’ and ‘numbers needed to treat’ to avoid one death or recurrence. Knowing how many women need to be screened (about 2560 for screening [95]) or to be (adjuvantly) treated to save one life should help us to remain modest in claiming victory of cervical cancer. On the other hand the relatively low and decreasing incidence and mortality rates from cervical cancer in industrialized countries are a clear sign of success and could be more prominent in the discussion on adopting new approaches with modest additional effects and sometimes substantial side effects to prevention, screening and/or treatment. Vaccination may help us in the battle against cervical cancer but the long term effects of vaccination may be limited as long as the vaccine does not cover a wider range of HPV-types, but are by definition unknown and be could be disturbed by side-effects like other,

globalizing, patterns of sexually transmitted infections. Cervical cancer screening therefore needs to exist next to vaccination for several years.

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Summary/samenvatting

Summary

In the Netherlands, approximately 2% of all newly diagnosed malignant tumours in women are cancers of the uterine cervix, corresponding to about 700 new cases of invasive carcinoma per year. A general practitioner sees a patient with newly diagnosed cervical cancer only once in 15 years and this may vary between once in 10 to once in 25 years. Every year about 250 women die from cervical cancer, which is about 1.5% of all deaths in women caused by cancer. However, partly due to the mass screening programme, incidence and mortality rates are decreasing and cervical cancer definitely is a decreasing problem. Just like in most other industrialized countries with some degree of screening, cervical cancer in the Netherlands is nowadays most frequent among women of lower socioeconomic status (SES), partly due to their lower participation in screening.

In **chapter 3** we explored geographical differences and trends in incidence of and mortality from cervical cancer within the Netherlands and Finland, which is a comparable, industrialized country.

Differences in incidence and mortality from cervical cancer in relation to SES and other sociodemographic factors are described in **chapter 3.1**. In the Netherlands, incidence of cervical cancer was higher in municipalities with a high prevalence of immigrants and with more individuals living on welfare. Furthermore, patients living in neighbourhoods with lower SES scores had higher FIGO stages, fewer adenocarcinomas and were younger at the time of diagnosis. These results emphasize the importance of future prevention programmes targeted at women of lower SES who also do not participate in opportunistic screening.

Comparable to the Netherlands, Finland has a well organized national screening programme for several decades and is comparable with respect to, e.g. fertility rate and age of mother at first birth. The aim of the study in **chapter 3.2** was therefore to compare the trends in the incidence of and mortality from cervical cancer in Finland and the Netherlands in relation to the introduction and intensity of the screening programmes. We found that incidence and mortality rates had been declining more rapidly in Finland than in the Netherlands, and that excess smear use in the Netherlands had become much lower since 1996 compared to Finland. On the basis of these results and the content of the screening programmes, we concluded that the decline in mortality in Finland seems almost completely related to the screening programme whereas in the Netherlands it was initially (during the 60's and 70's) considered to be a natural decline.

Differences in risk factors might also play a role: in contrast to Finland, the Netherlands generally has high population density in larger parts of the country and higher percentages of immigrants and (female) smokers. The greater excess smear use in Finland might also have affected incidence downwards.

Chapter 4 of this thesis describes the effectiveness and modification of mass screening programmes.

In the Netherlands, despite a national screening programme since 1996, invasive cervical cancers have been detected in non-screened but also in screened women. The aim of the study in **chapter 4.1** was therefore to determine differences between Pap-smear history, tumour characteristics and survival of patients with a tumour detected by the screening programme (SP) or outside the screening programme (OSP) in the region of the Comprehensive Cancer Centre Stedendriehoek Twente in the period 1992-2001. We found that 35% of the tumours which were diagnosed in the above mentioned period were SP tumours and 65% were OSP tumours. SP tumours had a lower stage and a decreased risk of death compared to the OSP group. In total, 61 women (23%) and 46 women had an abnormal Pap smear (Pap II or higher) five years and three years before the 'diagnostic smear', respectively. Furthermore, 37 women (14%) and 23 women (9%) had a normal smear five years and three years before diagnosis, respectively. On the basis of these results it could be concluded that SP tumours have a lower stage and a better prognosis and were probably slow growing tumours. Furthermore, detection and treatment of patients with suspicious smears was clearly suboptimal and more attention has therefore to be paid to prompt follow-up of suspicious smears.

Recently, debate has risen to lower the age at initiation of cervical cancer screening in the Netherlands, which is based on two assumptions. First, due to increased risk of HPV-infection, because of earlier sexarche, the incidence of cervical cancer might have been rising in age group 25-29 years. Second, there might have been an increase in the incidence of cervical cancer in age group 30-44 years and the corresponding preinvasive cervical lesions should be detected earlier. **Chapter 4.2** aims to answer the question whether the target age for cervical cancer screening should be lowered, based on defining (age-specific) incidence and mortality of cervical cancer in the Netherlands. Between ages 25 and 28, the absolute number of newly diagnosed cervical cancer annually varied between 0 and 9 per age year, since 1989. Significantly decreasing trends in incidence were observed for age groups 35-39 and 45-49 years. Annual numbers of deaths were fluctuating but with a decreasing trend in age groups 30-34 and 35-39 years. We concluded that lowering the age for cervical cancer screening does not seem to be useful at this time. Although the number of life

years gained is high per woman at these ages, the disadvantages of lowering the screening age, like anxiety and costs, are likely to become disproportionate.

In **chapter 5** trends in treatment and survival in two regions in the Netherlands and the relationship with comorbidity and adherence to treatment guidelines were explored.

Changes and variation in stage, treatment and survival in cervical cancer of patients diagnosed in the period 1989 to 2004 in the regions of the Comprehensive Cancer Centre Stedendriehoek Twente (CCCST) and the region of the Comprehensive Cancer Centre South (CCCS) in the Netherlands are described in **chapter 5.1**. We found that in FIGO IB-IIA 93% of patients were treated according to the national guidelines for treatment of cervical cancer; 47% of patients receiving radical hysterectomy + radiotherapy had negative lymph nodes. No survival benefit appeared to be found for patients receiving radical hysterectomy + radiotherapy. In FIGO IIB-IVA 76% of patients were treated according to the guidelines. The treatment recommendations were better implemented for patients with FIGO IB-IIA, but the role of adjuvant radiotherapy needs discussion. Within the broad spectrum of patients with FIGO IIB-IVA, individual patient and tumor characteristics remain of major importance for adequate treatment. Elderly patients with FIGO IIB-IVA were more likely to have received suboptimal treatment in this study and showed an independent increased risk of death, which confirms the urge for paying attention to treatment of elderly patients.

In general, treatment guidelines are based on the results of clinical trials in which patients with co-morbidity and/or older age often are excluded. However, treatment for individual patients will be affected by age and co-morbidity. Therefore, in **chapter 5.2** we studied the influence of age and co-morbidity on the treatment modalities chosen and the ultimate survival result of unselected patients with cervical cancer in the region of the Eindhoven cancer registry. We found that in patients with FIGO stages IB-IIA (excluding IB2), both age and co-morbidity significantly affected the choice of treatment. In multivariate survival analysis, age had independent prognostic value: the risk of dying increased with 2% per every additional year in age. In patients with FIGO stages IB2, IIB-IVA, especially age significantly affected the choice of chemoradiation. In multivariate survival analysis, co-morbidity and FIGO were independent prognostic factors: the death risk for patients with one co-morbid condition was twice as high as for patients without co-morbidity and the death risks of patients with FIGO IIIA, IIIB, and IVA were, respectively, 2.0, 3.5 and 7.7 times higher compared to patients diagnosed with FIGO IIB. We concluded that the treatment of elderly patients with cervical cancer and those with co-morbidity was rather different.

Furthermore, co-morbidity had independent prognostic value in patients with FIGO stages IB2, IIB-IVA. Development of age-specific guidelines incorporating levels and management of specific co-morbidity seems therefore warranted.

The clinical and prognostic evaluation of cervical and vaginal tumours other than squamous cell and adenocarcinomas is often hampered by the low incidence, and clinical and epidemiological studies on these uncommon tumours are scarce. Therefore **chapter 6.1** is a study on these rare cancers. We found that the less common histological types of cervical and vaginal cancer were clearly different from squamous cell carcinomas, especially with respect to age at diagnosis and survival rates. We found a significantly worse prognosis for patients with small cell neuro-endocrine cervical tumours and for patients with vaginal melanomas. Furthermore, we found patients with CCAC of the vagina and cervix across all age categories. We think that spreading population-based knowledge of effects of treatment of these uncommon tumours should improve awareness and thus prognosis. Furthermore, the diagnosis of patients with these tumours should be discussed in a multidisciplinary setting. If curative treatment is possible, these patients should be referred to specialised oncology centres, given the clinical complexity.

In **chapter 7** the results of the studies which are presented in this thesis were put into perspective and related to recent and expected future developments in order to find out how to decrease mortality from cervical cancer further in an effective way in industrialized countries with decreasing trends in incidence and mortality. We concluded that cervical cancer has on the one hand become rare in the Netherlands, but on the other hand relatively often affects young and middle aged women and therefore many life years could be lost. Despite the developments in cervical screening and the tendency to go for less radical treatment solutions, we must still consider the substantial anxiety (due to false-positive findings) and potential ‘overtreatment’ of women screened or treated for cervical cancer. Upon the adoption of new technologies it can be helpful to calculate ‘numbers needed to screen’ and ‘numbers needed to treat’ to avoid one death or recurrence. Knowing how many women need to be screened or to be (adjuvantly) treated to save one life should help us to remain modest in claiming victory of cervical cancer. On the other hand the relatively low and decreasing incidence and mortality rates from cervical cancer in industrialized countries are a clear sign of success and could be more prominent in the discussion on adopting new approaches with modest additional effects and sometimes substantial side effects to prevention, screening and/or treatment. Vaccination may help us in the battle against cervical cancer, but the the long

term effects of vaccination may be limited as long as the vaccine does not cover a wider range of HPV-types, are by definition unknown and be could be disturbed by side-effects like other, globalizing, patterns of sexually transmitted infections. Cervical cancer screening therefore needs to exist next to vaccination for several years.

Samenvatting

In Nederland worden per jaar ongeveer 700 nieuwe gevallen van invasieve baarmoederhalskanker gevonden. Hiermee blijkt baarmoederhalskanker niet voor te komen in de top tien van meest voorkomende kankers in Nederland: borstkanker wordt jaarlijks bij 11.800 vrouwen gevonden, dikkedarmkanker bij 4.750 vrouwen en longkanker bij 2.900 vrouwen. Een gemiddelde huisarts ziet 1 vrouw met baarmoederhalskanker in 15 jaar. Elk jaar sterven ongeveer 250 vrouwen aan baarmoederhalskanker; dit is ongeveer 1,5% van alle vrouwen die sterven aan kanker. Net als in andere geïndustrialiseerde landen met een bevolkingsonderzoek voor baarmoederhalskanker, is de incidentie van baarmoederhalskanker in Nederland het hoogst onder vrouwen met een lage sociaaleconomische status (SES), wat gedeeltelijk gerelateerd is aan hun beperktere deelname aan het bevolkingsonderzoek.

In **hoofdstuk 3** hebben we gekeken naar geografische verschillen in het voorkomen van (incidentie) en de sterfte aan (mortaliteit) baarmoederhalskanker in Nederland en verschillen met een ander, vergelijkbaar land.

Verschillen in de incidentie en mortaliteit van baarmoederhalskanker in relatie tot SES en andere sociaaldemografische factoren worden beschreven in **hoofdstuk 3.1**. We hebben gevonden dat de incidentie van baarmoederhalskanker in Nederland hoger was in gemeenten met een relatief hoger aantal immigranten en in gemeenten met veel mensen met een uitkering. Verder hadden de patiënten die woonachtig waren in buurten met een lage SES, tumoren met hogere stadia, minder vaak adenocarcinomen en waren ze jonger op het moment van diagnose. Deze resultaten benadrukken dat toekomstige preventieprogramma's voor baarmoederhalskanker zich wat meer moeten richten op vrouwen met een lage SES, die niet deelnemen aan het bevolkingsonderzoek.

Finland heeft net als Nederland een landelijk bevolkingsonderzoek baarmoederhalskanker, maar startte hiermee bijna 20 jaar eerder. Verder zijn Nederland en Finland vergelijkbaar voor wat betreft relevante kenmerken die te maken hebben met baarmoederhalskanker, namelijk vruchtbaarheid en de leeftijd van de moeder bij de geboorte van het eerste kind. Het doel van de studie in **hoofdstuk 3.2** was daarom om de trends in incidentie en mortaliteit van baarmoederhalskanker in Finland en Nederland te vergelijken, in relatie tot de introductie en de intensiteit van de bevolkingsonderzoeken. De uitvoering van de beide bevolkingsonderzoeken is in grote mate vergelijkbaar. Het voornaamste verschil is dat het 'aantal uitstrijkjes dat niet bijdraagt aan de dekking van het bevolkingsonderzoek' in Finland veel hoger is dan in Nederland.

Verder vonden we dat de incidentie van en de sterfte aan baarmoederhalskanker meer daalden in Finland dan in Nederland. We concludeerden dat de afname van de sterfte aan baarmoederhalskanker in Finland bijna geheel te relateren was aan het bevolkingsonderzoek. In Nederland wordt de afname vooral gezien als een natuurlijk proces, als gevolg van verbeterde seksuele hygiëne, maar ook door opsporing in een vroeger stadium door verbeterde diagnostiek. Verschillen in risico-indicatoren zouden ook een rol kunnen spelen: in vergelijking met Finland heeft Nederland een hogere bevolkingsdichtheid en sinds de jaren '70 een hoger percentage immigranten en een hoger percentage vrouwelijke rokers. Verder zal het enorme aantal 'uitstrijkjes dat niet bijdraagt aan de dekking van het bevolkingsonderzoek' in Finland ook de incidentie beïnvloed hebben.

Hoofdstuk 4 van dit proefschrift beschrijft de effectiviteit van en eventuele veranderingen in het bevolkingsonderzoek baarmoederhalskanker.

In Nederland werden ondanks het bestaan van het bevolkingsonderzoek baarmoederhalskanker sinds 1996 nog steeds invasieve tumoren gevonden bij zowel gescreende vrouwen als, logischerwijze, ook bij niet-gescreende vrouwen. Het doel van de studie in **hoofdstuk 4.1** was daarom om te kijken naar verschillen in de geschiedenis van de uitstrijkjes, tumorkenmerken en overleving van vrouwen met een tumor die werd gevonden in het bevolkingsonderzoek en vrouwen van wie de tumor werd gevonden buiten het bevolkingsonderzoek in de regio van het Integraal Kankercentrum Stedendriehoek Twente in de periode 1992-2001. We vonden dat 35% van de tumoren werd gevonden in het bevolkingsonderzoek en 65% werd gevonden buiten het bevolkingsonderzoek. De tumoren die in het bevolkingsonderzoek werden gevonden hadden een lager stadium en de vrouwen met deze tumoren hadden een lager risico op overlijden vergeleken met de vrouwen van wie de tumor was ontdekt buiten het bevolkingsonderzoek. Verder bleken 61 vrouwen 5 jaar voor de diagnose en 46 vrouwen 3 jaar voor de diagnose een abnormaal uitstrijkje te hebben gehad. Op basis van deze resultaten kan worden geconcludeerd dat de tumoren die in het bevolkingsonderzoek worden gevonden een lager stadium en een betere prognose hebben. Dit is waarschijnlijk het gevolg van het feit dat het bevolkingsonderzoek vooral de langzaam groeiende tumoren vangt, die over het algemeen een betere prognose hebben. Verder is gebleken dat de opsporing en de behandeling van patiënten met verdachte uitstrijkjes niet optimaal zijn geweest. Een goede follow-up van verdachte uitstrijkjes blijft dus belangrijk.

Recentelijk is een discussie gestart over het verlagen van de onderste leeftijdsgrens van het bevolkingsonderzoek baarmoederhalskanker in Nederland. Deze discussie is gebaseerd op twee veronderstellingen. Ten eerste

zou er een stijging te zien zijn in de incidentie van baarmoederhalskanker in de leeftijdsgroep 25-29 als gevolg van een hoger risico op HPV besmetting door de vroegere leeftijd waarop vrouwen voor het eerst geslachtsgemeenschap hebben. Ten tweede zou de incidentie van baarmoederhalskanker stijgen in de leeftijdsgroep 30-44 en verlaging van de leeftijdsgrens dient in dit geval om voorstadia van baarmoederhalskanker op te sporen om op die manier invasieve baarmoederhalskanker in de leeftijdsgroep 30-44 te voorkomen. In **hoofdstuk 4.2** proberen we de vraag te beantwoorden of de onderste leeftijdsgrens van het bevolkingsonderzoek baarmoederhalskanker inderdaad omlaag moet, gebaseerd op de leeftijdspecifieke incidentie en mortaliteit van baarmoederhalskanker in Nederland. We hebben gevonden dat het absolute aantal gevallen van baarmoederhalskanker bij vrouwen in de leeftijd 25 tot en met 28 jaarlijks varieerde tussen 0 en 9. Significant dalende trends in de incidentie werden gevonden voor de leeftijdsgroepen 35-39 en 45-49 jaar. Het aantal vrouwen dat per jaar sterft aan baarmoederhalskanker fluctueerde met een dalende trend in de leeftijdsgroepen 30-34 en 35-39 jaar. De incidentie bij 29-jarigen leek te stijgen, omdat zij al opgeroepen worden voor het bevolkingsonderzoek in het jaar dat ze 30 worden. Op basis van deze resultaten kunnen we concluderen dat het verlagen van de onderste leeftijdsgrens van het bevolkingsonderzoek baarmoederhalskanker op dit moment niet nodig is. Hoewel het aantal gewonnen levensjaren per vrouw die niet overlijdt aan baarmoederhalskanker hoog is zijn de nadelen van het verlagen van de leeftijd erg groot in termen van veroorzaakte angst en overbehandeling.

In **hoofdstuk 5** hebben we gekeken naar trends in de behandeling en overleving van baarmoederhalskanker in twee regio's in Nederland, de relatie met bijkomende ziekten (comorbiditeit) en het volgen van de richtlijnen.

Veranderingen en variatie in stadium, behandeling en overleving van vrouwen met baarmoederhalskanker die werden gediagnosticeerd in de periode 1989-2004 in de regio's van het Integraal Kankercentrum Stedendriehoek Twente en het Integraal Kankercentrum Zuid werden beschreven in **hoofdstuk 5.1**. In deze studie vonden we dat in patiënten die werden gediagnosticeerd in FIGO stadia IB-IIA 93% werd behandeld volgens de richtlijnen. Van de vrouwen die adjuvante radiotherapie kregen na radicale hysterectomie had 47% negatieve lymfklieren. In FIGO stadia IIB-IVA werd 76% van de patiënten behandeld volgens de richtlijnen. Er werd geen slechtere overleving gevonden voor patiënten die een radicale hysterectomie ondergingen gevolgd door radiotherapie, hoewel deze behandeling tegenstrijdig is met de richtlijnen. Hoewel ze niet altijd opgevolgd werden, waren de nationale richtlijnen beter geïmplementeerd voor de behandeling van patiënten met FIGO stadia IB-IIA dan voor patiënten met FIGO stadia IIB-IVA. Individuele patiënt- en

tumorkenmerken blijven relevant, speciaal bij de behandeling van patiënten met FIGO stadia IIB-IVA. Oudere patiënten met FIGO stadia IIB-IVA werden vaker suboptimaal behandeld en hadden een onafhankelijk verhoogd risico op overlijden. Dit bevestigt dat meer aandacht moet worden besteed aan de behandeling van oudere patiënten.

In het algemeen worden behandelingsrichtlijnen gebaseerd op de resultaten van klinische trials waarin patiënten met comorbiditeit en/of oudere patiënten vaak niet worden meegenomen. De behandeling van de individuele patiënt wordt echter vaak beïnvloed door leeftijd en comorbiditeit. Daarom hebben we in **hoofdstuk 5.2** gekeken naar de invloed van leeftijd en comorbiditeit op de gekozen behandeling en de overleving van patiënten met baarmoederhalskanker. We vonden dat in patiënten met FIGO stadia IB-IIA (uitgezonderd IB2) leeftijd en comorbiditeit significant van invloed waren op de keuze van behandeling. In de multivariate overlevingsanalyse had leeftijd onafhankelijke prognostische waarde: het risico op overlijden nam toe met 2% voor elk jaar dat de patiënt ouder is. In patiënten met FIGO stadia IB2, IIB-IVA beïnvloedde leeftijd de keuze voor chemoradiatie, hetgeen niet onlogisch lijkt. In de multivariate overlevingsanalyse waren comorbiditeit en FIGO stadium onafhankelijke prognostische factoren: het risico op overlijden voor patiënten met 1 comorbiditeit was twee keer zo hoog als voor patiënten zonder comorbiditeit en het risico op overlijden voor patiënten met FIGO stadium IIIA, IIIB, en IVA was hoger dan het risico voor patiënten met FIGO stadium IIB. Op basis van deze resultaten hebben we geconcludeerd dat de behandeling van oudere patiënten met baarmoederhalskanker en met comorbiditeit behoorlijk afwijkt van die van jongere patiënten zonder comorbiditeit. Verder had comorbiditeit onafhankelijke prognostische waarde in patiënten met FIGO stadia IB2, IIB-IVA. De ontwikkeling van leeftijdspecifieke richtlijnen waarin rekening wordt gehouden met de mate van comorbiditeit en het omgaan hiermee lijkt nuttig te worden.

De klinische en prognostische evaluatie van tumoren van de baarmoederhals en vagina, anders dan plaveiselcelcarcinomen en adenocarcinomen, wordt vaak gehinderd door het kleine aantal dat per jaar wordt gediagnosticeerd. Hierdoor zijn er maar weinig klinische en epidemiologische studies naar deze tumoren gedaan. Daarom hebben wij in **hoofdstuk 6.1** gekeken naar deze zeldzame vormen van kanker. We konden concluderen dat de minder frequent voorkomende histologische subtypen van baarmoederhalskanker en kanker van de vagina verschilden van plaveiselcelcarcinomen, met name voor wat betreft leeftijd op moment van diagnose en prognose. We vonden onder andere een significant slechtere prognose voor patiënten met ‘small cell’ neuroendocriene cervixtumoren en voor patiënten met melanomen in de vagina. Dankzij de

kankerregistratie is het eenvoudiger om kennis over de effecten van de behandeling van deze zeldzame tumoren zichtbaar te maken, waardoor de prognose zou kunnen verbeteren. ‘Clear cell’ adenocarcinomen (CCAC) van de baarmoederhals en vagina kwamen voor in alle leeftijdsgroepen. De richtlijnen voor het volgen van deze vrouwen zijn echter goed beschreven en ‘extra volgen’ van deze vrouwen is waarschijnlijk niet effectief, maar wel kostenverhogend. We stelden dat door verspreiding van kennis over de zeldzamere tumoren in de baarmoederhals en vagina de prognose van vrouwen met deze tumoren zou moeten verbeteren. Verder concludeerden we dat deze vrouwen multidisciplainir besproken moeten worden en als genezing nog een optie is, moeten ze worden doorverwezen naar speciale oncologische centra.

In **hoofdstuk 7** worden de studies die in dit proefschrift worden beschreven in perspectief geplaatst en gerelateerd aan recente en verwachte toekomstige ontwikkelingen. Dit om een bijdrage te leveren aan de discussie hoe in geïndustrialiseerde landen de sterfte aan baarmoederhalskanker op een kosteneffectieve manier verder kan worden verlaagd.

We concludeerden dat baarmoederhalskanker zeldzaam is geworden in Nederland, maar doordat het vaak jonge vrouwen en vrouwen van middelbare leeftijd treft kunnen vele levensjaren verloren gaan wanneer een vrouw sterft aan baarmoederhalskanker. Ondanks de introductie van nieuwe screeningstechnieken en het feit dat er steeds vaker wordt gekozen voor minder ingrijpende behandelingen, mogen we de angst (gerelateerd aan fout-positieve bevindingen tijdens de screening) en potentiële overbehandeling van vrouwen die zijn gescreend of behandeld voor baarmoederhalskanker niet vergeten. Bij het ontwikkelen van nieuwe technologieën kan het handig zijn om ‘numbers needed to screen’ en ‘numbers need to treat’ voor het voorkomen van een dode of terugkeer van de ziekte (recidief) te berekenen. Kennis van het aantal vrouwen dat moet worden gescreend (ongeveer 2560) of moet worden behandeld om één leven te redden zou ons wat bescheidener kunnen maken in het claimen van de overwinning op het gebied van baarmoederhalskanker. De relatief lage en dalende incidentie- en mortaliteitscijfers in geïndustrialiseerde landen zijn een bewijs van succes. Deze cijfers zouden meer prominent aanwezig mogen zijn in de discussie over het invoeren van nieuwe benaderingen met (middel)matige extra effecten, en soms substantiële neveneffecten, bij de preventie, screening en behandeling van baarmoederhalskanker.De introductie van HPV-vaccinatie kan een bijdrage leveren aan de strijd tegen baarmoederhalskanker. Echter, zolang de lange-termijneffecten van de vaccinatie niet duidelijk zijn, zal het bevolkingsonderzoek voor baarmoederhalskanker moeten blijven bestaan

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About the author

Maaike van der Aa was born in Oldenzaal, the Netherlands, on November 20 in 1978. After she graduated secondary schooling at ‘Thijcollege’ in Oldenzaal in 1997, she started to study Human Movement Sciences at Groningen University. She obtained her Masters’s degree in March 2002. During this study she also obtained the European Master Degree in Adapted Physical Activity at Leuven University, Belgium. In the period 2002 to 2003 she worked a researcher on lung diseases in the hospital Medisch Spectrum Twente in Enschede. In the same period she also worked as a researcher at Arbodienst Drienerlo in Enschede, where she studied the need for movement programmes among the customers of Arbodienst Drienerlo. Next to this, she studied the prevalence of repetitive strain injuries among students of Twente University. At May 1, 2003, she started to work as a researcher at the Comprehensive Cancer Centre Stedendriehoek Twente, where she is still working now. In the spring of 2004 she started part-time with her PhD project on cervical cancer, which resulted in this thesis.

Curriculum Vitae

Maaike van der Aa is 20 november 1978 geboren in Oldenzaal. Nadat zij in 1997 het diploma VWO had behaald aan het Thijcollege in Oldenzaal is zij begonnen met de studie Bewegingswetenschappen aan de Faculteit der Psychologische, Pedagogische en Sociologische Wetenschappen van de Rijksuniversiteit Groningen. Maart 2002 studeerde zij af. Tijdens de studie Bewegingswetenschappen heeft ze aan de Katholieke Universiteit Leuven de European Master Degree in Adapted Physical Activity behaald. Van 2002 tot 2003 heeft zij in het Medisch Spectrum Twente in Enschede als onderzoeker meegewerkt aan een promotieonderzoek naar longziekten. In dezelfde periode werkte zij ook als onderzoeker bij Arbodienst Drienerlo in Enschede, waar zij onder klanten van de arbodienst onderzoek heeft gedaan naar de behoefte aan bewegingsprogramma's. Daarnaast heeft zij onderzoek gedaan naar het voorkomen van RSI onder studenten van de Universiteit Twente. Op 1 mei 2003 is zij in dienst getreden bij het Integraal Kankercentrum Stedendriehoek Twente, als epidemioloog/onderzoeker. Zij ondersteunde het hoofd onderzoek en registratie bij o.a. documentatiestudies en het beantwoorden van aanvragen uit de kankerregistratie vanuit de regio. Begin 2004 is zij part-time begonnen aan haar promotieonderzoek naar baarmoederhalskanker dat uiteindelijk heeft geresulteerd in dit proefschrift.

Comprehensive Cancer Centre Stedendriehoek Twente

The aim of the Comprehensive Cancer Centre Stedendriehoek Twente (CCCST) is to provide cancer patients with optimal oncological and palliative care in the regions Twente, Stedendriehoek and Oost-Achterhoek. By means of coordination and mediation, the CCCST supports the improvement of the quality of and the cohesion within care. The CCCST works closely together with hospitals, nursing homes, general practitioners and other health care professionals.

One of the activities of the CCCST is the cancer registry. Every year between 5500 and 6000 newly diagnosed cancer patients are registered in the population-based regional cancer registry. The registration clerks collect the data of patients with cancer in the seven hospitals of the region. These data are used for scientific research by clinicians and epidemiologists and evaluation of quality of care. For more information: www.ikst.nl.

Integraal Kankercentrum Stedendriehoek Twente

Het IKST streeft naar optimale oncologische en palliatieve zorg voor de patiënt in de regio Twente, Stedendriehoek en Oost-Achterhoek. Door advisering, ondersteuning, bemiddeling en projectbegeleiding draagt het IKST bij aan verbetering van de kwaliteit van en de samenhang in het zorgproces. Het IKST werkt hierbij nauw samen met zorgaanbieders zoals ziekenhuizen, thuiszorginstellingen, verpleeg- en verzorgingshuizen en huisartsen.

Eén van de activiteiten van het IKST is de kankerregistratie. In het werkgebied van het IKST worden jaarlijks tussen de 5500 en 6000 nieuwe kankerpatiënten geregistreerd. Conform de landelijke afspraken registreren de registratiemedewerkers van het IKST gegevens van patiënten met kanker in de zeven ziekenhuizen in de IKST-regio. Deze gegevens door clinici en onderzoekers gebruikt voor o.m. het ondersteunen van wetenschappelijk onderzoek en evaluatie van zorg. Voor meer informatie: www.ikst.nl