Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study

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Abstract

Objective To study the long term risk of cervical and other cancers after treatment for cervical intraepithelial neoplasia.
Design Retrospective cohort study.
Setting University Hospital, Helsinki, Finland.
Participants 7564 women treated for cervical intraepithelial neoplasia during 1974 and 2001 and followed up through the Finnish cancer registry until 2003.
Main outcome measures Standardised incidence ratio for cervical cancer and other cancers.
Results During follow-up 22 cases of invasive cervical cancer occurred in women treated for cervical intraepithelial neoplasia (standardised incidence ratio 2.8, 95% confidence interval 1.7 to 4.2). The highest risk was during the second decade (10 cases observed: 3.1, 1.5 to 5.7). The standardised incidence ratio for cervical intraepithelial cancer type 1 was 3.1 (1.4 to 6.2) and for type 2 was 3.7 (0.9 to 10.7).
Conclusions The risk of cervical cancer in the first 20 years after treatment for cervical intraepithelial neoplasia is higher than in the average population. The risk of smoking related cancers is also increased.

Introduction

Worldwide, cervical cancer remains one of the leading causes of death from cancer among women.[1] In countries with organised screening programmes for cervical cancer, incidence rates and mortality have decreased by 60%-90%.[2] All treatments for cervical intraepithelial neoplasia have excellent short term results and the differences are minimal,[3] but only a few articles have studied long term outcomes after treatment. In the largest of these studies, the authors observed 2116 women for eight years after treatment and found that the incidence of cancer was reduced by 95%.[4] In none of the studies, however, could follow-up data be linked to national cancer and population registries, and thus data on incidence of disease and mortality in treated women was unknown.

We assessed the incidence of cervical and other cancers long term in women treated for cervical intraepithelial cancer in Finland by linking primary data with two Finnish registries.

Methods

Our study is based on data of women treated for cervical intraepithelial neoplasia at Helsinki Central University Hospital, Finland during 1974 and 2001. Records for each patient included name, personal identifier, date and method of treatment, and diagnosis on the basis of histopathology.

The primary data consisted of 22 939 visits or treatments of 7599 women. We linked these data with the Finnish population registry and the Finnish cancer registry[5] to identify cases of cancer. Follow-up was from six months after the first visit until death, emigration, or 31 December 2003. We chose a lag period of six months before diagnosing invasive cancer to exclude cancer diagnosed at the initial visit. After exclusions, 7564 patients remained for analysis.

The women were treated by knife or laser conisation, laser vaporisation, cold coagulation, or loop diathermy. At the first visit 2446 women were diagnosed as having CIN 1 precancerous lesions, 1543 as having CIN 2, 1334 as having CIN 3, and 2241 as having cervical intraepithelial neoplasia not otherwise specified.

We used cancer incidence rates in the population of southern Finland to calculate the expected numbers of cancer cases, stratified by sex, five year age groups, and five year calendar period. We present the results as standardised incidence ratios (ratio of observed to expected numbers of cases) with 95% confidence intervals (calculated on the presumption that the number of observed cases followed a Poisson distribution).

The mean number of visits per woman was 3.0 (range 1-31 visits). The mean number of visits for women with CIN 1 and CIN 2 lesions was 2.7 and 2.9, respectively, and for women with CIN 3 lesions it was 3.4. The mean age at the first treatment was 34.9 years (range 14-88 years). At the beginning of follow-up 43% of the patients were younger than 30, 52% were aged 30-59 (the group usually targeted for screening), and 5% were older than 60. The total follow-up time was 97 556 woman years. The average follow-up time was 11.9 years (range 0.5-28.0 years).

P+ *Cancer coding is on bmj.com*

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Table 1 Numbers of observed and expected cases of cancer, and standardised incidence ratios with 95% confidence intervals, by primary site

Primary site*	Observed cases	Expected cases	Standardised incidence ratio (95% CI)
Overall cancer	448	352	1.3 (1.2 to 1.4)
Anus	3	0.5	5.7 (1.2 to 17.0)
Lung or trachea	40	15	2.5 (1.9 to 3.5)
Breast	149	135	1.1 (0.9 to 1.3)
Vulva	6	1.5	4.1 (1.5 to 8.9)
Vagina	5	0.4	12.0 (3.9 to 28.0)
Cervix:			
CIN 3	3	1.4	2.2 (0.5 to 6.4)
CIN 2	3	0.8	3.7 (0.8 to 10.9)
CIN 1	8	2.6	3.1 (1.4 to 6.2)
CIN not otherwise specified	8	3.3	2.5 (1.1 to 4.9)
Overall	22	8.0	2.8 (1.7 to 4.2)
Corpus	19	20	1.0 (0.6 to 1.5)
Ovaries	21	17	1.2 (0.8 to 1.9)
Female genital organs	74	48	1.5 (1.2 to 1.9)
Other smoking related	45	26	1.7 (1.3 to 2.3)

CIN=cervical intraepithelial neoplasia.
Numbers of observed and expected cases of cervical cancer in relation with the stage of the preinvasive lesion.
*According to international classification of diseases, 10th revision (see bmj.com).

What is already known on this topic

Long term outcomes after treatment for precancerous lesions of the cervix are poorly documented

The highest risk of invasive cancer is during the 10 years after treatment

It has been proposed that only a small proportion of low grade lesions would progress to invasive cancer if not treated

What this study adds

The risk of invasive cervical cancer exists at least 20 years after treatment for cervical intraepithelial neoplasia

The peak of incidence of invasive cervical cancer cases is in the second decade after treatment

Women with low grade lesions are also at increased risk of developing invasive cancer

Results

We identified 448 new cases of cancer among 7564 women treated for cervical intraepithelial neoplasia—96 more cases than expected (table 1). Of these 96 excess cases, 26 were gynaecological cancers (standardised incidence ratio 1.5, 95% confidence interval 1.2 to 1.9). The risks were increased for cancers of the cervix (2.8, 1.7 to 4.2), vulva (4.1, 1.5 to 8.9), vagina (12.0, 3.9 to 28.0), lung or trachea (2.5, 1.9 to 3.5), other smoking related (1.7, 1.3 to 2.3), anus (5.7, 1.2 to 17.0), and any cancer (1.3, 1.2 to 1.4).

Of the 22 cases of invasive cervical cancer 11 were diagnosed 0.5-9 years after treatment (2.7, 1.4 to 4.8), 10 after 10-19 years (3.1, 1.5 to 5.7), and one after 20 years (1.4, 0.04 to 8.0) (table 2). The standardised incidence ratios of overall cancer increased linearly with treatment of cervical intraepithelial neoplasia. We found a strong correlation between an increased risk of lung cancer and long time since treatment.

CIN 1 and CIN 2 precancerous lesions were associated with the highest risk of developing into invasive cervical cancer (3.1, 1.4 to 6.2 and 3.7, 0.8 to 10.9; table 1).

Of the eight patients with CIN 1 lesions who subsequently developed invasive cancer, five returned for one follow-up visit, two returned for two visits, and one returned for three visits. The three patients treated for CIN 2 lesions that subsequently developed into invasive disease returned for one, two, and four visits. The three patients with CIN 3 lesions who subsequently developed invasive cancer had two, three, and five visits.

Discussion

The incidence of invasive cervical cancer among women treated for cervical intraepithelial neoplasia was about 23 per 100 000 woman years. A previous large study on long term outcomes after treatment estimated the rate to be 85 per 100 000 woman years.[4] In our study, follow-up of cancer incidence was based on a nationwide cancer registry, with systematic criteria for the reporting of invasive disease. We found that the relative risk of cervical cancer after treatment of preinvasive lesions was higher than that in the reference population, at least during the first and second decade of follow-up. This contrasts with that of the previous large study, which found that the risk of cancer did not increase during eight years' follow-up.

We also found that the risk of cervical cancer was increased in women diagnosed as having CIN 1 and CIN 2 lesions; the point estimates were higher than those for CIN 3 lesions. The explanation might lie in the general approach towards treatment and follow-up by grade of precancerous lesions. All lesions were treated without exception; however, patients with lower grade lesions (CIN 1 and CIN 2) are not followed-up in

Table 2 Cancer incidence in women by follow-up time since treatment for cervical intraepithelial neoplasia

	Follow-up time								
	0.5-9 years			10-19 years			20-28 years		
Primary site	Observed cases	Expected cases	Standardised incidence ratio (95% CI)	Observed cases	Expected cases	Standardised incidence ratio (95% CI)	Observed cases	Expected cases	Standardised incidence ratio (95% CI)
Overall cancer	169	140	1.2 (1.0 to 1.4)	199	159	1.3 (1.1 to 1.4)	80	53	1.5 (1.2 to 1.9)
Lung, trachea	12	5.6	2.2 (1.1 to 3.8)	18	7.1	2.5 (1.5 to 4.0)	10	2.7	3.8 (1.8 to 7.0)
Uterine cervix	11	4.1	2.7 (1.4 to 4.8)	10	3.2	3.1 (1.5 to 5.7)	1	0.7	1.4 (0.04 to 8.0)
Female genital organs	30	19.6	1.5 (1.0 to 2.2)	37	21.4	1.7 (1.2 to 2.4)	7	7.0	1.0 (0.4 to 2.1)
Other smoking related	20	10.2	2.0 (1.2 to 3.0)	17	12.0	1.4 (0.8 to 2.3)	8	4.2	1.9 (0.8 to 3.8)

a similarly systematic and long lasting way as are patients with high grade lesions. Inadequate follow-up is a major factor, as suggested in the literature.[6–9]

Treatment of cervical intraepithelial neoplasia is, however, effective. In an earlier study of CIN 3 lesions,[10] it was estimated that 28-39% of cases without treatment would progress to invasive cancer. Our data contained 837 cases of CIN 3 lesions in women aged 30-59, thus on the basis of the previous estimate, 234-326 would develop into invasive cervical cancers, not the three observed. The treatment effect might have been nearly 100%.

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Tellymedicine

In the past, doctors had to see a patient before they could make a diagnosis. Doctors were also restricted in whom they could tell about this diagnosis—the patient and his or her trusted next of kin, the nurse, and perhaps the odd interested colleague. Recent advances in technology first brought us telemedicine, where doctors can assist other doctors in making a diagnosis, guide surgical procedures, or even perform surgery themselves, without being physically near the patient.

More recently, we have seen tellymedicine. This enables us to make a diagnosis in patients for whom we have no responsibility. We don't need to examine them, nor do we need a formal invitation to become involved in their medical care. In fact, we may only know of these patients from watching them on television or from reading about them in a newspaper. One of the most accomplished tellydoctors is Dr Gupta, a neurosurgeon who is also a senior medical correspondent for the US Cable News Network (CNN) (www.cnn.com/2005/HEALTH/03/30/otsc.gupta/). Dr Gupta diagnosed coronary artery disease in former US president Bill Clinton almost before his cardiologist did.

Another recent triumph of tellymedicine was recorded during the death of the late pope. The reluctance of the pontiff's doctors to release information threatened to turn things into a private Vatican matter. Fortunately, tellydoctors in several countries used their skills in remote diagnostics to provide the international media with detailed information on the pope's medical condition during his last days.

Forensic medicine is one particular field that can benefit from tellymedicine. For instance, Volkert van der Graaf, the assassin of Dutch politician Pim Fortuyn, was admitted to a clinic for forensic psychiatry so that a single expert witness could report to the court. Because Volkert refused cooperation, this psychiatric evaluation was extremely lengthy. Fortunately, several "Tele" psychiatrists, after studying the media, were able to conclude that Volkert suffered from Asperger's syndrome, and informed the court and public of this through the media long before his trial.

In the UK, Professor David Southall sought a child protection investigation after watching a television programme. He claimed to see what others had not but for his pains was found guilty of serious professional misconduct by the General Medical Council.

Tellymedicine implies that an insightful diagnosis can be made through careful observation alone, and that modern physicians have lost this gift and have come to rely too much on their tradition of diagnostic tests and procedures, requiring the physical presence of the patient. Tellymedicine obviates all these costly and time consuming tests. Patients are spared pointless visits to our clinics. As an additional benefit, they can read their diagnosis in the newspapers or watch it on television in the comfort of their home.

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