EUROPEAN JOURNAL OF CANCER 48 (2012) 845–852

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Omission of excisional therapy is associated with an increased risk of invasive cervical cancer after cervical intraepithelial neoplasia III

E. Rapiti [a], M. Usel [a], I. Neyroud-Caspar [a], A. Merglen [a], H.M. Verkooijen [a,b], A.T. Vlastos [c], J.C. Pache [d], N. Kumar [d], C. Bouchardy [a,*]

[a] Geneva Cancer Registry, Institute for Social and Preventive Medicine, University of Geneva, 55 Bd de la Cluse, 1205 Geneva, Switzerland
[b] Department of Radiology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands
[c] Department of Gynaecology and Obstetrics, Geneva University Hospitals, 32 Bd de la Cluse, 1205 Geneva, Switzerland
[d] Department of Pathology, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva, Switzerland

ARTICLE INFO

Article history:
Available online 12 June 2011

Keywords:
Cervical intraepithelial neoplasia
Cervical cancer
Epidemiology
Gynaecological cancer
Treatment

ABSTRACT

Background: Using data from the population-based Geneva Cancer Registry we evaluated the risk of invasive cervical cancer following carcinoma in situ (CIS) or cervical intraepithelial neoplasia (CIN) III according to type of treatment.

Methods: Included in the study were all women diagnosed with CIS/CIN III in Geneva (Switzerland) between 1970 to 2002 ($n = 2658$) and followed for invasive cervical cancer occurrence until 31st December 2008. We calculated age and period standardised incidence ratios (SIR) and multiadjusted hazard ratios (HR) of invasive cervical cancer by treatment groups.

Results: During follow-up, 17 women developed invasive cervical cancer, conferring a SIR of 5.1 (95% confidence intervals [CI] 3.0–8.1). The risk of cervical cancer was significantly increased until 10 years after diagnosis. The risk was highest for women $\geqslant 50$ years (SIR = 7.3, 95% CI: 2.7–15.8) and for women who did not undergo excisional treatment (SIR = 25, 95% CI: 12.0–46.0). The multiadjusted HR of invasive cervical cancer for women who did not undergo surgical excisional treatment was 9.4 (95% CI: 2.8–32.2) compared with women who did.

Conclusion: Women diagnosed with CIS/CIN III are at increased risk of developing invasive cervical cancer. This risk is particularly high for women who did not have excision of cervical lesions.

1. Introduction

Every year, 500,000 new cases of invasive cervical cancer are diagnosed worldwide.[1] To prevent occurrence of cervical cancer, the currently recommended approach is cervical cytology screening[2,3] which aims to detect precursory lesions, such as cervical intraepithelial neoplasia (CIN). CIN represents the precancerous stage of invasive squamous cell carcinoma, usually associated with chronic human papillomavirus (HPV) infection.

High grade CIN II and CIN III require colposcopically directed biopsy and treatment when confirmed. Management

* *Corresponding author:* Tel.: +41 22 379 49 50; fax: +41 22 379 49 71.
E-mail address: Christine.BouchardyMagnin@unige.ch (C. Bouchardy).
0959-8049/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2011.05.002

methods for CIN II/CIN III include excision, destructive techniques, or hysterectomy, the latter usually upon the patient's request.[4,5] Treatment choice depends on location and extent of the lesion, patient's age, cost, and the provider's training and experience. Strict colposcopical and cytological follow-up is necessary, whatever treatment method used.[4,5]

Several studies demonstrated that women treated for CIN II/CIN III have a higher risk of developing cervical cancer than the general population[6–9] and women without CIN lesions at screening.[10] Persistence of HPV infection, reinfection, and inadequate follow-up of women are possible explanations for this increased risk.

Whereas it has been established that lack of treatment or incomplete excision of pre-invasive cervix lesions strongly increase the risk of invasive cancer,[11,12] the effect of treatment type on such risk has been poorly and inconclusively reported.[7,8,13] While one systematic review did not find destructive or excisional treatment to be obviously superior,[14,15] a recent Canadian study found that the risk of invasive cervical cancer was high for women treated for CIN, particularly if treated with cryotherapy, a destructive technique.[10]

The study by Cecchini et al. of women screened in the Florence programme confirmed these results. The authors reported that the incidence of invasive cervical cancer after conservative treatment of CIN II/III was higher than among women with a negative Pap-test.[16]

A Swedish study reported an almost doubled risk of cervical cancer following CIN III for women diagnosed in the 1990s compared with those diagnosed in the 1960s.[9] The authors hypothesised that the change in therapy patterns in the 1990s, with higher use of more conservative modes of treatment, could have caused the observed increase in the risk of developing invasive cervical cancer.

The aim of our study is to investigate the association between treatment types for cervical carcinoma in situ or CIN III and risk of subsequent invasive cervical cancer.

2. Materials and methods

We used data from the Geneva Cancer Registry, which records all incident cancers occurring in the population of the canton (approximately 447,000 inhabitants in 2007) since 1970. The cancer registry collects information from various sources and completeness of registration is considered high, as demonstrated by the very low percentage (<2%) of cases recorded from death certificates only.[17] The Geneva University Hospitals and the Pathology Laboratories in the canton are requested to report all cancer cases. Trained registrars systematically abstract data from medical and laboratory files and regularly contact private physicians to secure missing clinical and therapeutic data. Death certificates are consulted systematically.

Recorded data include sociodemographic characteristics, method of cancer detection, tumour characteristics (according to the International Classification of Diseases for Oncology ICD-O),[18,19] stage of disease at diagnosis, treatment during the first 6 months after diagnosis, second cancer occurrence, survival status, and cause of death (according to the classification of the World Health Organization).[20]

The cancer registry regularly assesses survival, taking as reference the date of confirmation of diagnosis or the date of hospitalisation (if it preceded the diagnosis and was related to the disease). Passive (standard examination of death certificates and hospital records) and, active follow-up (using the files of the Cantonal Population Office) are performed yearly. Trained tumour registrars establish the cause of death by systematically reviewing clinical records and questionnaires filled in by the patient's physician.

From 1970 to 1994 pre-malignant lesions of the cervix were recorded as carcinoma in situ (CIS) (ICD-O morphology code: 8010/2-8076/2);[18] and from the year 1995 both CIN III (ICD-O: 8077/2) and CIS (ICD-O: 8070/2) diagnoses were recorded according to the international guidelines for cancer registration.[19] A total of 3536 women were diagnosed with CIN III/CIS of the cervix (ICD-O localisation codes: 1800, 1801, and 1809) during the period 1970–2002. We excluded 668 women not resident in the canton, 60 women with previous invasive cancer (except non-melanoma skin cancer), 147 women with less than 6 months of follow-up, and three women who developed invasive cervical cancer during the first 6 months after diagnosis. The lag time of 6 months was set to exclude cancers diagnosed as part of the same initial CIN III diagnostic and treatment event. The final cohort included 2658 women.

The Geneva Cancer Registry records treatments given during the first 6 months after diagnosis of CIN III or CIS as excisional (including cold-knife conisation, laser cone biopsy, loop electrosurgical excision procedure, and hysterectomy), or other (including both destructive procedures, and no treatment). To retrieve the exact nature of the destructive treatment, we reopened all these files and reclassified treatments as follows: cryotherapy, other destructive treatment (including laser vaporisation, cold coagulation, electrotherapy, and diathermy), no treatment, and unknown.

Person-years at risk for subsequent development of invasive cervical cancer were computed for each woman from 6 months after the date of diagnosis of CIN III or CIS to the date of diagnosis of the invasive cervical cancer, date of death, date of loss to follow-up, or end of the study period (31st December 2008). The expected number of invasive cervical cancers was calculated by multiplying the person-years (stratified by 5-year intervals of age and calendar year) by the strata-specific invasive cervical cancer incidence rates of the female population of the Geneva canton. The ratio of the observed to the expected number denotes the standardised incidence ratio (SIR). This SIR represents the relative risk, adjusted for age and calendar year, of developing invasive cervical cancer in patients diagnosed with CIN III/CIS compared with women without such a diagnosis. We calculated 95% confidence intervals (95% CI) of the SIRs on the basis of the assumption that the observed followed a Poisson distribution. All *P*-values were two-sided and calculated by Fisher exact test.

SIRs were calculated by age-group (<35, 35–49, and $\geqslant$50 years), type of diagnostic confirmation (histology and cytology); time from diagnosis (0–4, 5–9, 10–14, 15–19, and 20–39 years), and treatment (excision, cryotherapy, other, none, and unknown). Calculations of SIRs were done with the PYRS programme.[21]

With Cox proportional hazards analysis we calculated the risks (hazard ratios [HRs]) of developing invasive cervical cancer adjusted for other prognostic variables. In univariate analysis, we identified all variables significantly associated with invasive cervical cancer development. With multivariate analysis, adjusting for all variables, we estimated the independent effect of treatment on invasive cervical cancer occurrence among women with CIN III/CIS. All analyses were done with SPSS software (Version 15; SPSS Inc., Chicago, IL, USA).

3. Results

During the study period, 1437 women were diagnosed with CIS and 1221 with CIN III. The cohort produced a total of 35,946 person-years. The median follow-up was 11.1 years. At the end of follow-up, 63.9% of the women were still alive ($n = 1699$), 8.5% deceased ($n = 225$), and 27.6% were lost to follow-up ($n = 734$).

The majority of women (81%) were <45 years old at diagnosis (Table 1). The median age was 34 years (SD = 11.5, range 16–89). Over 60% of the diagnoses occurred during the period 1990–2002 when the directives for CIN III registration were applied. The great majority was diagnosed through cytology screening (82%) and histologically confirmed in 90% of the patients. Eighty-seven percent of the women were treated with excisional procedure ($n = 2307$). Only 32% ($n = 88$) of the 275 cases without histological confirmation had excisional treatment.

During the study period, 17 women (0.6%) developed invasive cervical cancer. Seven of them, who had undergone excisional treatment of the CIN III/CIS (conisations) had positive or borderline margins, and 10 had no excision of the CIN III/CIS lesion (five underwent destructive treatment: three cryotherapy, one laser vaporisation, one electrotherapy, and five had no treatment). The overall cervical cancer incidence rate of the study population was 47.3/100,000 women (95% CI 27.6–75.7). Table 2 shows the estimated overall SIR and SIRs by age, type of diagnostic confirmation, time from diagnosis, and treatment type. Women diagnosed with CIN III/CIS were 5.1 (95% CI 3.0–8.1) times more likely to develop cervical cancer than the general population. This risk was highest in women $\geqslant$50 years (SIR = 7.3, 95% CI: 2.7–15.8). Women who had only cytological confirmation of their CIN III/CIS lesions were particularly more likely to develop invasive cervical cancer than the background population (SIR = 17.3, 95% CI: 6.3–37.4). The risk of cervical cancer was significantly increased up to 9 years after diagnosis (SIR for 0–9 years after diagnosis = 7.5, 95% CI: 4.4–12.1). Compared with the background population, women with excisional treatment had a non-significant increased risk of developing invasive cancer (SIR = 2.4, 95% CI: 1.0–4.9). This risk was much higher among women treated with cryotherapy (SIR = 16.8, 95% CI: 2.0–60.5), or with other destructive treatments (SIR = 24.1, 95% CI: 0.7–134). As expected, the highest increase in risk was observed among women with no treatment (SIR = 49.6, 95% CI: 18.2–110) (Table 2). When considering all patients with no excisional treatment the SIR was 25 (95% CI: 12.0–46.0). The SIR remained high even after removing women who received no treatment (SIR = 16.7; 95% CI: 6.1–36.9) from the number of observed cases (Table 2).

Age, type of confirmation of diagnosis, and treatment were significantly linked to invasive cervical cancer occurrence in univariate Cox analysis while social class, place of birth, marital status, period of diagnosis, sector of care, location of lesions, and methods of detection were not (Table 3). After adjustment for all variables, in comparison with women in the excisional group, the relative risk (HR) of cervical cancer was 7.5 (95% CI: 1.3–44.8) for women treated with cryotherapy, 17.0 (95% CI: 1.4–204) for those with other destructive treatments, 24.9 (95% CI: 5.6–110) for those without treatment, and 3.7 (95% CI: 0.6–22.7) for unknown treatment (Table 3). When considered together, patients who did not receive excisional treatment had an HR of 9.4 (95% CI: 2.8–32.2) of developing invasive cervical cancer as compared with women who had excisional treatment.

4. Discussion

Our study demonstrates a striking stepwise reduction in the risk of invasive cervical cancer after CIN III for patients with no treatment, ablative therapy and excisional therapy. Although the risk of invasive cervical cancer in patients with excisional therapy remained two times higher than that of the general population, for patients with ablative treatments or no therapy it was 25 and 50 times higher, respectively.

The risk is particularly increased among women $\geqslant$50 years at diagnosis of CIN III/CIS and persisted up to 10 years after diagnosis.

The rate of invasive cervical cancer after CIN III in our study is similar to that reported by other authors.[6,7,9,22–24] Consistent with other studies are also the findings that the risk of developing an invasive cervical cancer remains high for up to 10 years after the diagnosis of CIN III,[6,7,9,24–26] and the excess risk among women aged $\geqslant$50 years at diagnosis.[10] The finding of an excess risk among cases lacking histological confirmation is highly correlated with ablative treatment techniques such as laser therapy or cryotherapy for which there is no possibility of a histological evaluation.

Apart from two recent studies,[9,10] the impact of treatment for CIN III/CIS on the risk of invasive cancer has not been evaluated.[7,8,13] Strander et al. postulated that the increasing use of less invasive modalities could partly explain the increased risk of cervical cancer after a CIN III seen in recent years.[9] In a retrospective cohort of 37,142 women treated for CIN I, II, and III, Melnikow et al. reported that method of treatment of CIN strongly modifies the risk of subsequent invasive disease.[10] They reported higher rates of recurrence for the group treated with laser or cryotherapy than for the group treated with loop electrosurgical excision or cone biopsy. In particular, cryotherapy was associated with the highest risk of subsequent disease (adjusted odds ratio [OR] of 3.0, 95% CI: 2.1–4.6). This risk is lower than that observed in our cohort, probably because Melnikow's study had a shorter follow-up (4 years versus 11 in our study) and included in the analysis CIN I and II diagnoses, while in our cohort we only followed CIN III/CIS.[10] Cecchini et al. reported similar results among a cohort of 1667 women with CIN II or III enrolled in the screening programme of Florence, Italy: the highest risk of subsequent invasion was observed among women with local destructive

Table 1 – Patient, tumour, and treatment characteristics among 2658 women diagnosed with CIN III/CIS[A]. Geneva Cancer Registry 1970–2002.

Characteristics	Patients *N*	%	Invasive cervical cancer cases
Age (years)			
15–24	241	9.1	0
25–34	1140	42.9	4
35–44	762	28.7	4
45–54	298	11.2	4
⩾55	217	8.2	5
Place of birth			
Switzerland	1427	53.7	9
Other	1231	46.3	8
Marital status			
Single	778	29.3	1
Married	1407	52.9	11
Separated	389	14.7	4
Widow	83	3.1	1
Unknown	1	0.04	0
Socioeconomic class			
High	477	17.9	4
Middle	1411	53.1	10
Low	503	18.9	2
Unknown	267	10.0	1
Period of diagnosis			
1970–1979	434	16.3	5
1980–1989	615	23.1	4
1990–1999	1168	43.9	6
2000–2002	441	16.6	2
Method of detection			
Screening/check-up	2175	81.8	13
Symptoms	43	1.6	0
Fortuitous	115	4.3	0
Unknown	325	12.2	4
Sector of care			
Private	1755	66.0	14
Public	899	33.8	2
Unknown	4	0.2	1
Confirmation of diagnosis			
Histology	2379	89.5	11
Cytology	275	10.3	6
Unknown	4	0.2	0
Location of lesions			
Endocervix	520	19.6	6
Other	2138	80.4	11
Method of treatment			
Excision[a]	2307	86.8	7
Cryotherapy	108	4.1	2
Other destructive treatments[b]	31	1.2	1
No treatment	103	3.9	5
Unknown	109	4.1	2

[A] CIS: carcinoma in situ; CIN III: cervical intraepithelial neoplasia III.
[a] Laser conisation, LEEP (loop electrosurgical excision procedure), cold-knife conisation or hysterectomy.
[b] Laser vaporisation, electrocautery, diathermy, and cold coagulation.

treatment as compared with conisation (OR: 5.5, 95% CI: 0.5–66.5).[16]

In our study, the rate of invasive cervical cancer was marginally increased among women treated with excisional therapy, but highly increased among women who did not undergo excision of the CIN III/CIS lesions. More than 50% of the 17 cases of invasive cervical cancer may be attributable to total or partial removal of the lesions: five women did not receive any treatment, and five women with excisional treatment had positive or borderline margins.

Table 2 – Standardised incidence ratios (SIR) of developing invasive cervical cancer after CIN III/CIS[A] by age, confirmation of diagnosis, time from diagnosis and type of treatment. Geneva Cancer Registry 1970–2002.

	Number at risk	Observed cases	Expected cases	SIR	95% Confidence interval (CI)
Age-group					
<35	1381	4	1.04	3.9*	1.1–9.9
35–49	964	7	1.49	4.7**	1.9–9.7
⩾50	313	6	0.83	7.3***	2.7–15.8
Confirmation of diagnosis					
Histology	2379	11	2.99	3.7***	1.8–6.6
Cytology	275	6	0.35	17.3***	6.3–37.4
Time from diagnosis (years)					
0–4	2658	8	1.13	7.1***	3.0–13.9
5–9	2292	7	0.87	8.1***	3.2–16.6
10–14	1533	1	0.56	1.8	0.1–10.0
15–19	897	1	0.36	2.8	0.1–15.3
20–39	603	0	0.42	–	–
Type of treatments					
Excision[a]	2307	7	2.95	2.4	1.0–4.9
Cryotherapy	108	2	0.12	16.8*	2.0–16.8
Other destructive treatments[b]	31	1	0.04	24.1	0.7–134.0
None	103	5	0.10	49.6***	18.7–109.0
Unknown	109	2	0.13	15.2*	1.8–55.0
Total	2658	17	3.35	5.1***	3.0–8.1

[A] CIS: carcinoma in situ; CIN III: cervical intraepithelial neoplasia III.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

[a] Laser conisation, LEEP (loop electrosurgical excision procedure), cold-knife conisation or hysterectomy.

[b] Laser vaporisation, electrocautery, diathermy, and cold coagulation.

We observed an approximately 19-fold increased risk of invasive development among women who did not have any treatment as compared with women who underwent excision. Other studies reported similar results: when left untreated, the approximate rate of progression to invasion of a CIN III lesion increases from 12% to 36%.[11,27,28] In our study, most untreated women were lost to follow-up. It is known that patients with cervical precursor lesions encounter socioeconomic and cultural barriers in receiving adequate screening, treatment, and follow-up,[29–31] and as many as 27–70% of women with biopsy-proved high-grade dysplasia are expected to be lost to follow-up during the initial evaluation and will never undergo definitive treatment.[32,33]

Positive margins after conisation are a well-known risk factor for persistence/recurrence of CIN III. A recent meta-analysis estimated that in patients with incomplete excision the relative risk of post-treatment high-grade disease was 6.1 (95% CI: 3.8–9.6) compared with patients who had complete excision, and the overall prevalence of recurrence was 18%.[12]

There were no cases of invasive cervical cancer among women below the age of 25 years, in line with the general consensus that, although the peak of screen-detected precancerous lesions is in late 20s early 30s, 10–15 years after sexual debut, invasive cancer occurs on average approximately 20 years following development of precancerous lesions.[34] The average time between HPV infection and establishment of precancerous lesions seems to be much shorter than the average duration of precancer growth leading to invasion.[35] Cervical cytology screening in women aged between 20 and 24 years has been associated with little or no impact on rates of invasive cervical cancer up to age 30 years.[36] Our findings add weight to the idea that screening women under 25 years of age may not be useful and could expose women to unnecessary tests and treatments.

International guidelines state that destructive procedures are acceptable alternatives to excisional therapy in properly selected patients: when the entire transformation zone is visualised, the endocervical curettage is negative, when there is no evidence of glandular abnormality or invasive disease, and no discrepancy between cytology and histology.[14,37–41] The retrospective nature of our study does not allow us to appreciate how the patients under study were selected for one or the other procedure, and we can only speculate that the above-mentioned conditions were only partially met for the women selected for destructive treatments.

Another limitation is lack of information on other risk factors, such as smoking, HPV, or HIV infections. The persistence of risk factors common to pre-malignant, as well as malignant cervical lesions is one of the possible explanations for the increased risk of cervical cancer after CIN III. However, an underlying HPV infection would most likely result in later cancer occurrence, while in our, as well as in other studies, the majority of cancers occurred within 10 years of the CIN III diagnosis. Besides, these risk factors cannot explain the difference in risk between treatment groups as there are no reasons to be differently distributed by type of treatment. We had a high rate of lost to

Table 3 – Determinants of risk of invasive cervical carcinoma after CIN III/CIS[A]. Hazard ratios (HR) from univariate and multivariate Cox proportional hazards models. Geneva Cancer Registry 1970–2002.

Characteristics	HR univariate	P-value	HR multivariate	P-value
Age (years)				
15–24	–	–	–	–
25–34	1.00	–	1.00	–
35–44	1.4 (0.3–5.5)	0.650	1.1 (0.3–4.5)	0.912
45–54	3.4 (0.9–13.8)	0.081	2.3 (0.5–10.2)	0.276
⩾55	6.2 (1.7–23.1)	0.007	5.6 (1.3–24.0)	0.021
Place of birth				
Switzerland	1.00	–	1.00	–
Other	1.1 (0.4–2.8)	0.866	1.2 (0.4–3.5)	0.713
Marital status				
Single	1.00	–	1.00	–
Married	5.7 (0.7–43.9)	0.097	3.2 (0.4–26.2)	0.281
Separated	7.4 (0.8–66.2)	0.074	2.4 (0.2–24.0)	0.450
Widow	8.6 (0.5–137)	0.128	1.9 (0.1–37.7)	0.660
Unknown	–	–	–	–
Socioeconomic class				
High	1.00	–	1.00	–
Middle	0.8 (0.3–2.6)	0.739	0.7 (0.2–2.3)	0.518
Low	0.5 (0.1–2.4)	0.350	0.2 (0.0–1.4)	0.119
Unknown	0.5 (0.1–4.4)	0.528	0.3 (0.0–3.5)	0.366
Period of diagnosis				
1970–1979	1.00	–	1.00	–
1980–1989	0.6 (0.2–2.2)	0.430	0.3 (0.1–1.3)	0.104
1990–1999	0.5 (0.2–1.7)	0.286	0.5 (0.1–1.9)	0.312
2000–2002	0.5 (0.1–2.9)	0.469	0.6 (0.1–3.4)	0.541
Method of detection				
Screening/check-up	1.00	–	1.00	–
Symptoms	–	–	–	–
Fortuitous	–	–	–	–
Unknown	2.1 (0.7–6.3)	0.207	2.4 (0.7–8.6)	0.181
Sector of care				
Private	1.00	–	1.00	–
Public	0.3 (0.1–1.2)	0.083	0.6 (0.1–2.8)	0.488
Unknown	42.0 (5.5–321)	<0.001	40.7 (3.3–507)	0.004
Confirmation of diagnosis				
Histology	1.00	–	1.00	–
Cytology	4.8 (1.8–13.0)	0.002	0.8 (0.2–2.9)	0.677
Unknown	–	–	–	–
Location of lesions				
Endocervix	2.0 (0.8-5.5)	0.163	2.0 (0.7-6.0)	0.231
Other	1.00	–	1.00	–
Method of treatment				
Excision [a]	1.00	–	1.00	–
Cryotherapy	6.3 (1.3–30.2)	0.022	7.5 (1.3–44.8)	0.026
Other destructive treatments [b]	10.3 (1.3–83.7)	0.030	17.0 (1.4–204)	0.026
No treatment	18.9 (6.0–59.8)	<0.001	24.9 (5.6–111)	<0.001
Unknown	6.1 (1.3–29.4)	0.024	3.7 (0.6–22.7)	0.163

[A] CIS: carcinoma in situ; CIN III: cervical intraepithelial neoplasia III.
[a] Laser conisation, LEEP (loop electrosurgical excision procedure), cold-knife conisation or hysterectomy.
[b] Laser vaporisation, electrocautery, diathermy, and cold coagulation.

follow-up (28%), likely related to the fact that Geneva is an international city, with 43% of the population consisting of foreigners and a strong work-related migration rate. Women lost to follow-up were, in fact, younger, less likely born in Switzerland and had a higher social class. This could have contributed to an underestimation of the risk of invasive cervical cancer among younger women. However, no differences in the type of treatment were noted by follow-up status, therefore we would not expect any difference in the risk by type of treatment.

Optimal surveillance of women treated for a CIN III has not been well defined. After intensive follow up during the first

year after treatment, if all test results are normal most guidelines advise for routine screening with annual cytology for at least 20 years.[40,41] Our results with no excess of risk after 10 years of follow up, support the recommendations of the NHS Cervical Screening Programme for an annual follow up for at least 10 years after the treatment of CIN II or worse before returning to the routine screening interval of 3 or 5 years depending on age.[42]

This study, taken together with the increasing body of evidence in this area, strongly supports the use of excisional therapy for CIN III to reduce the subsequent risk of invasive cervical cancer. Overall, our observations confirm the importance of careful evaluation of these patients for adequate initial treatment selection.

Conflict of interest statement

None declared.

Acknowledgments

We thank Stina Blagojevic for technical and editorial assistance, and the cancer registry team for providing data and support.

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. *GLOBOCAN 2008, cancer incidence and mortality worldwide*. Lyon, France: International Agency for Research on Cancer; 2010.
2. Bray F, Loos AH, McCarron P, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:677–86.
3. International agency for research on cancer (IARC), editor. *Cervix cancer screening*. Lyon: IARC; 2005.
4. Wright Jr TC, Cox JT, Massad LS, et al. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003;**189**:295–304.
5. Janicek MF, Averette HE. Cervical cancer: prevention, diagnosis, and therapeutics. *CA Cancer J Clin* 2001;**51**:92–114.
6. Soutter WP, De Barros Lopes A, Fletcher A, et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet* 1997;**349**:978–80.
7. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer* 2006;**118**:2048–55.
8. Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. *BMJ* 2005;**331**:1183–5.
9. Strander B, Andersson-Ellstrom A, Milsom I, Sparen P. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. *BMJ* 2007;**335**:1077.
10. Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. *J Natl Cancer Inst* 2009;**101**:721–8.
11. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 2008;**9**:425–34.
12. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol* 2007;**8**:985–93.
13. Evans HS, Newnham A, Hodgson SV, Moller H. Second primary cancers after cervical intraepithelial neoplasia III and invasive cervical cancer in Southeast England. *Gynecol Oncol* 2003;**90**:131–6.
14. Martin-Hirsch PL, Paraskevaidis E, Bryant A, Dickinson HO, Keep SL. Surgery for cervical intraepithelial neoplasia. Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001318/frame.html [accessed 30.09.10].
15. Kyrgiou M, Tsoumpou I, Vrekoussis T, et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: the Cochrane colposcopy and cervical cytopathology collaborative group (C5 group) approach. *Cancer Treat Rev* 2006;**32**:516–23.
16. Cecchini S, Ciatto S, Iossa A, Ventura L, Zappa M. Re: cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. *J Natl Cancer Inst* 2009;**101**:1429–30.
17. Bouchardy C. Switzerland, Geneva. In: Curado MP, Edwards B, Shin HR, et al., editors. *Cancer incidence in five continents. vol. IX IARC Scientific Publications no. 160*. Lyon: International Agency for Research on Cancer; 2007. p. 369–70.
18. World Health Organization (WHO), editors. ICD-O international classification of diseases for oncology. 1st ed. Geneva: World Health Organization; 1976.
19. Percy CL, Van Holten V, Muir C, editors. ICD-O international classification of diseases for oncology. 2nd ed. Geneva: World Health Organization; 1990.
20. World Health Organization (WHO), editors. ICD-10 international statistical classification of diseases and health related problems. 10th revision. Geneva: World Health Organization; 1992.
21. Coleman MP, Hermon C, Douglas A. Person-Years (PYRS). A Fortran program for cohort study analysis. Lyon, France, International Agency for Research on Cancer; 1989.
22. Kalliala I, Dyba T, Nieminen P, Hakulinen T, Anttila A. Mortality in a long-term follow-up after treatment of CIN. *Int J Cancer* 2010;**126**:224–31.
23. Taylor TH, Bringman D, Anton-Culver H. Malignancies following in situ cervical cancer in Hispanic Americans and non-Hispanic Whites. *Gynecol Oncol* 2006;**103**:1012–6.
24. Mitchell H, Hocking J. Influences on the risk of recurrent high grade cervical abnormality. *Int J Gynecol Cancer* 2002;**12**:728–34.
25. Pettersson F, Malker B. Invasive carcinoma of the uterine cervix following diagnosis and treatment of in situ carcinoma. Record linkage study within a National Cancer Registry. *Radiother Oncol* 1989;**16**:115–20.
26. Shumsky AG, Stuart GC, Nation J. Carcinoma of the cervix following conservative management of cervical intraepithelial neoplasia. *Gynecol Oncol* 1994;**53**:50–4.
27. McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma in situ of the cervix. *Obstet Gynecol* 1984;**64**:451–8.
28. Chan JK, Monk BJ, Brewer C, et al. HPV infection and number of lifetime sexual partners are strong predictors for 'natural' regression of CIN 2 and 3. *Br J Cancer* 2003;**89**:1062–6.
29. Healthy people 2000: national health promotion and disease prevention objectives. US Public Health Service. DHHS Publication No. (PHS) 91-50213. Washington, DC: US Department of Health and Human Services, Public Health Service; 1991.

30. Orbell S, Crombie I, Robertson A, Johnston G, Kenicer M. Assessing the effectiveness of a screening campaign: who is missed by 80% cervical screening coverage? *J R Soc Med* 1995;**88**:389–94.
31. Breast and cervical cancer screening among underserved women. Baseline survey results from six states. The National Cancer Institute Cancer Screening Consortium for Underserved Women. Arch Fam Med 1995;4:617–24.
32. Spitzer M, Chernys AE, Seltzer VL. The use of large-loop excision of the transformation zone in an inner-city population. *Obstet Gynecol* 1993;**82**:731–5.
33. Santos C, Galdos R, Alvarez M, et al. One-session management of cervical intraepithelial neoplasia: a solution for developing countries. A prospective, randomized trial of LEEP versus laser excisional conization. *Gynecol Oncol* 1996;**61**:11–5.
34. Castle PE, Fetterman B, Akhtar I, et al. Age-appropriate use of human papillomavirus vaccines in the US. *Gynecol Oncol* 2009;**114**:365–9.
35. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet* 2007;**370**:890–907.
36. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case–control study of prospectively recorded data. *BMJ* 2009;**339**:b2968.
37. Alliance for cervical cancer prevention (ACCP) effectiveness, safety and acceptability of cryotherapy: a systematic literature review. Cervical cancer prevention issues in depth no. 1. Available from: http://www.alliance-cxca.org/english/publications.html#cciid [accessed 30.09.10].
38. Wright Jr TC, Massad LS, Dunton CJ, et al. 2006 Consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol* 2007;**197**:340–5.
39. Hunter MI, Holschneider CH. Cervical intraepithelial neoplasia: management. Available from: http://www.uptodate.com/online/content/topic.do?topicKey=gyne_onc/23946&selectedTitle=1~150&source=search_result [accessed 30.09.10].
40. The American College of Obstetricians and Gynecologists. Management of abnormal cervical cytology and histology. *Obstet Gynecol* 2008;112:1419-44.
41. The American College of Obstetricians and Gynecologists. Cervical cytology screening. *Obstet Gynecol* 2009;114:1409-20.
42. Colposcopy and programme management guidelines for the NHS Cervical Screening Programme. Available from: http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.html [accessed 28.04.11].