Cervical Intraepithelial Neoplasia Outcomes After Treatment: Long-term Follow-up From the British Columbia Cohort Study

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Background Information on the long-term risk of cervical intraepithelial neoplasia (CIN) recurrence among women treated for CIN is limited yet critical for evidence-based surveillance recommendations.

Methods We retrospectively identified 37 142 women treated for CIN 1, 2, or 3 from January 1, 1986, through December 31, 2000 (CIN cohort), from the British Columbia Cancer Agency cytology database and linked their records with cancer registry and vital statistics data. Treatment included cryotherapy, loop electrosurgical excision procedure, cone biopsy, and laser vaporization or excision. A comparison cohort contained 71 213 women with normal cytology and no previous CIN diagnosis. Follow-up continued through December 31, 2004. Among women in both cohorts under active surveillance, we compared rates of CIN 2 or 3 (CIN 2/3) and cervical cancer. Cumulative incidence rates of CIN 2/3 and 95% confidence intervals (CIs) were estimated by a life table approach by using annual rates. Cumulative rates of invasive cancer were examined by the person-years method.

Results Overall observed cumulative rates of CIN 2/3 in the first 6 years after treatment were 14.0% (95% CI = 13.84% to 14.15%) for women originally treated for CIN 3, 9.3% (95% CI = 9.09% to 9.42%) for CIN 2, and 5.6% (95% CI = 4.91% to 5.21%) for CIN 1. Annual rates of CIN 2/3 were less than 1% after 6 years. Initial diagnosis, age, and treatment type were associated with a diagnosis of CIN 2/3 after treatment, with 6-year adjusted rates for women aged 40–49 years ranging from 2.6% (95% CI = 1.9% to 3.4%) for treatment of CIN 1 with the loop electrosurgical excision procedure to 34.0% (95% CI = 30.9% to 37.1%) for treatment of CIN 3 with cryotherapy. Overall incidence of invasive cancer (per 100 000 woman-years) was higher in the CIN cohort (37 invasive cancers, 95% CI = 30.6 to 42.5 cancers) than in the comparison cohort (six cancers, 95% CI = 4.3 to 7.7 cancers). Cryotherapy, compared with other treatments, was associated with the highest rate of subsequent disease (adjusted odds ratio for invasive cancer = 2.98, 95% CI = 2.09 to 4.60).

Conclusion Risk of CIN 2/3 after treatment was associated with initial CIN grade, treatment type, and age. Long-term risk of invasive cancer remained higher among women treated for CIN, particularly those treated with cryotherapy.

J Natl Cancer Inst 2009;101:721–728

Organized cervical cytology screening programs in developed countries have accompanied marked decreases in cervical cancer incidence and mortality (1). In addition to the benefits of finding cancers at an early stage, detection and treatment of cervical intraepithelial neoplasia (CIN) appear to account for the decline in cervical cancer incidence (2). Although many women are treated for CIN annually, the Cochrane Colposcopy and Cervical Cytopathology Collaborative Group (3) recently highlighted the lack of international consensus on optimal surveillance strategies after treatment. Lack of data on long-term outcomes, including risks of recurrence among women treated for CIN, is a critical barrier to the formulation of evidence-based recommendations for follow-up surveillance strategies. Findings (4,5) from ALTS (ie, ASCUS-LSIL [atypical squamous cells of undetermined significance–low-grade squamous intraepithelial lesion] Triage Study) have been useful in providing data on outcomes for a period of 8–24 months after treatment, but information on the long-term risks of subsequent CIN or invasive cancer among

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See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djp089

CONTEXT AND CAVEATS

Prior knowledge

Only limited information on the long-term risk of cervical intraepithelial neoplasia (CIN) recurrence among women treated for CIN is available.

Study design

A retrospective cohort of women who were treated for CIN 1, 2, or 3 and a comparison cohort of women with normal cytology and no previous CIN diagnosis.

Contribution

The risk of subsequent CIN 2 or 3 (CIN 2/3) was associated with initial CIN grade, treatment type, and age. Two years after treatment for CIN, there was a rapid decline in the rate of subsequent diagnoses of CIN 2/3. However, 6 years after treatment the risk of invasive cancer continued to be higher among women treated for CIN than among those with no CIN diagnosis, although the risk of CIN 2/3 remained low. Risk was highest for women treated for CIN with cryotherapy.

Implications

Findings of this study support the shift in recommendations for screening of women with CIN from indefinite annual screening to an initial period of 6–18 months of more intensive annual examination, followed by a return to routine screening.

Limitations

Data were observational. Treatment patterns shifted during the study period. Among women treated with cryotherapy or laser ablation, neither satisfactory colposcopy results nor treatment according to guidelines could be documented.

From the Editors

women previously treated for CIN is limited. This information, however, is crucial for the formulation of rational, evidence-based, cost-effective strategies for treatment and follow-up.

Management recommendations for the treatment and follow-up of CIN have evolved over time. Findings (4,5) from ALTS led to recommendations for CIN treatment and follow-up by the American Society for Colposcopy and Cervical Pathology (ASCCP) (6). Current ASCCP recommendations for follow-up after treatment of CIN 2 or 3 (CIN 2/3) are a single human papillomavirus (HPV) test 6–12 months after treatment, two consecutive cytology tests or cytology with colposcopy 6 months apart, followed by routine screening if tests are normal (7). The interval for routine screening is unspecified, but the guidelines note that elevated risk of recurrent CIN or invasive cancer persists for many years after treatment and that follow-up should continue for at least 20 years, reflecting the conclusion of a recent systematic review of observational studies (8). Guidelines from the British Columbia Cancer Agency at present recommend colposcopy 4–6 months after treatment of CIN 2/3. If results are normal, follow-up cytology is recommended 12 months after treatment (9). During the study period (from January 1, 1986, through December 31, 2000), the recommendation for CIN 2/3 was for follow-up colposcopy with cytology at 3, 7, and 13 months after treatment and then annual cytology. For CIN 1, the ASCCP recommends follow-up without initial treatment, with HPV testing every 12 months or cytology every 6–12 months and a return to routine screening if the HPV test or two consecutive cytology tests are negative (7). In the 1980s and 1990s, early treatment of CIN 1 was common practice in the United States, whereas observation of women with CIN 1 with repeat cytology was considered usual care in British Columbia.

British Columbia has had an organized cervical cytology screening program in place since 1955. Since the 1980s, cervical cytology and follow-up results have been included in a single population-based database that links all cytology, colposcopy, and histology reports. Screening recommendations during the period covered by our study were that sexually active women be screened every 2–3 years after two negative annual tests but that high-risk women (ie, those with early onset of sexual activity or multiple partners) be screened annually (10).

We identified a retrospective cohort of women treated for CIN (ie, the CIN cohort) and followed these women for up to 18 years to examine the risks of subsequent CIN 2/3 and invasive cancer. We compared subsequent rates of CIN 2/3 and of invasive cancer in the CIN cohort with those of a low-risk cohort (ie, the comparison cohort) who had not previously been treated for CIN, and we followed these women for the same time period. Linkage with the British Columbia Cancer Registry identified all women with incident cases of cervical cancer in each cohort.

Participants and Methods

This study was reviewed and approved by the University of British Columbia Research Ethics Board and the University of California Davis Committee for the Protection of Research Subjects. It was considered exempt from written informed consent.

Cohort Description

The CIN cohort consisted of 37 142 women retrospectively identified who were treated for CIN 1, 2, or 3 from January 1, 1986, through December 31, 2000 (ie, the CIN cohort), from the British Columbia Cancer Agency cytology database. Their records were linked to cancer registry and vital statistics data. Follow-up continued through December 31, 2004. All women had a cytology test within the year before the CIN diagnosis and had documented treatment of CIN. Treatment included cryotherapy, a loop electrosurgical excision procedure, cone biopsy, and laser vaporization or excision. Women with no recorded treatment were excluded from the analysis. Because the grade of CIN found on the initial biopsy examination could differ from that found on excisional specimen among women who were treated with loop electrosurgical excision procedure or cone biopsy, we defined the index CIN diagnosis as the most severe pathological result occurring within a 6-month period. For example, a woman with an initial biopsy result of CIN 2 and a subsequent cone biopsy within 6 months that had a result of CIN 3 was considered to have CIN 3. Women who had a histological diagnosis of invasive cancer within 6 months of a biopsy examination with a result of CIN were considered to have had missed prevalent invasive cancer and were excluded from the study. Records of women treated with either cone biopsy or loop electrosurgical excision procedure and found to have positive surgical margins, those who were treated by hysterectomy or cervicectomy, and those with incomplete records were also excluded.

In British Columbia from 1986 through 2000, women were screened for cervical cancer by cytology (ie, Papanicolaou testing) through an organized cervical cancer screening program. Guidelines recommended follow-up of all abnormal results. A histological diagnosis of CIN 2/3 was treated with one of the following procedures: cone biopsy, loop electrosurgical excision procedure, laser excision or vaporization, or cryotherapy. For CIN 1, treatment was optional and was most common for women with persistent disease. Because we wished to understand the risks of persistence or recurrence of CIN after treatment, only women with documented treatment in the 6-month window starting from the time of index diagnosis were selected for the cohort. The most definitive treatment within the 6-month window was identified as the index treatment. Definitive treatment was defined by the following hierarchy (from most to least invasive): cone biopsy, loop electrosurgical excision procedure, laser excision or ablation, and cryotherapy.

The comparison cohort was selected from a 10% random sample of records of all women in the British Columbia cytology database from January 1, 1985, through December 31, 2000. We selected the comparison cohort to establish the baseline incidence of disease in a low-risk, well-screened population. To define a low-risk study sample, women aged 21 years or older with three consecutive normal cervical cytology tests and no previous history of CIN were included. We defined the index cytology as the third normal test. Women with a documented history of hysterectomy or cervicectomy before the study period and those with incomplete records were excluded.

The end of the observation period for the two cohorts was December 31, 2004. Records for both CIN and comparison cohorts were linked to the British Columbia Cancer Registry files to identify patients with invasive cancer who were not identified through the cytology database. If stage was not reported, pathology reports were reviewed to define the stage. Microinvasive cancers (International Federation of Gynecology and Obstetrics stage IA1) were considered to be stage I.

Follow-up started from the treatment date of the index diagnosis for women in the CIN cohort and from the index cytology test for women in the comparison cohort. Follow-up continued until a woman had a diagnosis of invasive cancer by histology, was documented to have had a hysterectomy or cervicectomy, died, or until December 31, 2004.

Statistical Analysis

Event occurrence (ie, cervical cytology, colposcopy, or recurrent disease) was measured by the elapsed time since index treatment. Analysis of subsequent disease occurrence was performed separately for a diagnosis of CIN 2/3 and for invasive cervical cancer.

The analysis of subsequent CIN 2/3 after treatment included treated subjects remaining in active surveillance via periodic cytology. Because CIN 2/3 is an asymptomatic state, only women undergoing periodic cytology had the potential for diagnosis. Rates of CIN 2/3 were computed by year since index treatment on the basis of the number of women under active surveillance, with the number of women in active surveillance diagnosed with CIN 2/3 in that year divided by the number in active surveillance screened in that year. Women were considered to be in active surveillance for a 3-year period after their last cytology, that is, women were not considered as being at risk for CIN 2/3 for a specific year if they had not also undergone cytology screening in at least one of the preceding 2 years. Women not in active surveillance were excluded from both the numerator and the denominator for the analysis of the years in question. Rates of CIN 2/3 were examined over time by index diagnosis (CIN 1, 2, or 3), index treatment (cryotherapy, laser excision or ablation, loop electrosurgical excision procedure, or cone biopsy), and age (21–29, 30–39, 40–49, or ≥50 years at index treatment for the CIN cohort and by age at index cytology for the comparison cohort).

Logistic regression analysis was performed to examine the independent effects of these factors on the odds of subsequent CIN 2/3 after treatment. Coefficients from this analysis were then applied to estimate annual incidence rates by time since treatment. Cumulative incidence rates of CIN 2/3 after treatment and their 95% confidence intervals (CIs) were estimated by a life table approach by using the annual rates.

Cumulative rates of invasive cancer subsequent to treatment for CIN were examined separately by the person-years method. Because invasive cervical cancer may be present in unscreened women with symptoms, we assumed that all women in the CIN and comparison cohorts were at risk until the first invasive cancer diagnosis, hysterectomy or cervicectomy, death, or the end of the observation period. Poisson regression analysis was used to examine the independent effects of index diagnosis, age, and treatment type during the first 10 years of cohort follow-up. Because of limited statistical power due to the relatively small number of women who were diagnosed with invasive cancer, treatment type was dichotomized as cryotherapy compared with any other treatment. Coefficients were then applied to predict annual incidence rates. Cumulative rates of invasive cancer were also examined over time for women considered to be under active surveillance, which was defined in the same way as for the estimates of CIN recurrence (ie, having at least one cytology test with any result in the preceding 2 years before a cancer diagnosis). All analyses were conducted with SAS/STAT software version 9.1.3 (SAS Institute, Cary, NC). All statistical tests were two-sided.

Results

We identified 63 722 women with a diagnosis of CIN between January 1, 1986, and December 31, 2000. Because our objective was to examine rates of CIN 2/3 and invasive cancer after treatment, 22 615 women with no record of treatment were excluded. In addition, 2776 women whose treatment was hysterectomy or cervicectomy, 1052 women who had either a cone biopsy or a loop electrosurgical excision procedure without clear margins, and 137 women with incomplete data were excluded. The final CIN cohort, therefore, was composed of 37 142 women. In this group, a total of 3013 women who were diagnosed with subsequent CIN 2/3 were identified. During the follow-up period, 809 women with cytology that was interpreted as moderate dysplasia or worse and no documented biopsy result within the next 2 years were censored from the cohort. Among the 809 censored, 85 had a subsequent diagnosis of CIN 2/3 that occurred more than 2 years after the abnormal test, three were diagnosed with invasive cancer, and 721 had no record of a pathological diagnosis in the follow-up period.

Table 1. CIN cohort distribution by index diagnosis, index treatment (cone biopsy, LEEP, laser excision or ablation, or cryotherapy), and age (n = 37 142)*

Index diagnosis	Age, y	No. of women (% of age group)			
		Cone	LEEP	Laser	Cryotherapy
CIN 1 (n = 6988)	21–29	132 (4.42)	194 (6.50)	917 (30.73)	1741 (58.34)
	30–39	246 (11.61)	221 (10.43)	516 (24.36)	1135 (53.59)
	40–49	238 (18.20)	192 (14.68)	254 (19.42)	624 (47.71)
	≥50	234 (40.48)	83 (14.36)	62 (10.73)	199 (34.43)
CIN 2 (n = 10 823)	21–29	353 (6.17)	577 (10.08)	1903 (33.24)	2892 (50.52)
	30–39	489 (14.56)	375 (11.17)	1007 (29.99)	1487 (44.28)
	40–49	381 (30.75)	161 (12.99)	266 (21.47)	431 (34.79)
	≥50	306 (61.08)	68 (13.57)	40 (7.98)	87 (17.37)
CIN 3 (n = 19 331)	21–29	2588 (27.40)	1075 (11.38)	2492 (26.38)	3291 (34.84)
	30–39	2902 (41.12)	843 (11.95)	1619 (22.94)	1693 (23.99)
	40–49	1288 (64.30)	215 (10.73)	222 (11.08)	278 (13.88)
	≥50	720 (87.27)	62 (7.52)	11 (1.33)	32 (3.88)
Total		9877	4066	9309	13 890

* CIN = cervical intraepithelial neoplasia; LEEP = loop electrosurgical excision procedure; laser = laser excision or ablation.

For the comparison cohort, 72 323 women were initially selected; 999 women were excluded because of a previous hysterectomy or cervicectomy, and 111 were excluded for incomplete data. The final comparison cohort was composed of 71 213 women. Within this group, there were 989 women with a first diagnosis of CIN 2/3 during the follow-up period.

The majority of women in the treatment cohort were treated for CIN 3. Younger women and women with CIN 1 and 2 were treated more often with cryotherapy, whereas women 50 years or older and those with CIN 3 more often underwent cone biopsy (Table 1). Women in the CIN cohort tended to be younger (82.6% were <40 years) than women in the comparison cohort (64.4% were <40 years) (Table 2). Rates of subsequent CIN 2/3 up to 15 years after treatment are shown in Figure 1 for the CIN and comparison cohorts by index diagnosis for women under active surveillance. Rates fell rapidly over the first 4 years, and within 6 years, annual rates of CIN 2/3 for all index diagnoses in the CIN cohort had fallen to less than 1% and were comparable to incidence of CIN in the comparison cohort. Rates were highest in the first 2 years after treatment and increased monotonically with CIN grade. Overall observed cumulative rates of CIN 2/3 for the first 6 years after treatment were 14.0% (95% CI = 13.84% to 14.15%) for women originally treated for CIN 3, 9.3% (95% CI = 9.09% to 9.42%) for CIN 2, and 5.6% (95% CI = 4.91% to 5.21%) for CIN 1.

Logistic regression analysis was used to estimate the overall adjusted rates of subsequent CIN 2/3 in the CIN cohort under active surveillance during the first 6 years of follow-up. Six years was chosen because of the low rates of CIN 2/3 after the first 6 years of follow-up (as shown in Figure 1). The analysis included age, index diagnosis, index treatment, and year since index treatment as independent variables. Age was categorized in decades. Interactions between age, index diagnosis, and index treatment were explored by use of forward selection, but year was restricted to be a main effect. The resulting model included statistically significant interactions for age and index diagnosis and for index diagnosis and treatment,

Table 2. Age at initial treatment or at index cytology test for CIN and comparison cohorts*

Age, y	No. in CIN cohort (%)	No. in comparison cohort (%)
21–30	18 155 (48.9)	24 322 (34.2)
30–39	12 533 (33.7)	20 822 (29.2)
40–49	4550 (12.3)	12 499 (17.6)
≥50	1904 (5.1)	13 570 (19.1)
Total	37 142 (100.0)	71 213 (100.0)

* The CIN cohort included women 21 years or older with a cytology test in the previous year, a first histological diagnosis of CIN 1, 2, or 3 between 1986–2000, and documented treatment. The comparison cohort was selected from a 10% random sample of women in the British Columbia Cancer Agency cytology database from 1985–2000, aged 21 years or older, who had three consecutive negative cytology tests and no history of CIN. The age range presented is for initial treatment for the CIN cohort, and for the index cytology test for the comparison cohort. CIN = cervical intraepithelial neoplasia.

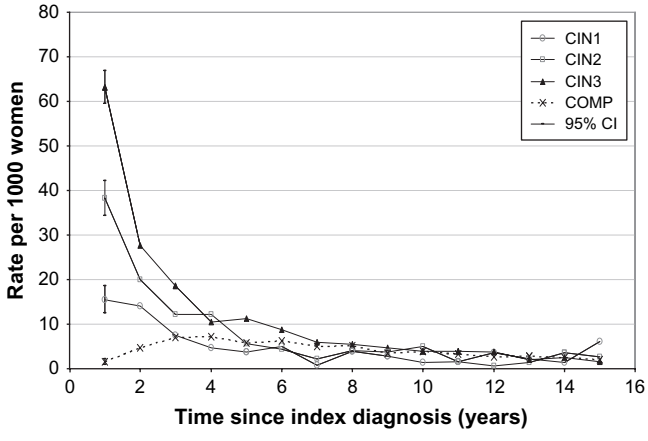

Figure 1. Incidence rates of cervical intraepithelial neoplasia 2 or 3 (CIN 2/3) per 1000 women by index diagnosis among women under active surveillance in the CIN and comparison (COMP) cohorts. The index event was treatment for the CIN cohort and normal cytology result at entry for the comparison cohort. **Error bars** = 95% confidence intervals.

Table 3. Estimated rates of CIN 2/3 per 1000 women in the initial 6-year period after treatment for CIN by index diagnosis, age group, and index treatment (cone biopsy, LEEP, laser excision or ablation, or cryotherapy)*

Index diagnosis	Age, y	Estimated rate of CIN 2/3 after treatment, No. per 1000 women (95% CI)			
		Cone	LEEP	Laser	Cryotherapy
CIN 1	21–29	28.1 (20.2 to 36.1)	23.3 (16.4 to 30.1)	45.6 (39.0 to 52.1)	54.7 (48.6 to 60.9)
	30–39	33.1 (23.9 to 42.3)	27.4 (19.4 to 35.3)	53.5 (45.1 to 61.8)	64.1 (56.2 to 72.0)
	40–49	31.9 (22.8 to 41.0)	26.4 (18.5 to 34.3)	51.6 (42.0 to 61.3)	61.9 (52.3 to 71.6)
	≥50	22.4 (14.7 to 30.0)	18.5 (11.5 to 25.5)	36.3 (25.1 to 47.5)	43.7 (31.1 to 56.2)
CIN 2	21–29	34.8 (28.2 to 41.5)	41.9 (34.8 to 49.0)	73.0 (66.6 to 79.4)	133.3 (124.5 to 142.2)
	30–39	35.0 (28.3 to 41.7)	42.2 (34.9 to 49.5)	73.0 (66.6 to 79.4)	134.1 (123.3 to 144.9)
	40–49	35.7 (28.4 to 43.0)	43.0 (34.6 to 51.4)	74.8 (64.4 to 85.3)	136.5 (119.2 to 153.8)
	≥50	29.5 (21.4 to 37.5)	35.5 (25.3 to 45.8)	62.1 (45.9 to 78.3)	114.1 (85.3 to 142.9)
CIN 3	21–29	56.3 (52.0 to 60.6)	86.1 (78.3 to 94.0)	117.2 (109.6 to 124.8)	241.6 (228.7 to 254.5)
	30–39	62.9 (58.1 to 67.6)	95.8 (87.0 to 104.7)	130.1 (121.3 to 138.9)	265.1 (249.3 to 281.0)
	40–49	85.3 (77.5 to 93.2)	129.0 (114.7 to 143.4)	173.6 (156.9 to 190.2)	340.0 (309.3 to 370.8)
	≥50	90.4 (77.3 to 103.4)	136.4 (113.7 to 159.0)	183.0 (154.1 to 212.0)	355.4 (300.1 to 410.7)

* Rates are based on logistic regression analysis. CIN = cervical intraepithelial neoplasia; LEEP = loop electrosurgical excision procedure; laser = laser excision or ablation; CI = confidence interval.

as well as main effects for age, diagnosis, treatment, and year (with details in Supplementary Table 1, available online).

In general, women 40 years or older and those with more severe index disease had higher rates of CIN 2/3 after treatment. The CIN 2/3 rates after treatment were lowest for cone biopsy and highest for cryotherapy. Initial diagnosis, age, and treatment type were all associated with a diagnosis of CIN 2/3 after treatment, with the 6-year adjusted rates for women aged 40–49 years ranging from 26.4 diagnoses per 1000 women (95% CI = 18.5 to 34.3 diagnoses per 1000 women) for treatment of CIN 1 with loop electrosurgical excision procedure to 340.0 diagnoses per 1000 women (95% CI = 309.0 to 370.8 diagnoses per 1000 women) for treatment of CIN 3 with cryotherapy (Table 3). For the comparison cohort, the 6-year cumulative rate of subsequent CIN 2/3 was 9.8 diagnoses per 1000 women (95% CI = 8.2 to 11.4 diagnoses per 1000 women) among women aged 40–49 years and was 54.8 diagnoses per 1000 women (95% CI = 50.2 to 59.3 diagnoses per 1000 women) among women aged 20–29 years (Table 4).

One hundred forty-five women were diagnosed with invasive cancer in the entire CIN cohort during the 18-year follow-up period, a rate of 37 cancers per 100 000 woman-years (95% CI = 30.6 to 42.5 cancers per 100 000 woman-years), compared with 49 women in the comparison cohort, a rate of six cancers per 100 000 woman-years (95% CI = 4.3 to 7.7 cancers per 100 000 woman-years). Among women in the CIN cohort who were under active surveillance and were considered at risk for up to 3 years after their last cytology test (with the same denominator that was used for the analysis of CIN 2/3), 49 cases of invasive cancer occurred during the follow-up period. The stage distribution for invasive cancers was similar for the CIN cohort and the comparison group, with most invasive cancers in early stages at diagnosis (Table 5). The cumulative rates of cancer in the CIN cohort and the CIN cohort under active surveillance increased steadily relative to the comparison group for the first 8 years of follow-up. After 8 years, the rates for the cohort under surveillance diverged from the overall CIN cohort, with higher rates for the overall CIN cohort were not significant different from rates for the CIN though under surveillance (Figure 2). From a Poisson regression analysis, independent risk factors for invasive cancer were identified as an initial diagnosis of CIN 3, treatment with cryotherapy (compared with all other treatments), and being 40 years or older (Table 6). Cryotherapy, compared with other treatments, was associated with the highest rate of subsequent disease (adjusted odds ratio for invasive cancer = 2.98, 95% CI = 2.09 to 4.60).

Discussion

This large, population-based cohort study with more than 300 000 woman-years of observation in the CIN cohort provided important information that could contribute to evidence-based guidelines for follow-up of women treated for CIN. For women under surveillance after treatment, risks for subsequent CIN 2/3 declined to that of incident CIN in low-risk women by 6 years after treatment. Rates of subsequent CIN 2/3 increased with age and initial CIN grade and varied by treatment, being highest for women older than 40 years who were treated for either CIN 2 or CIN 3 with cryotherapy. Previously, large population-based cohort studies from Sweden in 1989 (11) and 2007 (12) reported on invasive cancer rates after treatment for CIN but did not have information on the recurrence of CIN or whether women were under surveillance after treatment. In our study, we found that invasive cancer risk was markedly higher in women after treatment of CIN, even among those undergoing active surveillance, compared with a cohort of women without previous CIN.

Overall rates of CIN 2/3 declined rapidly for the first 2 years after treatment; however, during the first 6 years of follow-up, these rates ranged from 5% for women initially treated for CIN 1 to 14% for women treated for CIN 3. In ALTS, women with initial low-grade squamous epithelial lesions who were referred for early colposcopy had rates of subsequent CIN 2/3 of 8%–13% during a 24-month follow-up (13). Others (7,14) have estimated rates of subsequent CIN after treatment that ranged from 1% to 21%.

In this observational study, rates of subsequent CIN 2/3 could be measured only for women who chose to obtain follow-up cytology. We focused on estimating the risk of subsequent CIN in the women under active surveillance. This group of women included a

Table 4. Estimated rates of CIN 2/3 per 1000 women in the initial 6-year period for the comparison cohort by age group*

Age, y	Estimated rate of CIN 2/3 in comparison group, No. per 1000 women (95% CI)
21–29	54.8 (50.2 to 59.3)
30–39	26.3 (23.6 to 28.9)
40–49	9.8 (8.2 to 11.4)
≥50	10.9 (9.1 to 12.7)

* CIN 2/3 = cervical intraepithelial neoplasia 2 or 3; CI = confidence interval.

mean of 32 314 (87%) of the 37 142 women in the CIN cohort and 48 424 (68%) of the 71 213 women in the comparison cohort over the first 10 years. Our rates of CIN 2/3 cannot be applied to women who were lost to follow-up after treatment. Because of the linkage to the British Columbia Cancer Registry, however, we were able to identify all women who were diagnosed with invasive cervical cancer in British Columbia and thus to estimate the risk of subsequent invasive cancer for the entire cohort, with the exception of those who migrated out of the province. The lower rates of invasive cancers after the first 8 years of follow-up that appeared in women under active surveillance compared with women the overall CIN cohort indicate the importance of long-term surveillance of women after treatment for CIN.

It is biologically plausible that long-term cryotherapy efficacy may be lower than that of excisional procedures because removing rather than destroying tissue may provide greater protection. Higher cancer rates after cryotherapy may also be related to altered ability to adequately sample the transformation zone after treatment, perhaps because structural changes of the cervix after treatment for CIN differ between excisional and ablative procedures. Alternatively, our exclusion of women with incomplete excisional procedures (ie, those without clear surgical margins) may have underestimated the subsequent recurrence risk in women undergoing loop electrosurgical excision procedure and cone biopsy. The effect of treatment type on subsequent CIN has been inconsistent across studies. A meta-analysis of randomized controlled trials of CIN treatment outcomes by Nuovo et al. (15) found that the median follow-up time for these trials was only 12 months, with CIN rates of 5%–15%, and no statistically significant outcome differences between treatment modalities. No invasive cancers were reported during the follow-up of 3811 women in these studies. Two more recent randomized controlled trials concluded that women treated by loop electrosurgical excision procedure had a lower rate of CIN after treatment than those treated with cryotherapy (16) or laser vaporization (17). A report (18) of follow-up for 2116 women treated by cryotherapy, laser excision or ablation, or loop electrosurgical excision procedure for all grades of CIN in the United Kingdom found that the rate of invasive cervical cancer after treatment was 5.8 cancers per 1000 women for an 8-year period, whereas a long-term follow-up study (19) of 4417 women treated for CIN 3 with cone biopsy and whose excised specimen had clear margins found no woman with invasive cervical cancer during a median follow-up of 8.9 years. A recent international systematic review of invasive cancer risk after treatment for CIN found no statistically significant differences in the risk of invasive disease across treatment types (3).

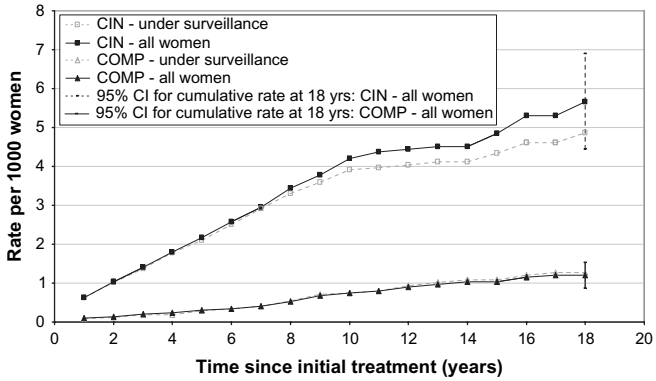

Figure 2. Cumulative rates of invasive cervical cancer over the follow-up period for all women in the cervical intraepithelial neoplasia (CIN) cohort, for women in the CIN cohort under active surveillance, for the comparison cohort (COMP), and for the comparison cohort under surveillance (COMP—under surveillance). We used the same definition as in the CIN cohort (ie, must have had a cervical cytology within the previous 2 years to be included for that year). **Error bars** = 95% confidence intervals.

The invasive cervical cancer rate in the CIN treatment cohort of 37 cancers per 100 000 woman-years fell between the rate in a Finnish cohort of 23 cancers per 100 000 woman-years (20) and the rate in an international systematic review of cohort studies of 56 cancers per 100 000 woman-years (8). The ongoing higher rate of invasive cancer among women in the CIN cohort, despite the decline in the rates of CIN 2/3, was also observed in the systematic review (8) and supports an underlying increased risk in this group. However, the optimal length and intensity of surveillance for this group remains unclear. Among the women who developed invasive cancers in our study, the relatively high proportion of stage I cancers (77%) attests to the benefits of ongoing surveillance,

Table 5. Stage distribution of invasive cervical cancer for all women in the CIN and comparison cohorts, by stage of cancer*

Stage	No. in CIN cohort (%)	No. in comparison cohort (%)
I	112 (77.2)	34 (68.6)
II	15 (10.3)	9 (19.6)
III	5 (3.5)	0 (0)
IV	3 (2.1)	1 (2.0)
Unknown	10 (6.9)	5 (9.8)
Total	145 (100)	49 (100)

* All women in the cohorts who developed cancer were included in this analysis. CIN = cervical intraepithelial neoplasia.

Table 6. Association between risk factors and risk of invasive cancer after treatment for CIN over the first 10 years of follow-up (n = 37 142)*

Factor (comparison)	Adjusted OR (95% CI)
Initial treatment (cryotherapy vs other)	2.98 (2.09 to 4.26)
Initial diagnosis (CIN 3 vs CIN 1 and 2)	4.10 (2.70 to 6.22)
Age (≥40 vs <40 y)	1.75 (1.12 to 2.74)

* Data are based on a Poisson regression analysis of the CIN cohort. Odds ratios were adjusted for initial treatment, initial diagnosis, and age, as appropriate. CIN = cervical intraepithelial neoplasia; OR = odds ratio; CI = confidence interval.

as compared with only 53% of cervical cancers that were diagnosed at stage I in the US Surveillance, Epidemiology and End Results cancer registry for the period from 1988 through 2003 (2).

Our study had several limitations. Interpretation of our results is limited by the nature of observational cohort data. Treatment patterns shifted in British Columbia over the study period, so that loop electrosurgical excision procedure became more common and laser excision and ablation became less common. Most treatment was provided in the provincial colposcopy clinics and hence was more likely to be relatively uniform and in accordance with guidelines for the study period. However, we were not able to document the presence of satisfactory colposcopy results among the women who were treated with cryotherapy or laser ablation. Although guidelines in British Columbia endorsed cryotherapy or laser ablation for women with satisfactory colposcopy only, we did not know how many women were treated in accordance with guidelines.

We have limited information on regional differences in surveillance practices or changes over time in British Columbia because most surveillance was provided by general practitioners. To evaluate further whether variation in treatment protocols or surveillance practices may have contributed to our findings, we examined the outcomes of women who were initially treated at a single urban tertiary hospital that treated and followed the highest volume of women with CIN in British Columbia and that also used consistent protocols. These outcomes were similar to those of overall dataset (data not shown). Testing for HPV was not performed in British Columbia during the study period, so we were limited to evaluating outcomes on the basis of surveillance with cervical cytology. Our analysis included only variables available in the database and could not examine the associations of socioeconomic status or race or ethnicity with outcomes.

The higher risk of CIN 2/3 and invasive cancer after treatment for women who were treated with cryotherapy, particularly for those treated for CIN 3, was substantial and differs from outcomes reported in some randomized trials (15). If confirmed, this finding creates a dilemma for providers and their patients when making decisions about treatment of CIN. In contrast to cryotherapy, excisional methods of treatment have been associated with an increased risk of both early complications of hemorrhage in randomized trials (15) and with an increased risk of preterm delivery and low birth weight in subsequent pregnancies in retrospective studies (21–24). Further, cryotherapy is less costly to provide and the technique is easier to learn, making it more readily available in low-resource settings in which most women needing treatment for CIN reside (23). Future randomized trials will need longer term follow-up to define the impact of treatment choice on subsequent CIN and invasive cancer.

These findings support the recent shift in the ASCCP guidelines for women who have been treated for CIN from indefinite annual screening to a return to routine screening after an initial period of more intensive follow-up that may take the form of cytology, HPV testing, or cytology with colposcopy during the first 6–18 months. Given the rapid decline in subsequent diagnoses of CIN 2/3 after the first 2 years but the ongoing elevated risk of invasive cervical cancer, it appears that consistency of follow-up for 10–20 years may be important for detecting disease after treatment. More intensive follow-up strategies are likely to be important for those women older than 40 years who were treated for CIN 3, particularly if they were treated with cryotherapy. Cost-effectiveness studies are needed to define optimal surveillance strategies that may differ by CIN grade, treatment type, and age.

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Funding

National Cancer Institute (grant 1R01CA109142).

Notes

The authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript The authors thank Catarina Kiefe, MD, PhD, for critical review of the manuscript and Mairin Rooney and Galen Sanderlin for assistance with the figures and tables.

Manuscript received July 17, 2008; revised March 3, 2009; accepted March 12, 2009.