

Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study

Björn Strander,¹ Agneta Andersson-Ellström,¹ Ian Milsom,¹ Pär Sparén²

EDITORIAL by Ronco and colleagues

¹Department of Obstetrics and Gynecology, Sahlgren's Academy, University of Gothenburg, SU/Östra sjukhuset, SE-416 85, Sweden

²Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Correspondence to: B Strander, Oncology Center, Sahlgren's University Hospital, SE-413 45 Gothenburg, Sweden
bjorn.strander@oc.gu.se

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ABSTRACT

Objective To study the long term risk of invasive cancer of the cervix or vagina after treatment for cervical intraepithelial neoplasia grade 3.

Design Prospective cohort study.

Setting Swedish cancer registry.

Participants All women in Sweden with severe dysplasia or cervical carcinoma in situ (equivalent to cervical intraepithelial neoplasia grade 3) treated during 1958-2002 (n=132 493) contributing 2 315 724 woman years.

Main outcome measures Standardised incidence ratios with risk of cancer in the Swedish general female population as reference, and relative risks in multivariable log-linear regression model, with internal references.

Results Women with previous cervical intraepithelial neoplasia grade 3 had an increased risk of invasive cervical cancer compared with the general female population (standardised incidence ratio 2.34, 95% confidence interval 2.18 to 2.50). The increased risk showed a decreasing trend with time since diagnosis for women treated later than 1970 but the risk was still increased after 25 years. An effect of age was found, with an accentuated increase in risk for women aged more than 50. The excess risk for cervical cancer associated with previous cervical intraepithelial neoplasia grade 3 has steadily increased since 1958. For vaginal cancer the standardised incidence ratio was 6.82 (5.61 to 8.21) but this decreased to 2.65 after 25 years. Adjustments in the multivariable log-linear regression model did not substantially alter these results.

Conclusions Women previously treated for cervical intraepithelial neoplasia grade 3 are at an increased risk of developing invasive cervical cancer and vaginal cancer. This risk has increased since the 1960s and is accentuated in women aged more than 50. The risk is still increased 25 years after treatment.

INTRODUCTION

Although most women treated for high grade dysplasias are protected from invasive cervical cancer, reports have shown an increased risk for dysplasia and invasive cervical cancer among treated women.¹⁻⁵

We investigated whether Swedish women treated for cervical intraepithelial neoplasia grade 3 have an excess risk of cervical and vaginal cancers.

METHODS

In November 2005 we retrieved all histopathology reports of cervical intraepithelial neoplasia grade 3 from the Swedish cancer register for 1958-2002. The register includes dates of death and emigration through linkages to the national Swedish causes of death register and national Swedish population register.

For women with a diagnosis of cervical intraepithelial neoplasia grade 3 we determined person time at risk and the number of observed and expected cervical cancers according to the yearly incidence, by five year age groups, from the general population. We calculated standardised incidence ratios with 95% confidence intervals. To account for prevalent cancers in the cohort we excluded the first year of follow-up. We calculated the absolute risk changes, presented as difference in incidence. For multivariable regression analyses we assumed that the observed number of cases followed a Poisson distribution, and we weighted the number of observed cases by the log of the number of expected cases.

RESULTS

Overall, 132 493 women had a diagnosis of cervical intraepithelial neoplasia grade 3 recorded in the Swedish cancer register during 1958-2000, contributing 2 315 724 woman years. Of these women, 881 had invasive cervical cancer more than one year after treatment for cervical intraepithelial neoplasia grade 3: overall standardised incidence ratio 2.30 (95% confidence interval 2.15 to 2.46) compared with the general population (table). The risk was significantly increased in all birth cohorts, except for the most recent, and there was an accelerated risk after age 50. For each decade since the 1960s the time trend was of increasing risk, with a standardised incidence ratio of developing invasive cancer after treatment for cervical intraepithelial neoplasia grade 3 almost twice as high if treatment was undertaken during 1991-2000 compared with 1958-70.

Controlling for period of diagnosis and time since diagnosis in the multivariable regression model, a

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trend ($P<0.001$) was found of increasing risk of cervical cancer with increasing age at diagnosis, with a noticeable acceleration after age 50 (see [bmj.com](#)). The time trend of increased risk for each decade since the 1960s also remained in the multivariable regression model ($P<0.001$). A slight decrease in relative risk was found by time since diagnosis ($P=0.04$), although none of the risk estimates significantly deviated from unity. Further analysis showed a significant interaction between period of diagnosis and time since diagnosis ($P<0.001$). Stratifying for time period showed an increased risk of acquiring cervical cancer with time after treatment during 1958-70, whereas the risk decreased with time for period of diagnosis after 1970 (see [bmj.com](#)): standardised incidence ratio 2.16 (1.51 to 2.59) up to 15 years after treatment and 1.50 (1.07 to 2.10) up to 25 years.

The risk of developing vaginal cancer after treatment for cervical intraepithelial neoplasia grade 3 was small

in absolute terms (111 cases): incidence 5/100 000 woman years. The observed number was, however, almost seven times higher than expected. The standardised incidence ratios showed an increased risk with age and with period of diagnosis but a decreased risk with time since diagnosis (table). In the multivariable regression analysis, however, a decreasing risk was found with period of diagnosis (see [bmj.com](#)). The decreased risk with time since diagnosis persisted. After 25 years it was one fifth of the risk in the reference follow-up period (2-4 years).

To account for possible misclassification of cervical cancers as vaginal cancers the data for cervical and vaginal cancers were pooled. In total, 990 cases were found: incidence rate 43/100 000 woman years. The risk of cervical or vaginal cancer after treatment for cervical intraepithelial neoplasia grade 3 was increased 2.5 times compared with the general population: standardised incidence ratio 2.48 (2.33 to 2.64).

Risk of invasive cervical cancer and vaginal cancer among women with previous cervical intraepithelial neoplasia grade 3 (CIN 3)

Variables	Cervical cancer					Vaginal cancer				
	No of cases	Expected No	Person years	SIR (95% CI)	Change in incidence/100 000	No of cases	Expected No	Person years	SIR (95% CI)	Change in incidence/100 000
All cases	881	382	2 315 724	2.30 (2.15 to 2.46)	21.5	111	16.28	2 324 157	6.82 (5.61 to 8.21)	4.1
Birth cohort:										
<1915	94	13	52 583	6.99 (5.65 to 8.55)	153.2	25	1.39	53 069	17.97 (11.63 to 26.53)	44.5
1915-29	225	84	376 018	2.66 (2.33 to 3.03)	37.3	44	6.45	377 678	6.83 (4.96 to 9.16)	9.9
1930-9	166	75	476 699	2.21 (1.89 to 2.57)	19.1	18	3.60	478 550	5.00 (2.96 to 7.91)	3.0
1940-9	191	113	761 352	1.69 (1.46 to 1.94)	10.2	16	3.45	763 960	4.64 (2.65 to 7.53)	1.6
1950-9	157	73	462 532	2.13 (1.81 to 2.49)	18.0	7	1.16	463 950	6.02 (2.42 to 12.41)	1.3
1960-9	47	20	163 772	2.28 (1.67 to 3.03)	13.8	1	0.23	186 950	4.34 (0.11 to 24.18)	0.4
≥1970	1	1	22 768	0.58 (0.01 to 3.22)						
Age at diagnosis of CIN 3 (years):										
<20	3	3	29 464	0.93 (0.19 to 2.73)	-0.8	0	0.04	29 507	0 (0 to 70.78)	0
20-29	158	114	779 005	1.38 (1.17 to 1.61)	5.6	12	2.12	780 702	5.67 (2.93 to 9.90)	1.3
30-39	305	147	898 004	2.07 (1.84 to 2.31)	17.6	14	5.01	901 839	2.80 (1.53 to 4.69)	1.0
40-49	203	85	456 020	2.37 (2.05 to 2.72)	25.7	40	5.70	457 502	7.02 (5.01 to 9.55)	7.5
50-59	123	23	114 626	5.19 (4.32 to 6.20)	86.6	21	2.20	115 603	9.54 (5.91 to 14.59)	16.3
60-69	65	6	29 995	10.24 (7.90 to 13.05)	195.5	13	0.87	30 364	15.02 (8.00 to 25.68)	40.0
70-79	22	1	7743	14.62 (9.16 to 22.13)	264.7	9	0.31	7776	29.39 (13.44 to 55.78)	111.8
≥80	2	0	868	16.1 (1.95 to 58.16)	216.2	2	0.04	864	50.36 (6.10 to 181.93)	226.9
Period of diagnosis:										
1958-70	241	127	647 924	1.89 (1.66 to 2.14)	17.5	47	6.93	650 115	6.79 (4.99 to 9.02)	6.2
1971-80	313	145	925 035	2.15 (1.92 to 2.40)	18.1	29	6.05	928 394	4.79 (3.21 to 6.88)	2.5
1981-90	244	85	569 220	2.86 (2.52 to 3.25)	27.9	27	2.59	571 523	10.43 (6.88 to 15.18)	4.3
1991-2002	83	23	173 545	3.52 (2.80 to 4.36)	34.2	8	0.71	174 125	11.24 (4.85 to 22.15)	4.2
Time since diagnosis (years):										
1-<2	71	21	126 772	3.28 (2.56 to 4.13)	17.7	10	0.35	126 934	28.43 (13.64 to 52.29)	7.6
2-4	169	62	357 979	2.70 (2.31 to 3.14)	38.9	15	1.13	358 671	13.31 (7.45 to 21.96)	3.9
5-9	242	92	528 115	2.61 (2.29 to 2.96)	29.7	26	2.14	529 757	12.15 (7.94 to 17.80)	4.5
10-14	168	75	446 732	2.23 (1.90 to 2.59)	28.3	20	2.50	448 548	8.01 (4.89 to 12.37)	3.9
15-19	103	55	353 676	1.84 (1.50 to 2.24)	20.7	14	2.79	355 321	5.01 (2.74 to 8.41)	3.2
20-24	66	38	253 887	1.73 (1.34 to 2.20)	13.3	14	2.85	255 076	4.91 (2.69 to 8.24)	4.4
≥25	62	36	248 563	1.72 (1.32 to 2.20)	11.0	12	4.52	249 851	2.65 (1.37 to 4.64)	3.0

SIR=standardised incidence ratio. SIR and change in absolute risk expressed as change in incidence per 100 000 woman years for whole population and stratified for birth cohort, age at diagnosis of CIN 3, period of diagnosis, and time (years) since diagnosis and the detection of invasive cancer.

DISCUSSION

Women have a high excess risk of developing invasive cervical cancer after treatment for cervical intraepithelial neoplasia grade 3. The risk has increased since the 1960s and is almost twice as high for women treated in the 1990s compared with those treated during 1958-70.

One possible explanation is differences in treatment modalities. The Swedish cancer register does not, however, include data on treatment. Over the period studied (1958-2000), the consensus in Sweden was to treat women with cervical intraepithelial neoplasia grade 3 and to offer intensified follow-up with cytology. We are confident that most of the cohort with cervical intraepithelial neoplasia grade 3 had been treated. In the 1960s severe dysplasia was treated by hysterectomy. During the 1980s conservative modes of treatment such as cryotherapy became popular. Large loop excision of the transformational zone was introduced in Sweden in 1990 and is now the dominant treatment for dysplasia in Sweden.⁶ Women of fertile age have been treated more conservatively since the 1960s, and they have a lower risk of cancer than older women. Despite this the changed patterns in therapy can help explain the trend over time, as the trend remained after adjustment for age in the multivariable regression model.

A possible shift in diagnostic criteria over time must also be considered. The incidence of cervical intraepithelial neoplasia grade 3 has been stable since 1968, however, with a 10% drop after the early 1980s, corresponding to treatment extended to women with less severe dysplasia. We can also speculate that the increased prevalence of human papillomavirus infection over the years has had a greater impact on women treated for cervical intraepithelial neoplasia grade 3 compared with the general population. Cervical intraepithelial neoplasia grade 3 is to a large extent caused by persistent infection with the virus. Thus this cohort has a proved susceptibility to high risk infection, which remains as a risk factor. Other risk factors for human papillomavirus infection as well as cervical cancer, such as number of partners, may also remain in women treated for cervical intraepithelial neoplasia grade 3.

The increased risk of cervical cancer in the cohort did not decline substantially in the 25-30 years after

treatment, but a stratified analysis showed opposite trends with period of diagnosis (see bmj.com). In women treated after 1970 the trend is of decreasing standardised incidence ratios, but their risk of cervical cancer is still increased compared with that of the general population. After 10 years the standardised incidence ratios for women with cervical intraepithelial neoplasia grade 3 treated before or after 1970 are similar.

The clinical implication of our findings is that women treated for cervical intraepithelial neoplasia need special programmes for long term follow-up, with cytology and possibly testing for human papillomavirus.

We have no clinical data on the women after treatment, but according to Swedish guidelines such women are offered frequent appointments for screening.⁷ It is not unreasonable to assume that these women have been more closely followed up than the general population. Still, the noticeable increase in incidence of cervical cancer for women aged more than 50 when treated could partly be due to lack of follow-up. Testing for human papillomavirus DNA has shown to be of some benefit in identifying women in whom treatment has failed in the short term⁸ but long term data are scarce.

The relative risk in women treated for cervical intraepithelial neoplasia grade 3 to develop vaginal cancer compared with the general population seems to be higher than for invasive cervical cancer. Our study confirms observations in smaller studies⁹ that cervical intraepithelial neoplasia grade 3 is related to vaginal cancer. These two cancers can be connected for at least two reasons. Firstly, about 60% of cases of vaginal cancer are related to high risk human papillomavirus infection^{10,11} and share this risk factor with cervical cancer, predominantly in younger women.¹² Secondly, vaginal cancer can also result from incompletely treated cervical intraepithelial neoplasia grade 3, regardless of whether hysterectomy has been carried out.

It was not possible to link cervical and vaginal cancers to hysterectomies on an individual basis. Swedish statistics for hysterectomies since 1998 indicate a slowly decreasing life time accumulated incidence,¹³ in accord with earlier studies showing that Sweden has a low incidence of hysterectomies compared with elsewhere.¹⁴

The risk of vaginal cancer after treatment of cervical intraepithelial neoplasia grade 3 seems to decrease with time. After adjusting for age at diagnosis and period of diagnosis in the multivariate analysis this risk after more than 25 years seems to be only a 10th of that 1 or 2 years after treatment, although this is still more than double that of the general population. The reason for this pattern is unclear.

The strength of this study is the size of the study cohort, comprising almost 2.5 million woman years after diagnosis of cervical intraepithelial neoplasia grade 3. Furthermore, the completeness of records in the Swedish cancer registry is high, and linkage to data on migration and deaths is possible. The weaknesses of this study are that we could not link the data to treatment type or to hysterectomies and we lacked information on how the women have been followed up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The risk of invasive cervical cancer is more than double that of the general population at least 10 years after treatment for cervical intraepithelial neoplasia grade 3

Long term incidence of vaginal cancer after treatment for cervical intraepithelial neoplasia grade 3 is poorly documented

WHAT THIS STUDY ADDS

Women are at an increased risk of invasive cervical cancer more than 25 years after treatment for cervical intraepithelial neoplasia grade 3

The risk of invasive disease is noticeably increased in women aged more than 50 when treated

The risk of vaginal cancer is increased in women treated for cervical intraepithelial neoplasia grade 3

CONCLUSION

Women treated for cervical intraepithelial neoplasia grade 3 are at increased risk of developing invasive cancer in the remaining cervix or vagina. This risk has increased with changes in treatment modalities since the 1990s compared with treatment in the 1960s, is higher for women who are older (≥ 50 years) at treatment, and remains increased 20 or more years after treatment compared with the general population. The question on how follow-up should be carried out is not resolved but this study implies that it has been insufficient. We should at least offer treated women cytological smears at regular intervals, preferably for at least 25 years, independent of age.

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Child wellbeing and income inequality in rich societies: ecological cross sectional study

Kate E Pickett,¹ Richard G Wilkinson²

EDITORIAL by Black and Jeffery

¹Department of Health Sciences, University of York, Heslington, York YO10 5DD

²Division of Epidemiology and Public Health, University of Nottingham Medical School, Queens Medical Centre, Nottingham NG7 2UH

Correspondence to: R G Wilkinson
Richard.Wilkinson@nottingham.ac.uk

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ABSTRACT

Objectives To examine associations between child wellbeing and material living standards (average income), the scale of differentiation in social status (income inequality), and social exclusion (children in relative poverty) in rich developed societies.

Design Ecological, cross sectional studies.

Setting Cross national comparisons of 23 rich countries; cross state comparisons within the United States.

Population Children and young people.

Main outcome measures The Unicef index of child wellbeing and its components for rich countries; eight comparable measures for the US states and District of Columbia (teenage births, juvenile homicides, infant mortality, low birth weight, educational performance, dropping out of high school, overweight, mental health problems).

Results The overall index of child wellbeing was negatively correlated with income inequality ($r=-0.64$, $P=0.001$) and the percentage of children in relative poverty ($r=-0.67$, $P=0.001$) but not with average income

($r=0.15$, $P=0.50$). Many more indicators of child wellbeing were associated with income inequality or children in relative poverty, or both, than with average incomes. Among the US states and District of Columbia all indicators were significantly worse in more unequal states. Only teenage birth rates and the proportion of children dropping out of high school were lower in richer states.

Conclusions Improvements in child wellbeing in rich societies may depend more on reductions in inequality than on further economic growth.

INTRODUCTION

A recent Unicef report, which assembled 40 indicators of child wellbeing in rich countries, concluded that children in Britain and the United States fared less well than in any of the other 21 countries included in its analysis.¹ Measures of child wellbeing are associated with socioeconomic status.² Ill health and social problems associated with low socioeconomic status tend to be more common in societies with bigger differences in income