RISK OF ANOGENITAL CANCER FOLLOWING DIAGNOSIS OF CERVICAL INTRAEPITHELIAL NEOPLASIA: A PROSPECTIVE POPULATION-BASED STUDY

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SUMMARY

Background: The first vaccine against human papillomavirus related disease is now available on the market. Although it is designed and tested mainly to protect against cervical lesions, it is also expected to be effective against other anogenital cancers. Associations between human papillomavirus and vaginal, vulvar and anal cancers are well established, but the full extent in terms of age and time since diagnosis of these associations are not well known.

Methods: We established a cohort of all women in Sweden who were between 18 and 50 years old at some time-point from 1968 to 2004. Using national registration numbers, we linked this cohort to nationwide population, migration, cancer and death registers. The relative risks of vaginal, vulvar, anal and rectal cancer among women with a history of a cervical intraepithelial neoplasm, grade 3, compared to women with no such history was estimated using multivariate Poisson regression.

Findings: Women with a history of a cervical intraepithelial neoplasm exhibited increased risks of cancer of the vagina (relative risk, 6·74; 95% CI 5·24 to 8·56), vulva (relative risk, 2·22; 95% CI 1·79 to 2·73), and anus (relative risk, 4·68; 95% CI 3·87 to 5·62). No excess risk was found for rectal cancer. The observed increased risks were not explained by smoking or socioeconomic status.

Interpretation: This study confirms the known association between history of CIN, presumed HPV infection, and increased risk of cancers of the vagina, vulva and anus using large and complete databases, but also shows that this risk varies by both the time from initial diagnosis of CIN3 and according to the age of the subject. Further studies are needed to clarify the type of HPV associated with this increase to determine the clinical applicability of new HPV vaccines to decrease this observed risk.

INTRODUCTION

It is well known that women with a history of a cervical intraepithelial neoplasia are at increased risks of vaginal**,** vulvar and anal cancer,[1-5] presumably due to human papillomavirus (HPV) infection. Specifically, HPV infection has been associated with anal cancer, non-keratinising vulvar cancer,[6-10] and to some extent also with vaginal cancer.[11] The risks of cancers of the vagina, vulva and anus associated with HPV infection is lower than what has been reported for grade 3 cervical intraepithelial neoplasias, or for invasive cervical cancer.[12] However, the extent of these associations still remain poorly characterised.

Although the incidence of anal and vulvar cancer is rapidly increasing,[13-15] cancers of the vagina, vulva, and anus are still rare.[14-16] In certain sub-populations, such as among men who have sex with men, anal cancer is comparably common.[17-19] The first vaccine against HPV related disease is now available on the market.[20-22] Although this vaccine, and another soon to be released, have mainly been developed and tested to prevent cervical intraepithelial neoplasia and invasive cervical cancer, they are expected to also prevent other anogenital cancers and in one case also genital condylomas.[20] Results from clinical trials of HPV vaccination have been extraordinarily good.[20-23]

Almost 100 percent of tissue samples from grade 3 cervical intraepithelial neoplasias are infected with HPV.[24] Therefore**,** estimation of the risk of anogenital cancer following diagnosis of a grade 3 cervical intraepithelial neoplasia could potentially further our understanding of the relationship between HPV infection and anogenital cancer. Since such data can be used to predict the potential effect of HPV vaccines, which is vital for the planning of health care and vaccination programs, we conducted a population-based cohort study to assess the risks of vaginal, vulvar, anal, and rectal cancer among women with a history of a grade 3 cervical intraepithelial neoplasia diagnosis.

MATERIAL AND METHODS

SUBJECTS

Since 1947, all residents of Sweden have been assigned a unique national registration number. This number is routinely used in everyday life and in contact with authorities and health care providers as well as a unique personal identifier in national population and health databases. From the Swedish National Population Register, we extracted the national registration number, date of birth and date of death for all women who were born between 1918 and 1986 (i.e. between 18 and 50 years at some point during the study period) and who were recorded as living in Sweden at some point between January 1st 1968 and December 31st 2004.

For all of these women, we performed record linkages with the Swedish Cancer Register to obtain the date of diagnosis, anatomical site and histological classification of all malignant and pre-malignant conditions recorded for each individual. Linkages with the Swedish multi-generation register and the national census databases from 1960, 1970, 1980 and 1990 provided information on parity and the type of occupation for purposes of socioeconomic classification. For a subset of women who had delivered a child in or after 1983, the Swedish Medical Birth Register provided information on smoking habits, as measured during antenatal care. Finally, to allow for correct censoring, the Swedish register of External Migration provided dates of first immigration and emigration.

STATISTICAL ANALYSIS

Follow-up for diagnosis of cancer for all identified women started on age 18, date of first immigration, or 1st of January, 1968 whichever occurred last. Follow-up was extended until death, emigration, diagnosis of first cervical malignancy of invasive or unknown type, or the 31st of December 2004, whichever occurred first. From the Swedish Cancer Register we identified the date of the first diagnosis of a grade 3 cervical intraepithelial neoplasia, i.e.

severe dysplasia or cancer in situ of the uterine cervix (International Classification of Disease, revision 7 [ICD-7] code 171, and World Health Organisation C24 code 144).[25] The Swedish Cancer Register also provided information on diagnoses of vaginal (ICD-7 code 176.1), vulvar (ICD-7 code 176.0), anal (ICD-7 code 154.1) and rectal (ICD-7 code 154.0) cancers.

We treated history of a grade 3 cervical intraepithelial neoplasia diagnosis as a time-dependent covariate, allowing women to contribute person-time as having a negative history until first registered diagnosis. Thereafter, time-at-risk was considered in strata as defined by the time that had passed since the first diagnosis (<1 year, 1-4, 5-9, or ≥10 years). Incidence rate ratios for diagnosis of cancer, comparing women with a prior diagnosis to those without, were estimated using a log-linear Poisson regression model. For all analyses, we considered confounding by attained age (18-29, 30-39, 40-49, 50-59, or ≥60 years), calendar period of observation (1968-1977, 1978-1987, 1988-1997, or 1998-2002), type of occupation (blue-collar worker, farmer, self-employed, white-collar worker, or other/unknown) and parity (nulliparous, 1, 2-3, or >3 children). In sub-analyses restricted to women who had delivered a child in 1983 or later, where we had access to information on cigarette smoking as measured during antenatal care, we also considered smoking as a potential confounder. Socioeconomic status (occupation), attained age, calendar period and smoking were also treated as time-dependent covariates, allowing individuals to move between categories with time. All variables were treated as categorical variables. Unless explicitly stated, all analyses excluded cancers diagnosed during the year directly following the first diagnosis of a grade 3 cervical intraepithelial neoplasia in order to avoid biased results from increased surveillance. To visualise the age-specific cancer risks, we constructed graphs with the crude incidence of vaginal, vulvar and anal cancer in 10 year age groups among those with and without a history

of a grade 3 cervical intraepithelial neoplasia. Confidence intervals for the incidence rates were constructed based on the assumption that the expected number of cancer cases follows a Poisson distribution.

All data processing and statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA). The conduct of this study was approved by the ethics committee at Karolinska Institutet, in Stockholm, Sweden.

ROLE OF THE FUNDING SOURCE

No funding was acquired for the research described here, as such no funding source was involved in the study design, data collection, analysis and interpretation, or in the drafting of the manuscript. The corresponding author had full access to all the data in the study, and had the final responsibility for the decision to submit the report for publication.

RESULTS

From the register of the Swedish population, we identified a total of 3,747,698 women who were eligible for analysis. The women were on average quite young; almost 50 percent of the risk time considered in the study was contributed by women less than 40 years old. Risk time was relatively evenly distributed across the study period, with a slight excess in the later decades. The study population is described in more detail in Table 1. During a median follow-up of 27 years (range, 0-37 years), a total of 91,229,349 person years accrued, 125,292 women received at least one diagnosis of a grade 3 cervical intraepithelial neoplasia and a total of 305,092 other malignant neoplasms were diagnosed. The mean age at diagnosis of a grade 3 cervical intraepithelial neoplasia was 35 years (SD 9·1). Among the subset of women for whom information on cigarette smoking was available, a larger proportion of those with a history of a grade 3 cervical intraepithelial neoplasia reported being former or current smokers - 42 percent (15,331 of 36,704) compared to 24 percent (206,724 of 853,775) in the group without.

Table 2 presents univariate and adjusted incidence rate ratios from the Poisson regression analyses. The risks of vaginal, vulvar and anal cancers were strongly associated with having a history of a grade 3 cervical intraepithelial neoplasia both in the univariate and adjusted analyses. The overall adjusted relative risk of vaginal cancer comparing women with a history of a grade 3 cervical intraepithelial neoplasia to those without was 6·74 (95% CI 5·24 to 8·56). For vulvar and anal cancer the relative risks were 2·22 (95% CI 1·79 to 2·73) and 4·68 (95% CI 3·87 to 5·62), respectively. Having a history of a grade 3 cervical intraepithelial neoplasia diagnosis conferred no excess risk of rectal cancer, the estimated relative risk was 0·98 (95% CI 0·87 to 1·10).

Restricting the analysis to women who had delivered a child in or after 1983, where adjustment also for smoking was possible, reduced the precision greatly but modified the relative risk estimates only to a small extent. Having a history of a grade 3 cervical intraepithelial neoplasia remained significantly associated with vaginal, vulvar and anal cancer. The relative risks estimated in the restricted analysis were 6·69 (95% CI 1·87 to 19·0) for vaginal cancer, 2·64 (95% CI 1·22 to 5·08) for vulvar cancer, 2·81 (95% CI 1·29 to 5·44) for anal cancer and 1·17 (95% CI 0·65 to 1·94) for cancer of the rectum. Models considering an interaction between the parameters for having a grade 3 cervical intraepithelial neoplasm history and smoking showed that the risk of any of the four malignancies was not significantly altered by smoking. P-values for interactions were 0.86, 0.39, 0.09, and 0.51 for vaginal, vulvar, anal, and rectal cancer, respectively, where $p>0.05$ indicates no interaction. As described in Table 3, for all four anatomical sites the relative risks varied considerably with the amount of time that had elapsed since the date of first diagnosis of a grade 3 cervical intraepithelial neoplasia. During the first year after the first such diagnosis, the risk of vaginal cancer was 42·9-fold higher compared with women who had no history of such a diagnosis (95% CI 18·2 to 84·7). Thereafter the relative risk dropped successively, but even 10 years after diagnosis, and beyond, the relative risk of vaginal cancer was 4·61 (95% CI 3·33 to 6·23). A similar pattern, with an initially high and thereafter decreasing relative risk, was evident also for vulvar cancer, whereas an almost opposite pattern, with an initially null and thereafter increasing relative risk, was observed for anal cancer. For cancers of the vulva and anus, the relative risks also remained noticeably elevated as long as 10 years after the first diagnosis of a grade 3 cervical intraepithelial neoplasia. The relative risk of rectal cancer did not differ significantly from unity at any point in the follow-up period.

Analyses stratified by attained age revealed that the risk of cancer conferred by a history of a diagnosis of a grade 3 cervical intraepithelial neoplasia was highly age dependent (Table 4). Women with a history of a grade 3 cervical intraepithelial neoplasia diagnosis who were between 18 and 29 years old had a 22·2-fold (95% CI 2·80 to 175) excess risk of vaginal cancer compared to those with no such history. For vulvar and anal cancer the relative risks in the youngest age category were of similar magnitude, 23·2- and 31·1-fold increased, respectively. The relative risks at these three sites remained significantly elevated also in the older age groups, but decreased gradually with increasing age. There was no significant association between having a history of a grade 3 cervical intraepithelial neoplasia and rectal cancer in any age group.

Plotting the crude incidence of cancers of the vagina, vulva and anus against attained age for women with and without a history of a grade 3 cervical intraepithelial neoplasia provided a supplementary picture. For cancers of the vagina and anus the relative risks clearly decreased with increasing age (Table 4), while the risk difference increased exponentially (Figure 1). For vulvar cancer, where the relative risk was much less pronounced in the older age groups (Table 4), the risk difference remained almost constant up to 70 years of age where it disappeared (Figure 1).

DISCUSSION

In this large population-based cohort study conducted among more than 3·7 million women over a period of 37 years, we have demonstrated a strong and consistent association between having a history of a grade 3 cervical intraepithelial neoplasia and cancers of the vagina, vulva and anus. The relative risks of these three cancers were considerably elevated for more than 10 years following first recorded cervical lesion. As was expected, we have found no evidence of such an association with cancer of the rectum.

Since HPV infection is present in almost all cervical lesions and is considered a necessary cause of grade 3 cervical intraepithelial neoplasia, from our observations, it is logical to assume that HPV plays an important role also in the causation of other anogenital cancers. Several previous studies have reported associations between HPV infection and cancers of the vagina,[11] vulva,[9] and anus.[6,7] In addition, there exists a number of studies on pattern of anogenital cancer following diagnosis of cervical intraepithelial or invasive malignancies.[1-5] However, neither of these studies have excluded the possibility of confounding by smoking or socioeconomic status, nor have they described the pattern of risk of anogenital cancer to the same level of detail as in this study.

The strengths of this study include the prospective and population-based design, the large sample size and extensive, as well as unbiased, follow-up time that allow detailed and meaningful characterisation of the risk profile associated with grade 3 cervical intraepithelial neoplasias. Strict reliance on the Swedish Cancer Register, which during the study period was considered at least 98 percent complete,[26] and the possibility to consider the effect of confounding by socioeconomic status as well as by smoking further strengthens our study. Since both cervical intraepithelial neoplasia of grade 3 and other anogenital cancer are related to smoking, socioeconomic status, and other life-style factors such as number of sexual

partners,[6,9,11,27] the observed relationships could in theory be explained by common risk factors. However, the relative risks observed changed only to a small extent and remained significantly increased when we controlled for smoking and socioeconomic status. We had no possibility to address dose-response relationships, something that could otherwise have been used to further test the hypothesis of a relationship between HPV and anogenital cancer.

Misclassification of the exposure is indeed possible, but likely to be small since 99 percent of the cervical lesions in our study were confirmed through biopsies. In addition, central pathology review of the diagnosis of grade 3 cervical intraepithelial neoplasias (severe dysplasia of the cervix) in the Swedish Cancer Register has previously revealed a misclassification of only 1 percent.[28] Therefore, almost all women with a history of a grade 3 intraepithelial neoplasia considered in this study will have been infected with HPV. However, since only a fraction of HPV infections lead to development of a cervical lesion, a considerable number of women in the unexposed group should in fact have been exposed to, and infected with HPV. Also, since cervical cancer screening, and registration, was initiated in Sweden only in the 1960's, a large number of women in the older age categories who had a diagnosis of a cervical intraepithelial neoplasia before nationwide screening will incorrectly be considered unexposed. Thus, the risk estimates presented here are probably underestimating the true relative risks that HPV infection confers. On the other hand, since development of severe dysplasia is a strong indicator of persistent infection with an oncogenic HPV subtype[27,29] our risk estimates should be reasonably accurate with regards to such infection. Although we did not have access to data on HPV subtype from tumour tissue, it seems logical to assume that the increased risks we observe are conferred by the

oncogenic HPV subtypes (primarily HPV 16 and 18) that are known to be associated with cervical lesions and other anogenital malignancies.[6,7,11,30]

Since the information on smoking we used for statistical adjustment was obtained from antenatal care registration, a certain degree of residual confounding from smoking is inevitable, but a recent report suggests that self-reported smoking information from pregnant women in Sweden carries a high validity.[31] It should, however, be noted that only current smoking is known to be a risk factor for anal cancer and the timing of the smoking measurements in our study might not match the age group at which anal cancers commonly occur **since** pregnant women might be younger.[32]

It can be assumed that increased surveillance of newly diagnosed women contributed to the elevated risks, especially for vaginal and to some extent also for vulvar cancer. As is evident from Table 3, this does not seem to have been the case for anal cancer. Consistent exclusion of the first year of follow-up should keep effects of surveillance minimal, but since women who are diagnosed with a cervical lesion are often followed closely for several years, it cannot be eliminated entirely. We speculate that the greatly increased risk in the time directly following diagnosis is also the result of local spread of HPV and to some extent also local infiltration of malignant cells.

For cancers of the vagina and anus, we observed decreasing relative risks and increasing risk differences with advancing age. Whereas this pattern can, at least partly, be explained by a greater number of undetected cervical intraepithelial neoplasms, i.e. misclassification of the exposure, in the older age groups, it is presumably also an effect of the very low incidence of these malignancies in young age groups. Thus, the very high relative risks seen in the youngest age groups should be interpreted with some caution.

In Sweden, cervical intraepithelial neoplasia has traditionally been treated by cold knife or laser conisation, cryo surgery, or loop electrosurgical excision procedure, neither being a risk factor for cancers of the anogenital region. Since all women who developed an invasive cervical cancer were censored, it is unlikely that local metastasis or treatment has had any important influence on our results. Although hysterectomy has never been a common treatment for severe dysplasia in Sweden, it is possible that among hysterectomised women, cervical cancers may have been misclassified as vaginal cancers.[16] However, in our cohort, only 6,791 (5 percent) of women who were diagnosed with a cervical intraepithelial neoplasm were hysterectomised within 5 years of diagnosis.

In conclusion, our study has provided further evidence of an association between a history of a grade 3 cervical intraepithelial neoplasia and cancers of the anogenital region. Although the evidence we provide in this study pointing towards HPV being the agent through which this effect is mediated only is of indirect nature, it seems a highly plausible explanation.

AUTHOR CONTRIBUTIONS

Both Gustaf Edgren and Pär Sparén participated in the design and conduct of this study as well as with the drafting and final approval of the manuscript.

CONFLICTS OF INTEREST

Gustaf Edgren: None

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FIGURE LEGENDS

Figure 1. Age-specific incidences of vaginal, vulvar, anal and rectal cancer in women with and without a history of a cervical intraepithelial neoplasia.*

*The first year following diagnosis of cervical intraepithelial neoplasia was excluded from the incidence calculations. The numbers in the tables may not add up due to rounding.

Table 1. Characteristics of the study population*

	No CIN History		**Positive CIN3 History**	
	N=3,747,698			
	Yrs. of follow-up (%)			
Total person-years of follow-up	88,927,325	(97.5)	2,302,024	(2.5)
Attained age				
<30	24,211,737	(27.2)	164,626	(7.2)
30-39	18,961,118	(21.3)	562,965	(24.5)
40-49	17,752,780	(20.0)	691,165	(30.0)
50-59	14,499,146	(16.3)	535,799	(23.3)
≥ 60	13,502,544	(15.2)	347,468	(15.1)
Socioeconomic status				
Blue-collar worker	26,721,141	(30.0)	871,633	(37.9)
Self-employed	2,494,191	(2.8)	80,695	(3.5)
Farmer	1,629,373	(1.8)	14,960	(0.6)
White-collar worker	33,656,290	(37.8)	967,320	(42.0)
Other/Unknown	24,426,331	(27.5)	367,416	(16.0)
Calendar period				
1968-1977	18,490,248	(20.8)	234,887	(10.2)
1978-1987	23,128,276	(26.0)	550,946	(23.9)
1988-1997	27,040,355	(30.4)	820,291	(35.6)
1998-2002	20,268,446	(22.8)	695,899	(30.2)

* CIN3 denotes cervical intraepithelial neoplasia, grade 3; the number of person-years may not add up because of rounding

Table 2. Relative risks of cancer of the vagina, vulva and anus comparing women with a history of cervical intraepithelial neoplasia, grade 3, to those without*

	Years of Follow-up†	Number of Events	Univariate	Adjusted**	Adjusted and Restricted‡
			Incidence Rate Ratio (95% Confidence Interval)		
Vaginal cancer					
CIN3 history	2,193,409	79	7.91 (6.17-10.0)	6.74 (5.24-8.56)	6.69 (1.87-19.0)
No CIN3 history	88,927,325	405	1.00 (ref)	1.00 (ref)	1.00 (ref)
Vulvar cancer					
CIN3 history	2,193,409	94	2.70 (2.17-3.30)	2.22 (1.79-2.73)	2.64 (1.22-5.08)
No CIN3 history	88,927,325	1,414	1.00 (ref)	1.00 (ref)	1.00 (ref)
Anal cancer					
CIN3 history	2,193,409	131	6.20 (5.13-7.42)	4.68 (3.87-5.62)	2.81 (1.29-5.44)
No CIN3 history	88,927,325	857	1.00 (ref)	1.00 (ref)	1.00 (ref)
Rectal cancer					
CIN3 history	2,193,409	274	1.20 (1.06-1.35)	0.98 (0.87-1.10)	1.17 (0.65-1.94)
No CIN3 history	88,927,325	9,281	1.00 (ref)	1.00 (ref)	1.00 (ref)

* CIN3 denotes cervical intraepithelial neoplasia, grade 3; CI denotes confidence interval

† The number of person-years does not add up to 91,229,349 since the first year following a CIN3 diagnosis has been excluded from the analyses

** Adjusted for attained age, calendar period, socioeconomic status and parity

‡ Adjusted for attained age, calendar period, socioeconomic status, parity and smoking; restricted to women who have delivered a child in or after 1983. The Follow-up time and number of events is therefore lower than for the univariate and adjusted analyses.

Table 3. Relative risks of cancer of the vagina, vulva, anus and rectum comparing women with a history of cervical intraepithelial neoplasia, grade 3, to those without, stratified by time since first diagnosis*

	Time since first diagnosis of Cervical Intraepithelial Neoplasia, grade 3				
	<1 year	**1-4 years**	**5-9 years**	**≥10 years**	**No CIN3 history**
	Incidence Rate Ratios (95% Confidence Interval)				
Vaginal cancer	42.9 (18.2-84.7)	19.3 (10.9-31.4)	15.4 (9.30-23.9)	4.61 (3.33-6.23)	1.00 (ref)
events/time	7/108,615	15/423,522	19/476,115	45/1,293,773	405/88,927,325
Vulvar cancer	5.97 (1.85-13.9)	1.87 (0.74-3.80)	2.41 (1.28-4.06)	2.23 (1.75-2.80)	1.00 (ref)
events/time	4/108,615	6/423,522	12/476,115	76/1,293,773	1,414/88,927,325
Anal cancer	0.00 (0.00-2.06)†	1.67 (0.41-4.36)	3.90 (2.08-6.60)	4.98 (4.07-6.04)	1.00 (ref)
events/time	0/108,615	3/423,522	14/476,115	115/1,293,773	857/88,927,325
Rectal cancer	1.91 (0.76-3.88)	0.70 (0.36-1.20)	1.20 (0.83-1.67)	0.97 (0.85-1.11)	1.00 (ref)
events/time	6/108,615	11/423,522	32/476,115	231/1,293,773	9,281/88,927,325

* CIN3 denotes Cervical intraepithelial neoplasia, grade 3; Adjusted for attained age, calendar period, socioeconomic status and parity; The number of person-years may not add up because of rounding

† For reasons of model convergence, these point estimates could not be estimated in the multivariate model and are therefore **taken** from the univariate model

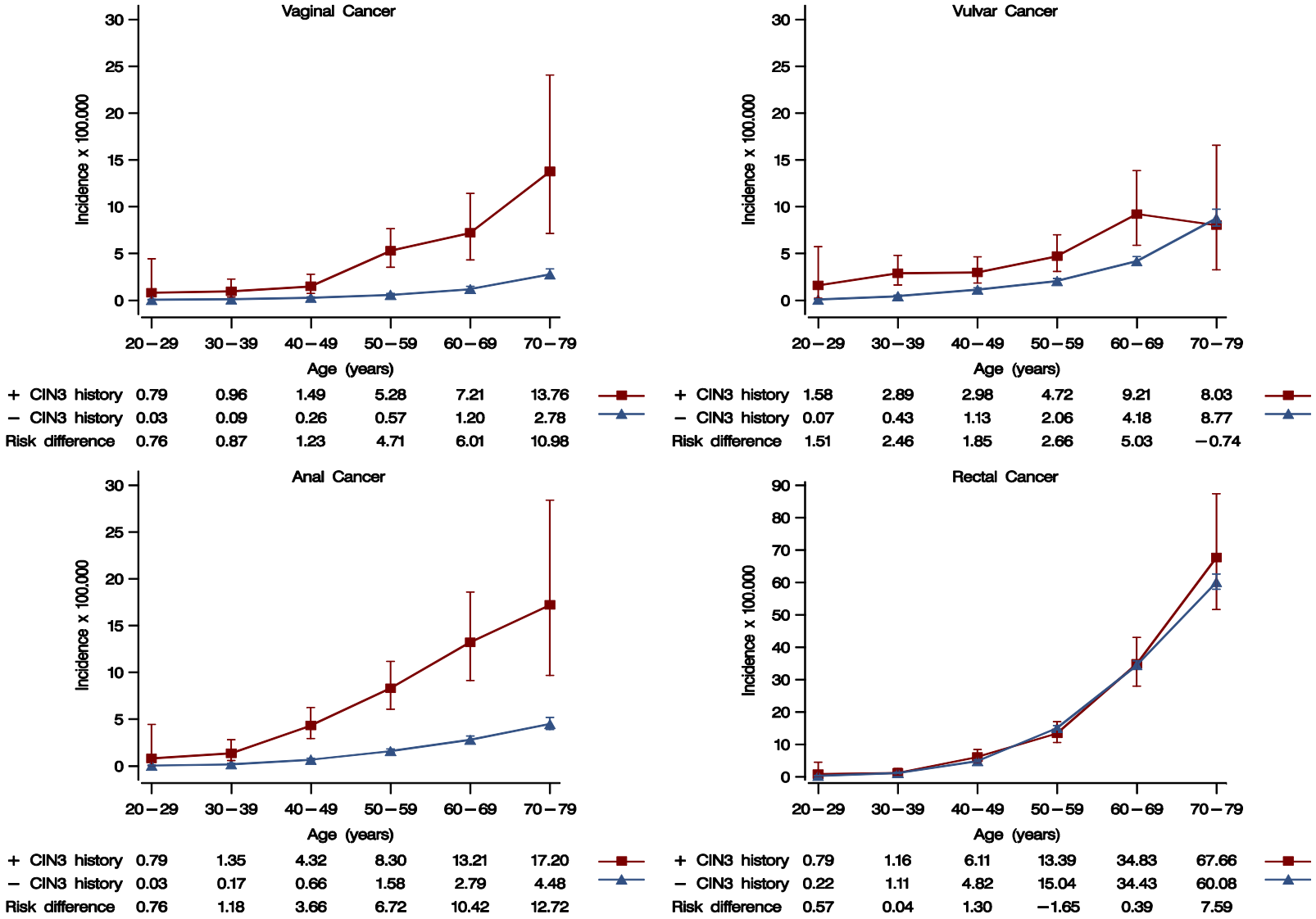
Table 4. Relative risks of cancer of the vagina, vulva, anus and rectum comparing women with a history of cervical intraepithelial neoplasia, grade 3, to those without, stratified by attained age*

	18-29 years	**30-39 years**	**40-49 years**	**50-59 years**	**≥60 years**
			Incidence Rate Ratios (95% Confidence Interval)†		
Vaginal cancer	22.2 (2.80-175)	10.2 (3.79-27.6)	5.63 (2.83-11.2)	9.19 (5.96-14.2)	5.54 (3.88-7.91)
CIN3 history, events/time	1/127,121	5/519,468	10/670,887	28/530,171	35/345,762
No CIN3 history, events/time	9/24,211,737	18/18,961,118	47/17,752,780	83/14,499,146	248/13,502,544
Vulvar cancer	23.3 (5.38-101)	6.76 (3.90-11.7)	2.59 (1.64-4.11)	2.23 (1.48-3.36)	1.52 (1.07-2.17)
CIN3 history, events/time	2/127,121	15/519,468	20/670,887	25/530,171	32/345,762
No CIN3 history, events/time	17/24,211,737	81/18,961,118	201/17,752,780	298/14,499,146	817/13,502,544
Anal cancer	31.1 (3.74-258)	7.59 (3.35-17.2)	5.82 (3.87-8.75)	4.70 (3.40-6.50)	3.97 (2.96-5.32)
CIN3 history, events/time	1/127,121	7/519,468	29/670,887	44/530,171	50/345,762
No CIN3 history, events/time	6/24,211,737	32/18,961,118	118/17,752,780	229/14,499,146	472/13,502,544
Rectal cancer	4.13 (0.57-29.9)	1.02 (0.45-2.30)	1.23 (0.90-1.68)	0.85 (0.67-1.08)	0.99 (0.84-1.16)
CIN3 history, events/time	1/127,121	6/519,468	41/670,887	71/530,171	155/345,762
No CIN3 history, events/time	45/24,211,737	211/18,961,118	855/17,752,780	2,181/14,499,146	5,989/13,502,544

* CIN3 denotes cervical intraepithelial neoplasia, grade 3; Adjusted for attained age, calendar period, socioeconomic status and parity.

† For all incidence rate ratio calculations, the reference group was those with no CIN3 history belonging in the same age strata.

FIGURE 1


Vaginal Cancer
Incidence x 100.000
0
5
10
15
20
25
30
20–29
30–39
40–49
50–59
60–69
70–79
Age (years)
+ CIN3 history 0.79 0.96 1.49 5.28 7.21 13.76
– CIN3 history 0.03 0.09 0.26 0.57 1.20 2.78
Risk difference 0.76 0.87 1.23 4.71 6.01 10.98
Vulvar Cancer
Incidence x 100.000
0
5
10
15
20
25
30
20–29
30–39
40–49
50–59
60–69
70–79
Age (years)
+ CIN3 history 1.58 2.89 2.98 4.72 9.21 8.03
– CIN3 history 0.07 0.43 1.13 2.06 4.18 8.77
Risk difference 1.51 2.46 1.85 2.66 5.03 –0.74
Anal Cancer
Incidence x 100.000
0
5
10
15
20
25
30
20–29
30–39
40–49
50–59
60–69
70–79
Age (years)
+ CIN3 history 0.79 1.35 4.32 8.30 13.21 17.20
– CIN3 history 0.03 0.17 0.66 1.58 2.79 4.48
Risk difference 0.76 1.18 3.66 6.72 10.42 12.72
Rectal Cancer
Incidence x 100.000
0
10
20
30
40
50
60
70
80
90
20–29
30–39
40–49
50–59
60–69
70–79
Age (years)
+ CIN3 history 0.79 1.16 6.11 13.39 34.83 67.66
– CIN3 history 0.22 1.11 4.82 15.04 34.43 60.08
Risk difference 0.57 0.04 1.30 –1.65 0.39 7.59