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Short Report

The relative risk of noncervical high-risk human papillomavirus-related (pre)malignancies after recurrent cervical intraepithelial neoplasia grade 3: A population-based study

Diede L. Loopik[1], Renée M. Ebisch[2], Joanna IntHout[3], Willem J. Melchers[4], Leon F. Massuger[5], Ruud L. Bekkers[2] and Albert G. Siebers[6,7]

[1]Department of Obstetrics and Gynaecology, Radboud Institute for Molecular Life Sciences, Radboud university medical center, Nijmegen, The Netherlands
[2]Department of Obstetrics and Gynaecology, Catharina Hospital, Eindhoven, The Netherlands
[3]Department of Biostatistics, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, The Netherlands
[4]Department of Medical Microbiology, Radboud university medical center, Nijmegen, The Netherlands
[5]Department of Obstetrics and Gynaecology, Radboud university medical center, Nijmegen, The Netherlands
[6]Department of Pathology, Radboud university medical center, Nijmegen, The Netherlands
[7]PALGA, The Nationwide Network and Registry of Histo- and Cytopathology, Houten, The Netherlands

Women with cervical intraepithelial neoplasia grade 3 (CIN3) have a long-lasting increased risk for noncervical high-risk human papillomavirus (hrHPV)-related (pre)malignancies. The aim of our study was to estimate this risk in women with recurrent CIN3 compared to women without a history of CIN3 and women with a single episode of CIN3. Women with a CIN3 diagnosis between 1990 and 2010 were obtained from the Dutch Pathology Registry (PALGA) and matched with a control group of women without CIN3. Analysis has been conducted in a subset of women with recurrent CIN3, defined as reoccurrence minimally 2 years post-treatment. Cases of noncervical hrHPV-related (pre)malignancies of the anus, vulva, vagina and oropharynx were identified until 2015 and incidence rate ratios (IRRs) were estimated. Then, 1,797 women with recurrent CIN3 were included with a median age of 34 years (range 18–76) and 31,594 person-years of follow-up. Women with recurrent CIN3 had an increased risk of developing noncervical hrHPV-related (pre)malignancies compared to women without CIN3 with an IRR of 25.96 (95%CI 6.32–106.58). The IRR was 2.48 (95% CI 1.87–3.30) compared to women with a single episode of CIN3. Studies on posttreatment follow-up and prophylactic hrHPV vaccination are warranted.

Introduction

Around 4.8% of the cancers worldwide can be attributed to high-risk human papillomavirus (hrHPV) infection. Close to 100% of cervical cancer cases are hrHPV related, while hrHPV is causally associated with 88% of anal, 43% of vulvar, 70% of vaginal and 13–56% of oropharyngeal cancers.[1] The introduction of cervical cancer screening programs has drastically decreased incidence and mortality from cervical cancer, due

Ruud L. Bekkers's current address is: GROW, School for Oncology & Developmental Biology, Maastricht University Medical Center, PO Box 616, 6200MD, Maastricht, The Netherlands

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Abbreviations: 95% CI: 95% confidence interval; AIN: anal intraepithelial neoplasia; CIN: cervical intraepithelial neoplasia; hrHPV: high-risk human papillomavirus; IR: incidence rate; IRR: incidence rate ratio; PALGA: the nationwide network and registry of histo- and cytopathology in the Netherlands; RR: risk ratio; VAIN: vaginal intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia

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Correspondence to: Diede L. Loopik, E-mail: diede.loopik@radboudumc.nl

What's new?

Most cervical and many anogenital cancer cases are high-risk human papillomavirus (hrHPV) infection-related. However, the risk of noncervical hrHPV-related (pre)malignancies after recurrent cervical intraepithelial neoplasia grade 3 (CIN3) remains poorly studied. This study found that women with recurrent CIN3 had an increased risk of developing non-cervical hrHPV-related (pre)malignancies compared to women without CIN3, with an incidence rate ratio (IRR) of 25.96. The IRR was 2.48 compared to women with a single episode of CIN3. Besides intensified cervical screening, women with recurrent CIN3 may thus benefit from increased awareness of other hrHPV-related (pre)malignancies and adjuvant hrHPV-vaccination to prevent noncervical hrHPV-related cancers.

to early treatment of precancerous lesions.[2] It has been shown that women who are treated for cervical intraepithelial neoplasia grade 3 (CIN3) have an increased risk of not only developing cervical but also noncervical hrHPV-related cancers.[3–8] A persistent hrHPV infection that caused a CIN3 may also affect the entire anogenital region.[9] These women seem to be less capable to clear the infection and are susceptible to reinfection/reactivation. This all could lead to a long-term increased risk for noncervical hrHPV-related (pre)malignancies. The burden of noncervical hrHPV-related cancers among women approximates 46,435 cases annually worldwide, including 14,787 anal cancers, 25,600 vulvar/vaginal cancers and 6,048 oropharyngeal cancers.[10] Especially women with recurrent CIN3, defined as reoccurrence minimally 2 years posttreatment of CIN3, may have an even higher risk of developing noncervical hrHPV-related (pre)malignancies. These subgroups of women have already proven twice that they have an impaired immunity to clear hrHPV infection. To the best of our knowledge, the risk of noncervical hrHPV-related (pre)malignancies after recurrent CIN3 has not been studied before. Identifying women at risk for noncervical hrHPV-related (pre)malignancies, may help us to adjust follow-up strategies. Besides those women with recurrent CIN3 may benefit from intensified cervical screening to prevent cervical cancer, they may also benefit from an increased awareness for other hrHPV-related (pre)malignancies and adjuvant prophylactic hrHPV vaccination, to prevent cervical and noncervical hrHPV-related cancers. The aim of this population-based study was therefore to estimate the risk of noncervical hrHPV-related (pre)malignancies in women with recurrent CIN3 compared to women without a history of CIN3 and women with a single episode of CIN3.

Materials and Methods

We performed an analysis in a subset of women from a previously conducted retrospective population-based cohort study.[8] Women diagnosed with CIN3 were identified from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA; Houten, The Netherlands) between January 1, 1990, and December 31, 2010. CIN3 was defined as histologically proven severe dysplasia or carcinoma *in situ*. Adenocarcinoma *in situ* was not included. In our study, we included women with recurrent CIN3, defined as reoccurrence minimally 2 years posttreatment of CIN3. Women with a benign dermal nevus, but who were never diagnosed with CIN3 or cervical cancer, were selected from PALGA as a control group. Random frequency matching was done by age and year of detection within 5 years range, and population density areas. For the selection of women with recurrent CIN3, we excluded women with a cervical cancer diagnosis within 2 years after CIN3 diagnosis. Outcomes were the development of any noncervical hrHPV-related premalignancy, any noncervical hrHPV-related malignancy, or both. Cases of noncervical hrHPV-related premalignancies included histologically proven anal intraepithelial neoplasia grade 3 (AIN3), vulvar intraepithelial neoplasia grade 3 (VIN3) and vaginal intraepithelial neoplasia grade 3 (VAIN3). Cases of noncervical hrHPV-related malignancies included histologically proven carcinomas of the anus, vulva, vagina and oropharynx. For each of the three outcomes only the first appearance was considered and women were censored at age on March 1, 2015, or when they reached the average age at death for women in the Netherlands, which was 80.5 years in 2016.

Person-years at risk and the number of observed (pre)malignancies of each site were calculated. Poisson regression was used for the estimation of the incidence rates per 100,000 person-years and the incidence rate ratios (IRRs) for women with recurrent CIN3 compared to the matched control group and women with a single episode of CIN3. Statistical analysis was performed with SAS version 9.2 (SAS Institute, Cary, NC).

Ethics approval and consent to participate

The study was approved by the scientific committee of the Dutch Pathology Registry (PALGA). The study was exempt from institutional review board approval because data were gathered retrospectively and analysed anonymously. The study was performed in accordance with the Declaration of Helsinki.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

The original study included 89,018 women with CIN3 and an equal number of women without a history of CIN3 or worse in the control group.[8] Women with a cervical cancer diagnosis or hysterectomy within 2 years after CIN3 diagnosis were excluded (9,809/89,018; 11.02%). In total 1,797 (2.0%) women with recurrent CIN3 were included in our study and were

Table 1. Observed number of noncervical hrHPV-related (pre)malignancies, person-years at risk, estimated incidence rates per 100,000 person-years and incidence rate ratios of noncervical hrHPV-related (pre)malignancies for women with cervical intraepithelial neoplasia grade 3 and recurrent cervical intraepithelial neoplasia grade 3 compared to the matched control group

	CIN3 *vs.* no ≥CIN3 history (n = 89,018)[1]				Recurrent CIN3 *vs.* no ≥CIN3 history (n = 1,797)			
	Observed n	Person-years	IR (95% CI)	IRR (95% CI)	Observed n	Person-years	IR (95% CI)	IRR (95% CI)
Any noncervical hrHPV-related premalignancy[2]								
CIN3	634	1,259,306	50.35 (46.58–54.42)	12.75 (9.56–17.00)	Recurrent CIN3	51	31,208	163.42 (124.20–215.03)	50.80 (7.02–367.62)
No ≥CIN3	50	1,266,192	3.95 (2.99–5.21)		No ≥CIN3	1	31,088	3.22 (0.45–22.84)	
Any noncervical hrHPV-related malignancy[3]					Any noncervical hrHPV-related malignancy[3]				
CIN3	299	1,265,176	23.63 (21.10–26.47)	6.24 (4.60–8.46)	Recurrent CIN3	15	31,465	47.67 (28.74–79.08)	14.83 (1.96–112.24)
No ≥CIN3	48	1,266,520	3.79 (2.86–5.03)		No ≥CIN3	1	31,101	3.22 (0.45–22.83)	
Any noncervical hrHPV-related (pre)malignancy[4]					Any noncervical hrHPV-related (pre)malignancy[4]				
CIN3	847	1,259,306	67.26 (62.88–71.95)	9.68 (7.77–12.05)	Recurrent CIN3	52	31,123	167.08 (127.32–219.26)	25.96 (6.32–106.58)
No ≥CIN3	88	1,266,192	6.95 (5.64–8.57)		No ≥CIN3	2	31,077	6.44 (1.61–25.73)	

[1]Based on Ebisch *et al.*[8]
[2]Any noncervical hrHPV-related premalignancy includes AIN3, VIN3 and VAIN3. After the first premalignancy, women were censored.
[3]Any noncervical hrHPV-related malignancy includes anal cancer, vulvar cancer, vaginal cancer and oropharyngeal cancer. After the first malignancy, women were censored.
[4]Any noncervical hrHPV-related (pre)malignancy includes anal cancer, AIN3, vulvar cancer, VIN3, vaginal cancer, VAIN3 and oropharyngeal cancer. After the first (pre)malignancy, women were censored.
Abbreviations: AIN3, anal intraepithelial neoplasia grade 3; CIN3, cervical intraepithelial neoplasia grade 3; hrHPV, high-risk human papillomavirus; IR, incidence rate; IRR, incidence rate ratio; VAIN3, vaginal intraepithelial neoplasia grade 3; VIN3, vulvar intraepithelial neoplasia grade 3; 95% CI, 95% confidence interval.

matched with an equal number of women from the control group. The median age at recurrent CIN3 diagnosis was 34 years (range 18–76), and 34 years (range 15–75) in the control group. The median follow-up was 18 years (range 4–23) in both groups. Without censoring for noncervical hrHPV-related (pre)malignancies, we calculated 31,594 and 31,112 person-years at risk for women with recurrent CIN3 and the control group, respectively. We found eight anal, 29 vulvar and 14 vaginal grade 3 premalignancies, and nine vulvar and six vaginal cancers in the group of women with recurrent CIN3. Only two noncervical hrHPV-related (pre) malignancies (one VIN3 and one vulva carcinoma) were found in the control group *versus* 52 in the group of women with recurrent CIN3 (after the first (pre)malignancy women were censored). The incidence rates and IRRs of noncervical hrHPV-related (pre)malignancies are shown in Table 1. Women with recurrent CIN3 had an increased risk of developing any noncervical hrHPV-related premalignancy (IRR 50.80; 95% CI 7.02–367.62) and had an increased risk of developing any noncervical hrHPV-related malignancy (IRR 14.83; 95% CI 1.96–112.24) compared to women without CIN3. For comparison, the IRRs of women with a single episode of CIN3 compared to women without CIN3 from the original study are shown as well. For women with recurrent CIN3 the IRR of any noncervical hrHPV-related (pre)malignancy was 2.48 (95% CI 1.78–3.30) compared to women with a single episode of CIN3.

Discussion

This population-based cohort study identified 1,797 women with recurrent CIN3 between 1992 and 2012 and showed an increased risk of developing noncervical hrHPV-related (pre) malignancies compared to women without CIN3 with an IRR of 25.96 (95% CI 6.32–106.58). The IRR was 2.48 (95% CI 1.87–3.30) compared to women with a single episode of CIN3.

To the best of our knowledge, the risk of noncervical hrHPV-related (pre)malignancies after recurrent CIN3 has not been studied before. Previous studies have found a risk ratio (RR) of 2.2–5.0 for vulvar cancer and a RR of 5.5–18.5 for vaginal cancer in women with single episode of CIN2 or CIN3.[3–8] Only Ebisch *et al.* found a much higher IRR of 86.1 for vaginal cancer, but with a wide confidence interval.[8] We did not find any anal or oropharyngeal cancers in our analysis and therefore an IRR could not be calculated for these cancers. RRs in women with a single episode of CIN3 found in previous studies, were 1.8–5.9 for anal cancers,[3–8] and 5.5 for oropharyngeal cancer.[8]

Women with recurrent CIN3 seem to be less capable to clear hrHPV and are susceptible for reinfection/reactivation. HrHPV infection often affects the entire anogenital region, and this may explain the increased risk for (pre)malignancies of the anus, vulva and vagina.[9] Women in follow-up after recurrent CIN3 may also have a higher chance of early detection of these noncervical hrHPV-related (pre)malignancies during physical

examination compared to women without a CIN3 diagnosis, which could lead to an overestimation of the RRs.

Women with recurrent CIN3 may benefit from increased awareness on other hrHPV-related (pre)malignancies by treating those premalignancies before they progress to cancer. Further research is needed to define an optimal follow-up strategy. As 63–95% of the noncervical hrHPV-related cancers are attributable to HPV16 and HPV18, they may also benefit from prophylactic hrHPV vaccination.[10] The hrHPV vaccine has been approved for the prevention of (pre)malignancies of the vulva and vagina, and studies are underway to evaluate the efficacy in the prevention of anal and oropharyngeal cancer. However, a protective effect of the hrHPV vaccine in women with a prevalent hrHPV infection has not been proven yet and further research is needed.

In conclusion, women with recurrent CIN3 had an increased risk of developing noncervical hrHPV-related (pre)malignancies compared to women without CIN3 with an IRR of 25.96 (95% CI 6.32–106.58). The IRR was 2.48 (95% CI 1.87–3.30) compared to women with a single episode of CIN3. Studies on follow-up strategies and prophylactic hrHPV vaccination to prevent this increased risk are warranted.

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