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Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age

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ABSTRACT

Objective: The purpose of the present study is to investigate the trends in incidence of both usual (u) and differentiated (d) vulvar intraepithelial neoplasia (VIN) separately, their malignant potential and the relation with other HPV related anogenital lesions in the Netherlands during a 14-year-period.

Methods: The incidences of both types of VIN and vulvar SCC were retrieved from the Nationwide Netherlands Database of Histo- and Cytopathology. Population data were retrieved from the Database of Statistics Netherlands.

Results: In the study period, the incidence of uVIN and dVIN increased, while the incidence of vulvar SCC remained stable. The overall percentage of uVIN patients that were later diagnosed with vulvar SCC was 5.7%, which was significantly lower than the percentage for dVIN patients (32.8%). In addition to this 5.6-fold increased conversion rate, the time of progression from dVIN to SCC development was significantly shorter than that of uVIN ($p = 0.005$). Percentage of uVIN patients that were later diagnosed with SCC significantly increased with age ($p = 0.005$), whereas the time to SCC significantly shortened with age ($p = 0.05$). Forty-one percent of uVIN patients had a past, concomitant or future HPV-associated lesion of the lower genital tract, which is in contrast to the 3% for dVIN patients.

Conclusions: An increase in diagnoses of both uVIN and dVIN has not led to an increase in vulvar SCC incidence. The malignant potential of dVIN is higher than that for uVIN. For uVIN the malignant potential increases with age.

1. Introduction

Vulvar squamous cell carcinoma (SCC) is the fourth most common gynaecological type of cancer with an annual incidence of 2–3 per 100,000 women.[1,2] Vulvar SCC usually arises from premalignant vulvar intraepithelial neoplasia (VIN). In general, there are two different types of VIN, i.e. differentiated VIN (dVIN) and usual VIN (uVIN) that both can progress towards vulvar SCC.[3–5] Whereas uVIN is causally related with human papillomavirus (HPV) infection, dVIN is HPV unrelated.[5]

dVIN is a recently recognised but difficult to diagnose entity for clinicians as well as pathologists.[4,6] dVIN is found

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adjacent to 70–80% of vulvar SCCs, but solitary dVIN lesions are rare. This may be caused by a relatively brief intraepithelial phase before progression to invasive carcinoma,[7–9] and suggests a high malignant potential of dVIN. dVIN is often seen in a background of lichen sclerosis (LS) and occurs in elderly women (mean age 65).[10] The aetiology of vulvar SCC via LS and dVIN is largely unknown. The HPV-associated (mainly HPV 16 and 18) uVIN mainly leads to non-keratinising vulvar SCC and it primarily affects younger women around the age of 45.[11] uVIN lesions are seen adjacent to approximately 20–30% of vulvar SCCs. Multicentric intraepithelial or invasive squamous neoplasia (of cervix, anus or vagina) occurs in approximately 53–66% of uVIN patients.[11,12] Most of these lesions are cervical (intraepithelial) neoplasias, as in most countries, as well as in the Netherlands, well-organised mass screening programmes exist for the prevention of cervical carcinoma. In contrast to the presumed high malignant potential of dVIN, SCC percentages of 3–5% were found in patients treated for uVIN.[11,13–15]

The incidence of uVIN is increasing worldwide,[1,14–19] which is in concordance with the increase in HPV prevalence. Despite the increase in uVIN, no increase in the overall incidence of SCC of the vulva has been seen.[1,17,20] In some publications, an increase in SCC incidence in young women was reported, possibly due to the younger age of first sexual intercourse and the increasing incidence of HPV infections.[16,21–23] Since the introduction of the new nomenclature, the incidence of uVIN and dVIN lesions has not been studied separately. The aim of the present study is to investigate the trends in incidence of both types of VIN, their malignant potential and the relation with other HPV related anogenital lesions in the Netherlands during a 14-year-period.

2. Materials and methods

Data concerning the incidence of VIN and vulvar SCC were collected via PALGA, the Nationwide Netherlands Database of Histo- and Cytopathology,[24] which has national coverage from 1991 onwards. Analogous with other studies concerning the incidence of cancer and using cancer registry data,[25–27] we calculated the incidence of VIN and vulvar SCC.

2.1. VIN

All patients with a primary VIN lesion diagnosed between 1st January 1992 and 31st December 2005 in the Netherlands were selected and a total number of 2935 patients were retrieved. We excluded patients with the first diagnosis of VIN diagnosed before 1992 with a recurrent lesion between 1992 and 2005. For all patients, the first report that mentioned VIN was included. For every pathology report, all VIN lesions were subdivided into usual or differentiated VIN. We based this subdivision on the conclusion drawn by the pathologist and additional indications mentioned in the reports (See Fig. 1). In the analyses we adopted the new International Society for Study of Vulvovaginal Disease (ISSVD) classification[4] (we did not include VIN 1 lesions, and grouped VIN 2 and 3 together as uVIN). We only included solitary VIN lesions, (i.e. not adjacent to vulvar SCC). VIN lesions that progressed

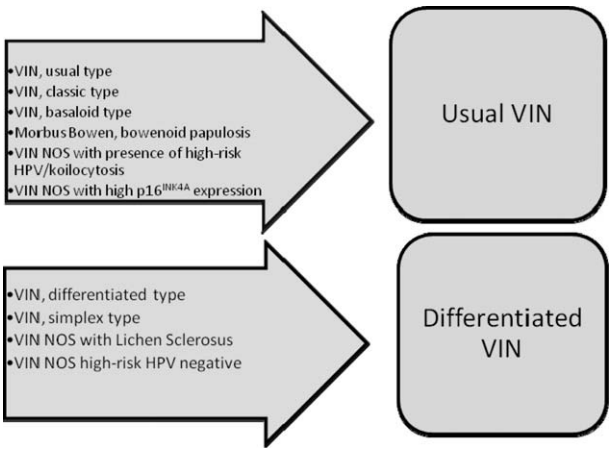

Fig. 1 – Histological diagnoses that support the diagnosis of usual or differentiated VIN. VIN NOS: VIN not otherwise specified.

to vulvar SCC within three months were excluded, as these were considered 'missed invasion'. A total number of 1893 patients were available for analyses, including 1826 uVIN patients and 67 dVIN patients.

For each patient with VIN, prior and subsequent pathology reports of vulvar biopsies or excisions were available and when a vulvar SCC occurred more than three months after the first histological diagnosis of VIN, it was scored as malignant progression. In addition, the pathology reports contained all histological reports of biopsies or excisions of the female lower anogenital tract.

2.2. Vulvar SCC

The PALGA database revealed 4648 patients with vulvar carcinoma between 1st January 1992 and 31st December 2005 in the Netherlands. We excluded patients with a non-squamous vulvar carcinoma and patients with the first diagnosis of vulvar SCC diagnosed before 1992 with a recurrent lesion between 1992 and 2005. For all patients, the first report that mentioned vulvar SCC was included. The total number of primary vulvar SCC patients was 2701.

2.3. Population data

Population data in order to calculate European Standardised Rates (ESR) of the Netherlands were obtained from the Database of Statistics Netherlands (http://www.cbs.nl/).

2.4. Statistical analysis

Incidences of both types of VIN and vulvar SCC were calculated per 100.000 person years (ESR). Age was categorised into 15-year strata (15–29, 30–44, 45–59, 60–74, over 75 years of age). Differences between the incidences over time were calculated using the univariate general linear model. Student's *t*-tests were used to compare the mean ages and times to SCC development. A significance level of $p < 0.05$ was chosen.

3. Results

In the study period, 2701 patients were identified with vulvar SCC, 1826 patients with solitary uVIN and 67 patients with solitary dVIN. The median age of patients with uVIN (47.8 years) and dVIN (67.0 years) differed significantly ($p < 0.001$). The median age at the diagnosis of vulvar SCC patients was 70.4 years, which is significantly higher compared to uVIN, but comparable with dVIN.

In order to determine trends in incidence of vulvar SCC, uVIN and dVIN, their incidences over the 14-year study period were calculated (Fig. 2). The incidence of uVIN almost doubled from 1.2/100.000 patients in 1992 to 2.1/100.000 patients in 2005 ($p < 0.001$). The incidence of dVIN increased ninefold from 0.013/100.000 patients to 0.121/100.000 patients ($p = 0.019$). In contrast, the incidence of vulvar SCC remained unchanged from 2.6/100.000 patients in 1992 to 2.5/100.000 patients in 2005 ($p = 0.670$). To determine the age with highest incidence rate of vulvar SCC, uVIN and dVIN, the age specific incidences were calculated (Fig. 3). A gradual and strong increase in vulvar SCC incidence was observed starting at the age of 60. uVIN showed a bimodal peak incidence at the ages of 40–44 and at 75–79. dVIN had the highest prevalence at the ages of 75–79. Of all premalignant lesions, uVIN was diagnosed in 98.9% of all VIN lesions in 1992, which decreased to 94.5% in 2005, despite the overall increase in uVIN incidence (Fig. 2). Conversely, the diagnosis of dVIN increased in this time period to 5.5% of all VIN lesions in 2005, with a significant increase in especially the last three years of the study period.

With the objective to study possible differences in the incidence of malignant progression from VIN to vulvar SCC, the incidence of SCC more than three months after the initial diagnosis of VIN was determined. The overall percentage of uVIN patients subsequently diagnosed with vulvar SCC was 5.7% (104 patients). The risk of a subsequent diagnosis of SCC significantly increased with the age of diagnosis of uVIN, beginning with 2.7% for the age group 15–29 and increasing to 8.5% for the group >75 years of age ($p = 0.005$) (Fig. 4). In addition, the time between diagnosis of uVIN and SCC significantly shortened with increasing age; 50 months for the 15–29 age group and 25 months for the >75 age group (Fig. 5).

Fig. 3 – Age specific incidence for vulvar SCC, u- and dVIN from 1992 to 2005. A gradual and strong increase in vulvar SCC was found. uVIN shows a bimodal peak incidence at the ages of 40–44 and 75–79. dVIN has the highest prevalence at the ages of 75–79. Left y-axis: uVIN and dVIN incidence; right y-axis: vulvar SCC incidence.

The number of dVIN patients that were subsequently diagnosed with SCC was too small to give a trend over a 14-year study period (20 patients) but the overall percentage of dVIN lesions with subsequent diagnosis of SCC was 32.8%. The median time from uVIN towards SCC was 41.4 months (range 3–156 months), whereas the median time from dVIN to SCC was significantly shorter: 22.8 months (range 3–8.4 months) ($p = 0.005$). Thirty percent of all SCCs after the diagnosis of uVIN developed within 1 year of follow-up after the diagnosis of uVIN.

The database contained additional information about previous, concomitant or subsequent intraepithelial neoplasia of the cervix, vagina and/or anus (CIN, VAIN and/or AIN, respectively). Forty-one percent of patients with uVIN had an associated HPV induced lesion of the lower female anogenital tract, comprising cervical, anal and vaginal (pre) neoplasia

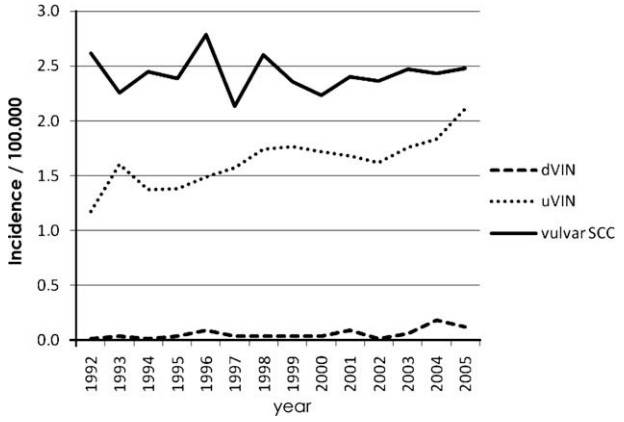

Fig. 2 – Overview of incidence vulvar SCC, uVIN and dVIN for all patients. The incidence of vulvar SCC remained stable, whereas the incidences of both types of VIN increased.

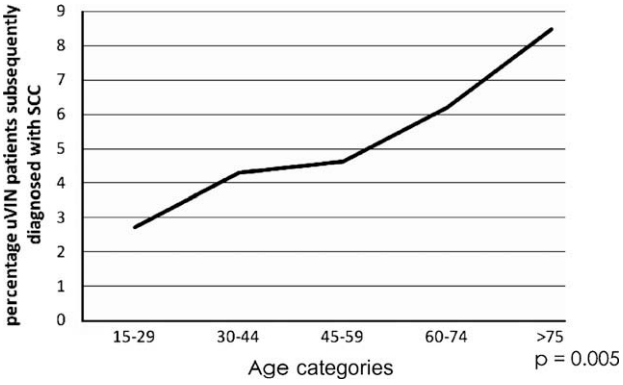

Fig. 4 – Percentage of patients with uVIN who were subsequently diagnosed with vulvar SCC. The percentage of uVIN patients showed a significant increase with age.

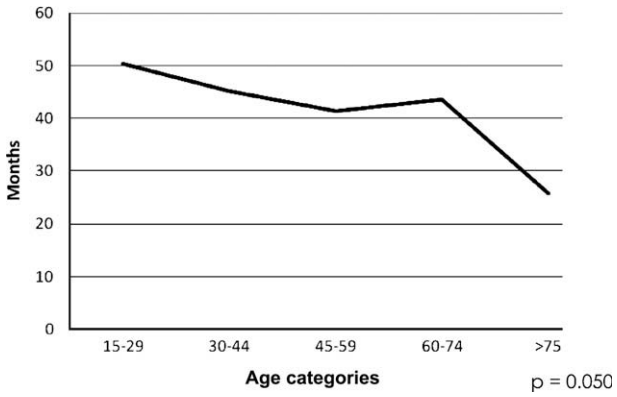

Fig. 5 – Time from usual VIN to vulvar SCC development. The time from uVIN to vulvar SCC significantly decreases with increasing age.

or combinations of those (Table 1). This percentage remained stable from 1992 to 2005. We found that the most common type was a CIN lesion or cervical carcinoma (33.5% of all uVIN patients). In contrast, epithelial abnormalities of the genital tract were observed in only two of the 67 patients diagnosed with dVIN.

4. Discussion

During the 14 year study period, the incidence of uVIN and dVIN increased significantly, while the incidence of vulvar SCC remained stable. In the recent years, vulvar premalignant lesions have gained more public awareness, and a more liberal use of biopsies may have led to the observed increase in incidence worldwide.[1,14,16–19] Increased awareness not only contributes to the doubling in uVIN diagnoses, but also it may result in the removal of these lesions at an early stage of disease before these become invasive. In addition, the malignant potential of uVIN lesions is considered to be low: about 3–5% of all uVIN patients progress towards SCC,[13–15] and is in line with our data (5.7%).

Other studies reported impressive increases in uVIN incidence up to 400% increase.[1,14,16–18] Some of those also reported an increase in vulvar SCC in young patients,[16,17,21–23] but in this study incidence of vulvar SCC under the age of 44 remained stable. There are several differences between these previous publications and this study. First, we excluded recurrent VIN lesions; in addition, we excluded patients with a VIN lesion that developed into a vulvar SCC within three months, because it is most likely that the diagnosis of (micro) invasive SCC was missed. Furthermore, we used a different statistical method; the above-mentioned studies mostly studied two cohorts and compared them with a χ^2 test. Our data give an overview of the trends over a 14-year-period, and we have calculated whether there was an increase or decrease over those years. Finally, the incidence of HPV related lesions of the lower female genital tract may not show an increase as found in several other countries, possibly due to a limited increase in HPV prevalence. For example, the incidence of adenocarcinoma *in situ* lesions of the cervix has not increased in the Netherlands, which is in contrast with the incidence in the United States of America (USA).[27]

The overall percentage of dVIN patients subsequently diagnosed with vulvar SCC was 32.8%, which was significantly higher compared to uVIN patients (5.7%). Furthermore, the time period between diagnosis of VIN and SCC was significantly shorter for dVIN than for uVIN patients (22.8 compared to 42 months). dVIN is a recently recognised, and difficult to diagnose lesion due to the high degree of cellular differentiation, absence of widespread architectural disarray, nuclear pleomorphism and diffuse atypia.[28] Default from the assumption that about 75% of the vulvar SCCs is HPV unrelated (2075 SCCs in this study) and has dVIN as premalignant lesion (67 solitary dVIN lesions in this study), the incidence of solitary dVIN may be extremely underreported. This may be explained by the fact that dVIN as a solitary lesion, or even adjacent to SCC, may be easily mistaken for benign dermatosis or epithelial hyperplasia.[6] It is thought that dVIN has a short intraepithelial period and a rapid progression towards SCC, and therefore is less likely to be found without the presence of a carcinoma.[7–9] The percentage of dVIN patients later diagnosed with vulvar SCC (32.8%) would probably be even higher and the time to SCC would be shorter when invasion within three months after dVIN were included. It is unlikely that dVIN is a new lesion that somehow developed in the past few years. We presume that of all lesions previously diagnosed as benign dermatosis or epithelial hyperplasia, a large proportion would currently be diagnosed as dVIN. As such, trends in increased incidence of dVIN in the past years are merely a reflection of increased diagnosis of dVIN as a newly described entity rather than a truly increased incidence. Currently, well-defined histopathological features and immunohistological staining exist to recognise dVIN more easily.[6,9,28,29] This is reflected in the increased diagnosis of dVIN as a solitary lesion in the last three years of the study. A large study on the incidence of dVIN either as a solitary lesion or adjacent to SCC is needed to elucidate this point.

Table 1 – Overview of prevalence of previous, concomitant or subsequent multicentric HPV-associated intraepithelial neoplasia or invasive carcinomas.

	VAIN	AIN	AIN + VAIN	CIN	CIN, AIN	CIN, AIN, VAIN	CIN, VAIN	No multicentric HPV-associated lesion
1826 uVIN	45 (2.5%)	89 (4.9%)	7 (0.4%)	471 (25.8%)	93 (5.1%)	10 (0.6%)	37 (2.0%)	1074
67 dVIN	2 (2.9%)	0	0	0	0	0	0	65

A bimodal peak incidence of uVIN incidence was observed at 40–44 and 75–79 years of age (Fig. 3). As the incidence of SCC strongly increases with age, the time from uVIN to vulvar SCC is much longer for the patients aged 40–44 than for patients aged 75–59. For uVIN patients, we found that the percentage of uVIN patients that are subsequently diagnosed with vulvar SCC increased with the age of uVIN diagnosis. In addition, the time from uVIN towards the diagnosis of SCC was significantly shorter for patients in the older age group. This has not been described before but is in line with two reports on the recurrence of CIN after treatment.[30,31] This finding may possibly be explained by altered immunity for elderly women compared to younger women. In young women, uVIN may reflect the immaturity of the immune system and a hindered elimination of HPV. In older women uVIN may reflect a failure of the immune system to suppress HPV resulting in recurrent uVIN lesions and possibly vulvar SCC. In their review, van Seters and colleagues found that the patients with uVIN who were subsequently diagnosed with SCC often had immunosuppressant treatment,[15] which is supportive for a role for the immune system. Another explanation may be that older women are less likely to perform self examination of the vulvar region than younger women.

Forty-one percent of uVIN patients had a past, concomitant or future HPV-associated lesion of the female lower anogenital tract, whereas dVIN patients hardly presented these types of lesions. In two other reports, percentages of 53%[12] and 67%[11] were found, which are higher than those reported in this study. In contrast to the study of Hampl and colleagues[12] we did not include vulvar condylomas as an associated HPV induced vulvar lesion. Vulvar condylomas are merely caused by low-risk HPV 6 and 11, which is in contrast to the high-risk HPV types that are associated with uVIN, CIN, VAIN and AIN. As a result, the malignant potential of vulvar condylomas is thought to be negligible. CIN lesions were the most frequently found associated lesions, which is not unexpected as in the Netherlands women aged 30–60 years are screened for cervical abnormalities every five years. The majority of HPV-associated lesions of the female lower genital tract may be prevented by the current HPV 16–18 vaccines that have been introduced recently and implemented in national vaccination programmes, as the majority of these HPV lesions are caused by these HPV types. The multicentricity of the HPV induced lesions argues to examine the entire lower female genital tract for possible HPV induced lesions, once a lesion is found.

In conclusion, this study has demonstrated that an increase in both types of VIN has not led to an increase in the incidence of vulvar SCC. In addition, dVIN lesions are rarely seen as a solitary lesion, but are diagnosed more often in the last years of the study, most likely as a result of recently established histopathological criteria. The malignant potential of dVIN is higher than that for uVIN. For uVIN, the malignant potential increases with age.

Conflict of interest statement

None declared.

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