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Vulvar intraepithelial neoplasia: Incidence and long-term risk of vulvar squamous cell carcinoma

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Abstract

The risk of vulvar squamous cell carcinoma (VSCC) in patients with high-grade vulvar intraepithelial neoplasia (VIN) is considered lower in high-grade squamous intraepithelial lesion (HSIL) compared to differentiated VIN (dVIN), but studies are limited. Our study investigated both the incidence of high-grade VIN and the cumulative incidence of VSCC in patients with HSIL and dVIN separately. A database of women diagnosed with high-grade VIN between 1991 and 2011 was constructed with data from the Dutch Pathology Registry (PALGA). The European standardized incidence rate (ESR) and VSCC risk were calculated, stratified for HSIL and dVIN. The effects of type of VIN (HSIL vs dVIN), age and lichen sclerosis (LS) were estimated by Cox regression. In total, 1148 patients were diagnosed with high-grade VIN between 1991 and 2011. Between 1991-1995 and 2006-2011, the ESR of HSIL increased from 2.39 (per 100 000 woman-years) to 3.26 and the ESR of dVIN increased from 0.02 to 0.08. The 10-year cumulative VSCC risk was 10.3%; 9.7% for HSIL and 50.0% for dVIN (log rank $P < .001$). Type of VIN, age and presence of LS were independent risk factors for progression to VSCC, with hazard ratios of 3.0 (95% confidence interval [CI] 1.3-7.1), 2.3 (95% CI 1.5-3.4) and 3.1 (95% CI 1.8-5.3), respectively. The incidence of high-grade VIN is rising. Because of the high cancer risk in patients with dVIN, better identification and timely recognition are urgently needed.

KEYWORDS
dVIN, HSIL, incidence, vulvar intraepithelial neoplasia, vulvar squamous cell carcinoma

1 | INTRODUCTION

Vulvar squamous cell carcinoma (VSCC) accounts for more than 90% of all vulvar cancers.[1] The etiology of these tumors is recognized to be diverse.[2,3] About 15% to 25% of the VSCCs are induced by high-risk human papillomavirus (HPV), whereas the majority of VSCCs are HPV-negative and associated with lichen sclerosus (LS).[4-8]

VSCC develops from precursor lesions, covered by the term high-grade vulvar intraepithelial neoplasia (VIN). The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) terminology of vulvar squamous intraepithelial lesions classifies high-grade VIN into high-grade squamous intraepithelial lesion (HSIL) and differentiated VIN (dVIN).[9] Studies have shown that most patients with high-grade VIN are diagnosed with HSIL, and in 75% to 85% of HSIL lesions HPV positivity has been demonstrated.[4,8,10] On the contrary, dVIN is only diagnosed in a small subset of patients with

Abbreviations: CI, confidence interval; dVIN, differentiated VIN; ESR, European Standardized Rate; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; ISSVD, International Society for the Study of Vulvovaginal Disease; LS, lichen sclerosus; PALGA, nationwide network and registry of histopathology and cytopathology in the Netherlands; SIL, Squamous Intraepithelial Lesion; uVIN, usual VIN; VIN, vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma; WHO, World Health Organization.

high-grade VIN, is independent of HPV and is associated with the presence of LS.

In our study, we aimed to estimate (a) the incidence of high-grade VIN diagnosed between 1991 and 2011 in the Netherlands, and (b) the long-term VSCC incidence in patients with high-grade VIN, stratified for HSIL and dVIN.

What's New?

High-grade squamous intraepithelial lesions (HSILs) and differentiated vulvar intraepithelial neoplasia (dVIN) are established risk factors for vulvar squamous cell carcinoma. Lesions classified as dVIN are less common than HSILs but potentially more aggressive. Our study, based on investigation of more than 1100 patients diagnosed with high-grade VIN between 1991 and 2011, demonstrates a rising incidence of both HSIL and dVIN. Ten-year cumulative risk of vulvar cancer was significantly greater for dVIN than HSIL. The findings highlight the importance of timely identification and classification of dVIN precancerous lesions and a potential need for risk stratification to prevent overtreatment in HSIL patients.

2 | MATERIALS AND METHODS

2.1 | Study design, data collection and study population

For our study, women diagnosed with high-grade VIN were selected from a historical cohort. Detailed characteristics of this historical cohort have been described previously.[11] In short, a database was constructed with data from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA), which reached nationwide coverage in 1991. All vulvar pathology reports of patients with a diagnosis of LS, VIN and/or VSCC diagnosed up to June 2011 were collected. To obtain a dataset reflecting a representative set of the Dutch female population, pathology data of all laboratories in the provinces Noord-Holland and Flevoland were selected, because these laboratories supply the regional collaborating hospital network, including referral centers and the three centers of gynecologic oncology in Amsterdam. The provinces Noord-Holland and Flevoland are situated in the northwest of the Netherlands and represented 17.4% to 18.7% of the female population in the Netherlands between 1991 and 2011.[12] Since nationwide coverage of PALGA was obtained in 1991, only patients with incident high-grade VIN diagnosed thereafter were included in our study. From this cohort, additional follow-up data up to 2018 were collected. All 18 604 pathology reports were reviewed to categorize the pathology results. Patients with high-grade VIN were excluded from the analyses when they had a history of VSCC.

2.2 | Classification of high-grade VIN

All high-grade VIN cases were classified into HSIL or dVIN, based on the diagnosis in the pathology report and according to the 2015 ISSVD terminology. HSIL was termed "vulvar intraepithelial neoplasia usual type" (uVIN) in the 2004 ISSVD terminology, "squamous intraepithelial lesion" (SIL) in the 1994 World Health Organization (WHO) terminology and "VIN2" or "VIN3" in the 1989 WHO terminology. Therefore, HSIL included the following diagnosis: usual type of VIN, morbus Bowen, bowenoid papulosis, erythroplasia of Queyrat, VIN2, VIN3, high-grade VIN (not otherwise specified) and carcinoma in situ. DVIN included, in addition to dVIN, also vulvar dystrophy with atypia and simplex VIN.

2.3 | Presence of LS

Histopathological diagnoses LS and possible LS were both categorized as LS, as previously described.[11] Possible LS included cases with interface dermatitis that could fit with an early phase of LS. Only biopsy proven (possible) vulvar LS reported prior to the diagnosis of high-grade VIN or within an interval of 3 months after incident VIN diagnosis, was included.

2.4 | Statistical analysis

2.4.1 | Incidence of high-grade VIN

The crude incidence rate of high-grade VIN was calculated from the number of patients diagnosed with high-grade VIN. The total number of woman-years was calculated from the female population in Noord-Holland and Flevoland (retrieved from Statistics Netherlands).[12] The European Standard Population (2013) was used to calculate the European Standardized Rate (ESR). Calendar year at time of diagnosis was stratified into the periods 1991-1995, 1996-2000, 2001-2005 and 2006-2011. Because a subgroup of patients with high-grade VIN was diagnosed with concurrent VSCC, analyses were performed with and without cases with concurrent VSCC. High-grade VIN with concurrent VSCC was defined as a diagnosis of VSCC within 3 months from VIN diagnosis.

2.4.2 | Risk of VSCC in patients with VIN

The incidence rate of VSCC per 100 000 woman-years at risk was calculated among patients with high-grade VIN without concurrent VSCC. The Kaplan-Meier method was used to adjust for censoring. Follow-up time was calculated from the date of the first histological diagnosis of high-grade VIN to the date of the first histological diagnosis of VSCC. Patients who did not develop VSCC had an end date set equal to the earliest date of either their expected date of death or the date of data extraction from PALGA. The expected date of death was retrieved from age-dependent life expectancy tables of Statistics Netherlands at the time of the last vulvar pathology report.[12]

Differences between Kaplan-Meier curves were evaluated by log-rank tests. Multiple Cox regression analyses and Wald tests were

performed to assess the effects of multiple risk factors. Median age in different strata were compared by Mann-Whitney *U* or Kruskal-Wallis Tests. The level of statistical significance was set at .05. Statistical analysis was performed using IBM SPSS Statistics software for Windows version 24.0 (IBM Corporation, Armonk, NY).

3 | RESULTS

3.1 | Characteristics of the study population

The baseline characteristics of the study population are presented in Table 1. Between 1991 and 2011, 1148 patients were diagnosed with incident high-grade VIN, comprising 1116 (97.2%) patients with HSIL and 32 (2.8%) patients with dVIN.

Biopsy proven LS was present in 112/1148 (9.8%) patients with high-grade VIN. LS was more common in patients with dVIN (14/32; 43.8%) than in patients with HSIL (98/1116; 8.8%, $P < .001$).

Concurrent VSCC was seen in 254 (22.1%) patients with high-grade VIN and was more often seen in patients with dVIN (62.5%) than in patients with HSIL (21.0%, $P < .001$).

The total number of patients diagnosed with high-grade VIN increased by calendar period, from 188 incident cases between 1991 and 1995 to 385 incident cases between 2006 and 2010. The number of newly diagnosed patients increased between 1991-1995 and 2006-2010 from 187 to 367 for HSIL and from 1 to 18 patients for dVIN.

Median age at time of high-grade VIN diagnosis was 49.8 years and ranged from 16.1 to 95.4 years. The median age was significantly higher in patients with dVIN (70.3 years) compared to patients with HSIL (49.2 years, $P < .001$), as well as in patients with concurrent VSCC (68.7 years) compared to patients without concurrent VSCC (45.7 years, $P < .001$). Median age at time of high-grade VIN diagnosis increased by calendar period, from 44.9 years between 1991 and 1995 to 53.2 years between 2006 and 2011 ($P < .001$).

TABLE 1 Baseline characteristics of the study population

	n	%	Age, median (range)	*P*
High-grade VIN	1148	100	49.8 (16.1-95.4)	
HSIL	1116	97.2	49.2 (16.1-95.4)	
dVIN	32	2.8	70.3 (40.3-85.3)	<.001
Lichen sclerosus				
No	1036	90.2	48.3 (17.4-95.4)	
Yes	112	9.8	68.5 (16.1-91.5)	<.001
Concurrent VSCC				
No	894	77.9	45.7 (16.3-92.3)	
Yes	254	22.1	68.7 (30.0-95.4)	<.001
Period				
1991-1995	188	16.4	44.9 (16.1-92.5)	
1996-2000	247	21.5	45.2 (17.8-91.5)	
2001-2005	296	25.8	49.7 (19.6-93.9)	
2006-2011	417	36.3	53.2 (20.3-95.4)	<.001

Abbreviations: dVIN, differentiated VIN; HSIL, high grade squamous intraepithelial lesion; VIN, high-grade vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma.

3.2 | Incidence of high-grade VIN

The crude incidence rates of high-grade VIN with and without concurrent VSCC in relation to age are shown in Figure 1. The incidence rate of high-grade VIN without concurrent VSCC showed a peak of 5.1 per 100 000 woman-years between the age of 35 and 40 (Figure 1A, continuous line). The incidence of patients with high-grade VIN including patients with concurrent VSCC, showed a peak incidence of 7.6 between the age of 85 and 89 (Figure 1A, interrupted line).

Stratification for HSIL and dVIN (Figure 1B) revealed that incidence rates of HSIL were very similar to those of high-grade VIN, reflecting the large overlap between the two groups. In contrast, the incidence rates of dVIN had a different pattern, with a disease onset after the age of 50 years and with most women diagnosed with concurrent VSCC (Figure 2B).

The ESRs and crude incidence rates of high-grade VIN with and without concurrent VSCC are displayed in Table 2A,B, respectively. Overall, the ESR of high-grade VIN without concurrent VSCC was 2.99 per 100 000 woman-years; 2.95 for HSIL and 0.05 for dVIN (Table 2B). The ESR increased from 2.41 in period 1991-1995 to 3.33 in period 2006-2011 (+38.2%); from 2.39 to 3.26 (+36.4%) for HSIL and from 0.02 to 0.08 (+300.0%) for dVIN. The ESR of high-grade VIN including concurrent VSCC was 3.97 per 100 000 woman-years; 3.85 for HSIL and 0.13 for dVIN (Table 2A). The ESR increased from 2.87 in period 1991-1995 to 4.75 in period 2006-2011 (+65.5%); from 2.87 to 4.46 (+55.4%) for HSIL and from 0.02 to 0.28 (+1300.0%) for dVIN.

3.3 | Incidence of VSCC in patients with high-grade VIN

To analyze the incidence rate of VSCC in patients with high-grade VIN, 254 patients with concurrent VSCC were excluded from the analysis. The remaining 894 patients had a median follow-up time of 13.9 years (range, 0.3-27.4 years), with a total of 12 435 woman-years available for analyses. The incidence rate of VSCC was 861 per 100 000 woman-years. During follow-up, 107/894 (12.0%) patients were diagnosed with incident VSCC; 100/882 (11.3%) patients with HSIL and 7/12 (58.3%) patients with dVIN. Median progression time to VSCC was 4.0 years (ranging from 0.3 to 24.2 years) after high-grade VIN diagnosis; 4.1 years for HSIL and 1.4 years for dVIN, which was not significant ($P = .449$).

The cumulative incidence of VSCC is shown in Figure 2. In patients with high-grade VIN, the cumulative VSCC incidence after 27.4 years was 15.7% (95% confidence interval [CI], 12.0%-19.4%). The cumulative VSCC incidence increased rapidly the first 5 years and

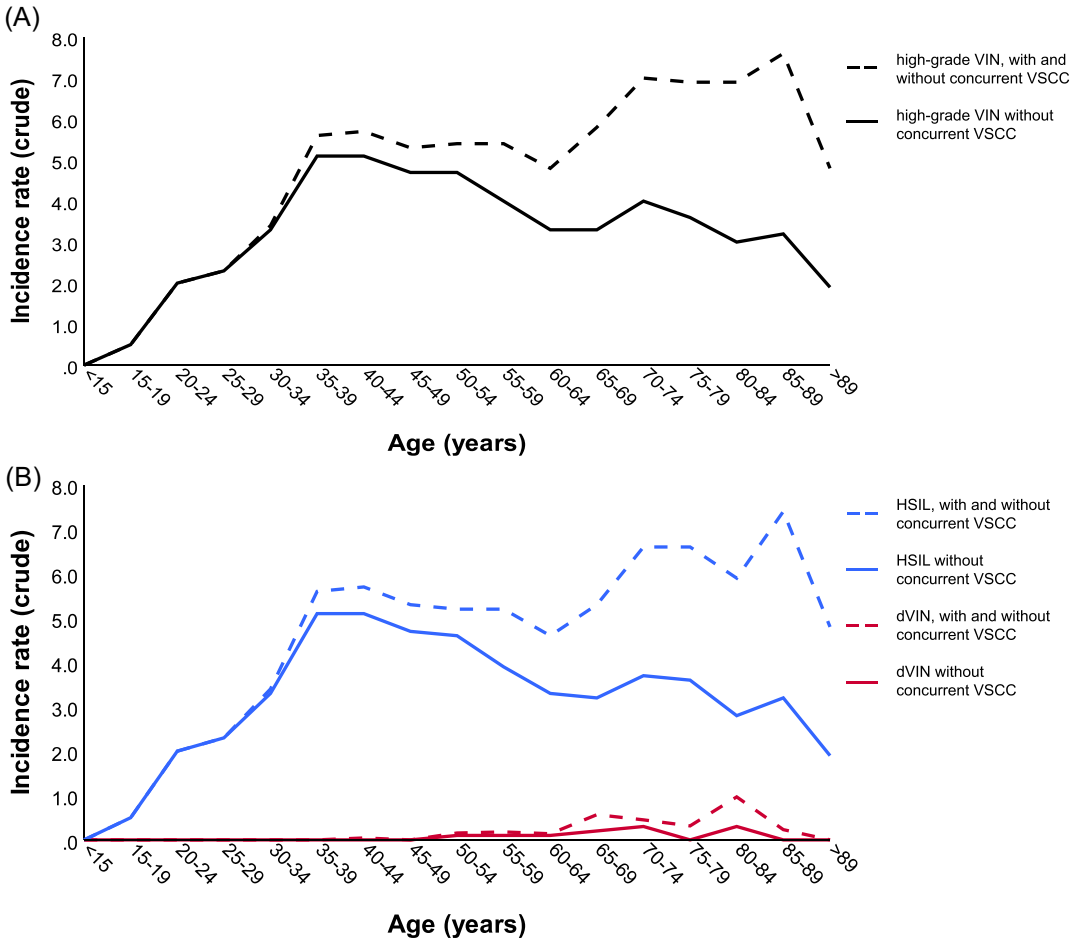
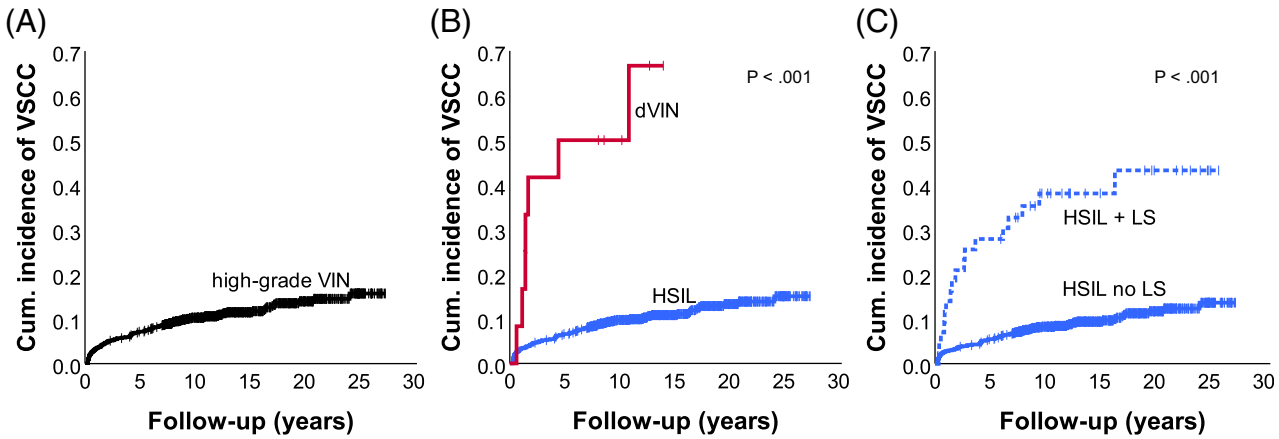


FIGURE 1 A, All high-grade VIN. B, high-grade VIN stratified for HSIL (blue line) and dVIN (red line). Interrupted lines represent VIN, both with and without concurrent VSCC. Continuous lines include VIN without concurrent VSCC. dVIN, differentiated VIN; HSIL, high-grade squamous intraepithelial lesion; VIN, vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma [Color figure can be viewed at wileyonlinelibrary.com]



Cum. incidence of VSCC (%)	7.2	10.3	11.5	140	15.7	
Remaining cases	894	824	630	367	184	46

dVIN	50.0	50.0	66.7*			
HSIL	6.6	9.7	10.8	13.3	15.1	
dVIN	12	6	4	0*		
HSIL	882	818	626	367	184	46

HSIL + LS	27.9	38.1	38.1	43.3	43.3	
HSIL no LS	5.5	8.3	9.4	11.7	13.6	
HSIL + LS	43	31	20	13	9	2
HSIL no LS	839	787	606	354	175	44

FIGURE 2 A, All high-grade VIN. B, High-grade VIN stratified for HSIL (blue line) and dVIN (red line). C, HSIL stratified for presence of LS (interrupted line) and absence of LS (continuous line). *after 14 years of follow-up. dVIN, differentiated VIN; HSIL, high grade squamous intraepithelial lesion; LS, lichen sclerosus; VSCC, vulvar squamous cell carcinoma [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 European standardized rate (ESR) and crude incidence rate of high-grade vulvar intraepithelial neoplasia (VIN) per 100 000 woman-years between 1991 and 2011

Age (years)	′91-′11	′91-′95	′96-′00	′01-′05	′06-′11	′91-′11	′91-′95	′96-′00	′01-′05	′06-′11	′91-′11	′91-′95	′96-′00	′01-′05	′06-′11
A	High-grade VIN (n = 1148)					HSIL					dVIN				
<30	0.89	0.93	0.94	0.94	0.77	0.89	0.93	0.94	0.94	0.77	0.00	0.00	0.00	0.00	0.00
30-49	5.01	4.00	5.25	5.25	5.36	5.00	4.05	5.25	5.21	5.33	0.01	0.00	0.00	0.04	0.00
50-69	5.33	3.38	4.17	5.53	7.09	5.09	3.29	4.17	5.34	6.57	0.24	0.08	0.00	0.19	0.52
≥70	6.92	4.69	5.83	7.40	9.08	6.46	4.69	5.71	6.91	8.00	0.47	0.00	0.12	0.49	1.07
All ages															
Incidence crude	3.77	2.75	3.49	4.00	4.54	3.70	2.70	3.50	3.90	4.30	0.11	0.02	0.01	0.11	0.24
Incidence ESR	3.97	2.87	3.65	4.20	4.75	3.85	2.87	3.63	4.07	4.46	0.13	0.02	0.02	0.13	0.28
B	High-grade VIN (n = 894)					HSIL					dVIN				
<30	0.89	0.93	0.94	0.94	0.77	0.89	0.93	0.94	0.94	0.77	0.00	0.00	0.00	0.00	0.00
30-49	4.53	3.91	4.85	4.53	4.72	4.52	3.91	4.85	4.49	4.72	0.01	0.00	0.00	0.04	0.00
50-69	3.92	2.49	3.44	4.05	4.96	3.82	2.41	3.44	3.93	4.82	0.10	0.08	0.00	0.13	0.14
≥70	3.45	3.12	2.23	4.12	4.10	3.30	3.12	2.23	3.88	3.81	0.15	0.00	0.00	0.24	0.29
All ages															
Incidence crude	2.93	2.38	2.81	3.09	3.30	2.90	2.40	2.80	3.00	3.20	0.04	0.02	0.00	0.07	0.07
Incidence ESR	2.99	2.41	2.84	3.16	3.33	2.95	2.39	2.84	3.08	3.26	0.05	0.02	0.00	0.08	0.08

Note: A. High-grade VIN, total group with and without concurrent VSCC. B. High-grade VIN without concurrent VSCC.

TABLE 3 Prognostic factors for vulvar squamous cell carcinoma (VSCC) in women with high-grade vulvar intraepithelial neoplasia (VIN)

	Univariate analysis High-grade VIN				HSIL				dVIN				Multivariate analysis High-grade VIN			
	n	HR	(95% CI)	*P*	n	HR	(95% CI)	*P*	n	HR	(95% CI)	*P*	n	HR	(95% CI)	*P*
Type of VIN																
HSIL	882	1.0											882	1.0		
dVIN	12	8.2	3.8-17.7	**<.001**									12	3.0	1.3-7.1	**.013**
Age (years)																
<50	530	1.0			529	1.0			1	1.0			530	1.0		
≥50	364	2.3	1.5-3.4	**<.001**	353	2.5	1.7-3.8	**<.001**	11	3.3	0.0-3.5[10]	.146	364	2.3	1.5-3.4	**<.001**
Lichen sclerosus																
No	845	1.0			839	1.0			6	1.0			845	1.0		
Yes	49	5.2	3.2-8.4	**<.001**	43	4.8	2.9-8.1	**<.001**	6	1.2	0.3-5.6	.782	49	3.1	1.8-5.3	**<.001**
Period																
1991-1995	162	1.0			161	1.0			1	1.0			162	1.0		
1996-2000	199	0.7	0.4-1.2	.205	199	0.7	0.4-1.3	.252	0	—			199	0.8	0.5-1.4	.394
2001-2005	229	0.7	0.4-1.3	.288	224	0.7	0.4-1.2	.198	5	0.0	0.1-9.6	.981	229	0.8	0.4-1.3	.328
2006-2011	304	0.8	0.5-1.3	.342	198	0.7	0.4-1.3	.260	6	0.0	0.1-10.9	.999	304	0.8	0.4-1.3	.336

Note: Cox regression analysis was performed to calculate the hazard ratio (HR) and 95% confidence interval (CI). Adjustments were made for all factors in the table. Statistical significance is presented in bold.

more or less linear thereafter (Figure 2A); after 5 years the cumulative incidence was 7.2% (95% CI, 5.4%-9.0%), after 10 years 10.3% (95% CI, 8.3%-12.3%), after 15 years 11.5% (95% CI, 9.3%-13.7%) and after 20 years 14.0% (95% CI, 11.3%-16.7%).

In patients with dVIN, the 10-year cumulative VSCC incidence was much higher (50.0%; 95% CI, 21.8%-78.2%) than in patients with HSIL (9.7%; 95% CI, 7.7%-11.7%), $P < .001$, Figure 2B). Patients with HSIL and LS had a significantly higher 10-year cumulative VSCC incidence compared to patients with HSIL without LS, respectively 38.1% (95% CI, 23.2%-53.0%) vs 8.3% (95% CI, 6.3-10.3, log rank $P < .001$, Figure 2C).

Univariate Cox regression analysis of type of high-grade VIN, age at time of VIN diagnosis, LS and calendar period showed that type of VIN, age and LS were independent risk factors for VSCC (Table 3). Patients with dVIN had a 8.2 times higher cancer risk than patients with HSIL. Patients with an age of 50 years or older at time of VIN diagnosis had a 2.3 times higher cancer risk than patients under the age of 50 years, and patients with LS had a 5.2 times higher cancer risk than patients without LS. Corrected for all variables in the multivariate cox regression analysis, the variables type of VIN, age and LS remained independent risk factors for VSCC (Table 3), with hazard ratios of respectively 3.0, 2.3 and 3.1.

4 | DISCUSSION

In this unique, large series of patients with high-grade VIN, we observed an increased incidence over time and a 10-year cumulative vulvar cancer risk of 10.3%, which was highly dependent on type of VIN, presence of LS and age at diagnosis. Our study on 1148 women with high-grade VIN demonstrated a much higher cancer risk of 50.0% in patients with dVIN compared to a risk of 9.7% in patients with HSIL after 10 years of follow-up.

Studies on the vulvar cancer risk in patients with VIN are scarce. A 5-year cumulative cancer risk of 0% was found in one study, including only 18 patients with HSIL.[13] Absolute cancer risks have been reported slightly more often, ranging 2.3% to 6.6% after an average follow-up time of 3 years.[14-21] Consistent with these findings, we found a 5-year cumulative cancer risk of 6.6% and an absolute cancer risk of 5.7% after 3 years in our series of 882 patients with HSIL. The stable vulvar cancer risk over time found in our study, makes life-long surveillance of patients with HSIL necessary. Of note, the reported cancer cases reflect outcome after treatment, meaning that the risk of invasive cancer in patients with untreated VIN is likely to be higher.

While dVIN is considered to be more aggressive than HSIL, cancer risks have been assessed only in a limited number of studies.[13,19,22,23] Consistent with the aggressive nature of dVIN, we found an absolute cancer risk of 58% in 12 patients with dVIN after 14 years of follow-up. In another small series of seven patients with dVIN, an absolute cancer risk of 86% after 6 years was reported.[13] A larger study including 67 patients with dVIN found an absolute cancer risk of 33% after 14 years of follow-up.[19] However, in this latter study, dVIN also included patients with high-grade VIN in combination with LS or a negative HPV test result.[19] This definition of dVIN might bias the results as the occurrence of high-grade VIN and LS can coexist independently. The aggressive nature of dVIN might be explained by a relative short intraepithelial phase before progression to invasive carcinoma. This is supported by our study in which the interval to

carcinoma was 1.4 years for dVIN and 4.1 years for HSIL, although this difference was not statistically significant. The malignant potential of dVIN was also reflected by the high number of patients with dVIN presenting with concurrent VSCC, which was 62.5%, compared to 21.0% in patients with HSIL.

In our study, only 32 (2.8%) of all 1148 high-grade VIN cases were reported as dVIN, which is consistent with the low prevalence described by others.[19,24] Because dVIN is often difficult to recognize for patients as well as for clinicians, including pathologists, it may partly explain why so few patients have been diagnosed with dVIN.[23,25,26] Signs of dVIN can be variable and often subtle, leading to misdiagnoses and inadequate clinical care due to diagnostic delay, especially in centers with limited exposure to this rare disease.[27-29] It has been shown that dVIN was missed in 42% of biopsies initially diagnosed as LS in a series of patients who developed VSCC.[30] The current classification dividing high-grade VIN into HSIL and dVIN is morphology-based rather than biologically defined, but not all HPV-independent VIN have a dVIN morphology.[31-33] HPV status of the VIN lesions was not systematically examined during regular care in our study cohort. Consequently, the influence of HPV status on the clinical course could not be adequately investigated. Additional studies are needed to investigate whether a biologically defined classification in HPV-induced and HPV-independent VIN with the use of both morphology and laboratory tests can lead to better categorization of patients with high-grade VIN.

In addition to type of VIN, presence of LS and higher age also proved to be important risk factors for vulvar cancer development in our study. Altered immunity could explain the higher incidence of VSCC in patients with VIN and LS and in elderly patients with VIN, although it has never been confirmed that vulvar LS is an autoimmune condition.[34,35] Furthermore, longer-standing, untreated VIN lesions at time of diagnosis in older patients could account for the high cancer risk in this patient group. Interestingly, we noted an incidence of LS of 8.8% in patients with vulvar HSIL, which is high compared to the estimated incidence of 1.5% to 2.5% in the general or gynecologic population.[11,36,37] Dysregulated immunity could be a possible explanation for the coexistence of LS and HSIL. Alternatively, patients with HSIL and LS might in fact have HPV-independent high-grade VIN with the same aggressive course as dVIN. Further research investigating detailed information of clinicopathological aspects, including HPV status, is needed to clarify the relationship between HSIL and LS.

In our study, we observed an incidence of high-grade VIN of 3.8 per 100 000 women-years, which corresponds to incidences reported in the literature (ie, 0.23 to 5.0 per 100 000 woman-years).[38-40] Also in line with others, we observed an increased incidence of +38.2% in our 20-year study period.[15,40] There are several plausible explanations for the rising incidence of high-grade VIN. First, aging of the population could have led to more VIN diagnoses in elderly patients. This is supported by the increased incidence of high-grade VIN in older age groups as observed in our study cohort. Second, an increased burden of HPV-related disease could have contributed to the rising incidence of VIN.[38-40] Of note, as VIN was diagnosed in our study cohort in the pre-vaccination era, no effect of HPV vaccination was expected. However, with second generation HPV vaccination, virtually all cases of vulvar HSIL are potentially preventable in the coming decades.[41-43] Third, vulvar pathology has gained more public and clinical awareness, which subsequently could have led to more clinical visits and vulvar biopsies in patients with VIN.[44]

One of the strengths of our study is the large study size of 1148 patients with VIN, which is a high number given the rarity of the disease. Consequently, we were able to study HSIL and dVIN separately, thereby providing new evidence that HSIL and dVIN are two distinct disease entities. Second, selection bias of our study cohort was limited by the use of data covering a well-identified region, instead of the use of institutional data, making our study results representative for the general population. Lastly, accurate long-term cancer risk in patients with VIN could be estimated because long-term follow-up data up to 27.4 years were available.

Our study also has some limitations. Our results are primarily based on reported long-term pathology data without additional revision of the pathology slides. Since the classification of VIN has been changed over time and awareness of the dVIN entity was limited in the early study period, revision of the pathology slides could have resulted in more accurate categorization into HSIL and dVIN. In addition, limited clinical data were available. Only information on biopsy proven LS was available, thereby missing clinically diagnosed LS. Alternatively, LS might have been underreported when co-existing next to dVIN tissue.

In conclusion, high-grade VIN is a heterogeneous disease comprising two different disease entities, with a rising incidence. An alarmingly higher cancer risk and shorter interval to cancer was found in patients with dVIN compared to patients with HSIL. Earlier and more adequate identification of these precursor lesions with high cancer risk is therefore of utmost importance. In contrast to dVIN, the cancer risk of HSIL is relatively low, except for when LS is present. Hence, patients with HSIL could benefit from risk stratification to reduce overtreatment. Molecular biomarkers that could identify dVIN at an early stage and that could cancer risk stratify HSIL are therefore highly needed.[45,46]

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CONFLICT OF INTEREST

Renske Steenbergen is minority shareholder of Self-screen B.V., a spin-off company of VUmc. Self-screen holds patents related to the detection of HPV-induced cancers issued.

Nikki Thuijs, Marc van Beurden, Annette Bruggink, Hans Berkhof and Maaike Bleeker declare no conflicts of interest.

ETHICS STATEMENT

The local Medical Ethics Committee confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study.

DATA AVAILABILITY STATEMENT

Data can be made available upon reasonable request.

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