Risk of Development of Vulvar Cancer in Women With Lichen Sclerosus or Lichen Planus: A Systematic Review

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Objective: Vulvar lichen sclerosus (VLS) and possibly vulvar lichen planus (VLP) are associated with an increased vulvar cancer (VC) risk. We analyzed the risk of VC and its precursors after a diagnosis of VLS or VLP.

Materials and Methods: A search was performed to identify articles describing the development of vulvar neoplasia in women with VLS or VLP. This systematic review was registered with the PROSPERO database.

Results: Fourteen studies on VLS included 14,030 women without a history of vulvar neoplasia. Vulvar cancer, differentiated vulvar intraepithelial neoplasia (dVIN), and vulvar high-grade squamous intraepithelial lesion occurred in 2.2% (314/14,030), 1.2% (50/4,175), and 0.4% (2/460), respectively. Considering women with previous or current VC, the rate was 4.0% (580/14,372). In one study, dVIN preceded VC in 52.0% of the cases. Progression of dVIN to VC was 18.1% (2/11).

The risk was significantly higher in the first 1–3 years after a biopsy of VLS and with advancing age; it significantly decreased with ultrapotent topical steroid use.

For the 14,268 women with VLP (8 studies), the rates of VC, dVIN, and vulvar high-grade squamous intraepithelial lesion were 0.3% (38/14,268), 2.5% (17/689), and 1.4% (10/711), respectively.

Conclusions: Vulvar lichen sclerosus is associated with an increased risk of VC, especially in the presence of dVIN and with advancing age. Ultrapotent topical steroids seem to reduce this risk. An increased risk of developing VC has been suggested for VLP. Hence, treatment and regular life-long follow-up should be offered to women with VLS or VLP.

Key Words: lichen sclerosus, lichen planus, vulvar cancer, vulvar intraepithelial neoplasia, HSIL, steroids, clobetasol propionate

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Women have a one in 232–333 chance of developing vulvar cancer (VC) during their lifetime, and the cancer is derived from 2 pathways: vulvar high-grade squamous intraepithelial lesion (HSIL) associated with human papillomavirus (HPV) infection, and differentiated vulvar intraepithelial neoplasia (dVIN) associated with vulvar dermatosis, the latter being the cause of 75% of the cases.[1–6] Vulvar HSIL is commonly more frequent than dVIN. The latter represents less than 10% of all VIN diagnosis,[7] but the risk of progression to invasion is much higher for dVIN. Thuijs et al.[8] showed a 10-year cumulative VC risk of 10.3% in women with VIN: 9.7% for HSIL and 50.0% for dVIN.

Vulvar lichen sclerosus (VLS) and lichen planus (VLP) are T-cell–mediated inflammatory dermatoses. Vulvar lichen planus may involve the extragenital skin as well as the vagina and may be associated with an increased risk of oral cancer.[9,10] Extragenital involvement by VLS is less common (<20%) and that of the vagina is rare.[11,12]

Vulvar lichen sclerosus has been associated with an increased risk of VC, estimated at approximately 5%.[13] More recently, a possible relationship between VLP and VC has also been suggested. However, it remains debatable whether dVIN develops in a field of VLP or if other pathways may explain a possible increased risk of VC in these women.[14] The use of ultrapotent topical steroids is the first-line treatment for both VLS and VLP and is believed to reduce the risk of VC in women with VLS; however, because the risk of cancer in VLP is unknown, the impact of dermatosis treatment on cancer development is likewise unknown.

The magnitude of risk is largely unknown; for instance, an Italian study published in 1995, which included 211 women with VLS, out of which 3 developed VC, estimated a relative risk of nearly 250 compared with the general female population.[15] More recently, in Finland, the standardized incidence ratio (SIR) of VC in women with VLS was of 33.6 (95% CI, 28.9–38.6).[16] This gray area is even more significant when we add to the equation the role and risk of dVIN—the true precursor lesion of VC associated with vulvar dermatoses. Although the risk is well established, given the rarity and the complexity of the clinical and histological diagnosis, much is still unknown regarding its natural history.[17]

Knowing the true risk of development of VIN and VC in women with VLS or VLP can help in the planning of strategies for the diagnosis, treatment, and follow-up of the affected women, as well as in the design of awareness strategies. While the HPV vaccine is already showing a significant reduction in the number of cases of cervical cancer, the impact on VC will be lower, as most cases arise in the context of VLS rather than because of HPV infection.[7]

The objectives of this systematic review were (1) to assess the risk of VC and precursors arising in VLS and VLP and (2) to explore factors associated with the development of neoplasia.

METHODS

A literature search was conducted using several databases (PubMed, PubMed Central, Google Scholar, Cochrane, Embase, and clinicaltrials.gov) using the search strings ([lichen sclerosus] OR [lichen sclerosis] OR [lichen planus]) AND ([cancer] OR [carcinoma] OR [vulvar intraepithelial neoplasia] OR [VIN] OR [HSIL] OR [high-grade squamous intraepithelial neoplasia]) from January 1985 to June 2021, with language restricted to English, Spanish, Italian, French, and Portuguese. Only studies on humans were considered. The study protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews[18] and registered in the PROSPERO database (CRD42021257096).

The abstracts retrieved were checked for eligibility (first by title and then by abstract) by 2 of the authors; those that passed this initial screening were fully evaluated to assess eligibility for inclusion in the final analysis. Letters, book chapters, guidelines, congress presentations, case reports, and reviews were not included but were checked for additional sources. The available figures

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were used to calculate the overall rate of development of new lesions during follow-up.

It was not possible to evaluate statistical heterogeneity using the Cochrane χ^2, the τ^2, and/or the I^2 because there were not at least 3 articles reporting the same outcome.

The lack of standardized core outcome settings precluded the performance of the meta-analysis. This has been a common problem when meta-analyses are attempted for vulvar dermatoses. Using cancer SIR as the outcome is an option, but we evaluated other outcomes as well.[19]

Because of the nature of the study, institutional review board approval was not considered necessary.

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RESULTS

Of the 416 studies initially selected (231 after the exclusion of duplicates), 22 were considered for the analytic synthesis: 14 on VLS[1,15,16,20–30] and 8 on VLP[10,31–37] (see Figure 1).

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The 14 studies selected concerning VLS involved 14,372 women, with ages ranging from less than 2 to 95 years (see Table 1). Some studies included women with a previous or current VC, representing 342 women. The definition of current VC was variable, with some authors excluding women who were diagnosed up to 3 months[1] or 6 months[30] after the initial diagnosis. The follow-up time for women varied between 1 and 331 months. The reported median follow-up time ranged between 20 months and 9.4 years. The overall rate of preexisting, diagnosed at enrollment, or diagnosed during follow-up VC was 4.0% (580/14,372).

When considering women who developed VC during follow-up, the average rate was 2.2% (314/14,030), ranging from 0% to 2.7% in different studies. There was no trend with this rate over the years, but Bleeker et al.[1] found a 100% increase in risk between 1991 and 2011. In one study, it was concluded that VLS does not increase the risk of development of VC.[20] Jones et al.[23] did not find a relationship between VC risk and presence or duration of symptoms, or vulvar structural changes. An increased incidence with age was shown in 2 studies; in one study, age greater than 70 years was a significant risk factor,[1,28] whereas in 2 study, it was shown that the likelihood of a diagnosis of VC was higher in the first[16] to third year[30] after the diagnosis of VLS.

Combining the 4 studies that evaluated or reported on the development of dVIN, the rate was 1.2% (50/4,175). In one study, dVIN preceded VC in 52.0% of cases[1]; 18.1% (2/11) of dVIN progressed to VC.[22,29] Two studies reported the development of vulvar HSIL in women with VLS (0.4% [6/1,442]).[28,29]

Considering the 7 studies in which the use of clobetasol propionate was mentioned, 4 did not discuss its effect in terms of risk

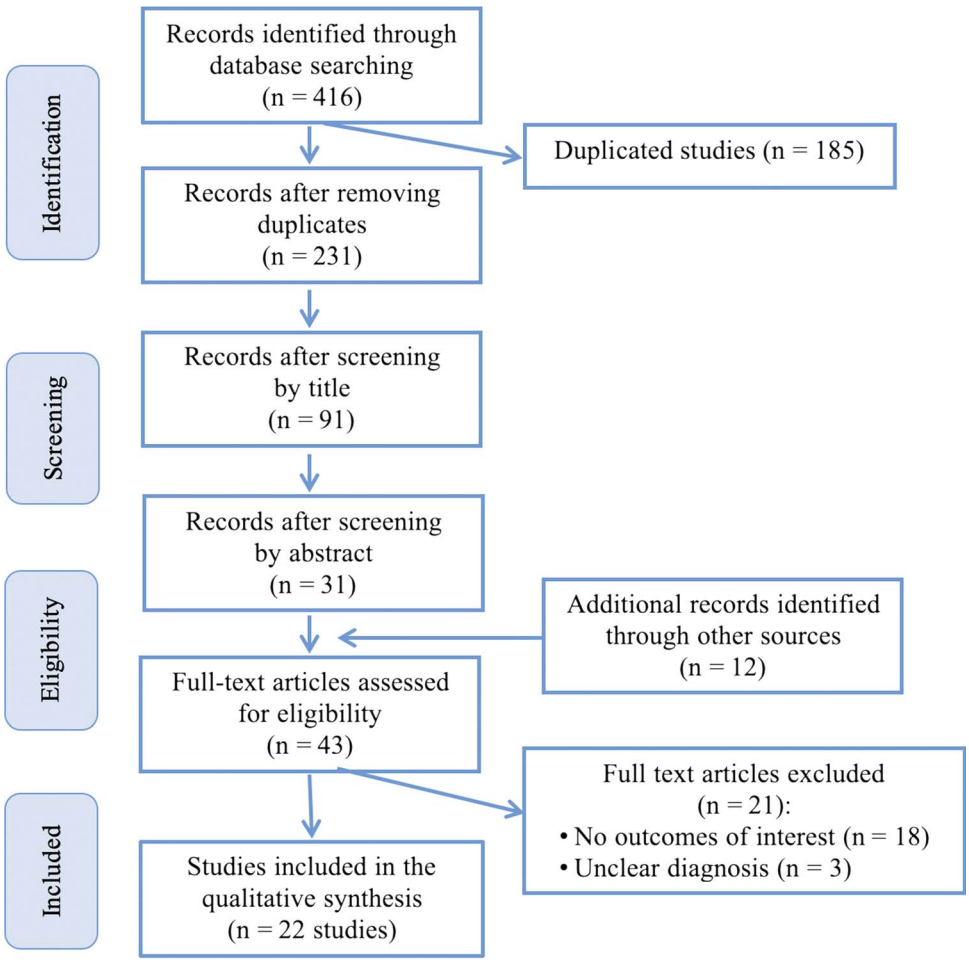

FIGURE 1. Preferred Reporting Items for Systematic Reviews.

TABLE 1. Studies Included in the Systematic Review Involving Women With VLS

Study	Location and period of study Aim of the study Type of study	LS participants Age Follow-up Diagnostic criteria Treatments	Women who developed VC or VIN	Calculated rates
Hart et al.[20] (1975)	Washington, United States Objective: to determine the malignant potential of VLS Retrospective	$N = 92$ (enrolled 107; 5 with VC at enrollment, 1 with CIS, 9 without follow-up information) Age = 4–82 y (median = 47 y) Median follow-up = 9.4 y (1 mo–22 y) Histological	VC $n = 1$ (after 12 y of follow-up)	–Rate of new VC: 1.1% (1/92) –Overall rate of VC: 4.7% (6/98)
Carli et al.[15] (1995)	Firenze, Italy 1982–1994 Objective: to analyze the risk of VC on VLS lesions Prospective cohort	$N = 211$ Mean age = 59.6 ± 12.6 y (range = 25.3–87.6 y) Median follow-up = 20 [8–42] mo (maximum = 147 mo) Histological Clobetasol (132/211, after 1989), testosterone (79/211),	VC $n = 3$ Age: 71, 71.8, 73.4 y Time to invasion: 1,085, 1,736, 1,763 d >3 y of follow-up Age: 73.4 y	–Rate of new VC: 1.4% (3/211)
Diakomanolis et al.[21] (2002)	Athens, Greece 1997–2000 Objective: to evaluate the efficacy and safety of the regular use of clobetasol in postmenopausal women with severe VLS Prospective cohort, single center	Screened for enrolment: 137 Included: $N = 54$ (group 1, women using clobetasol as required for control of symptoms; group 2, regular use of clobetasol) Postmenopausal women Mean age = 60.2 y (range = 43–81 y) Follow-up of 12 mo Clinical and/or histological Previous VC or VIN excluded	VC $n = 0$	–Rate of new VC: 0% (0/54) –Overall rate of VC: 2.2% (3/137)
Cooper et al.[22] (2004)	Oxfordshire, United Kingdom 10-y period Objective: To record the clinical features, symptomatic response to topical steroids, and resolution of clinical signs in a cohort of female patients with VLS Retrospective	$N = 327$ (74 girls [diagnosis <16 y], 253 women) Mean age (women) = 63.8 y (range = 39–82 y) Mean time of follow-up = 66 mo (range = 4–350 mo) Clinical (girls) and/or histological (women) Ultrapotent topical steroids in 208/253 women (50% of girls and 89% of women)	VC $n = 7$ dVIN $n = 5$ (1 case progressed to VC) Mean age of VC = 63.8 y (range = 39–82 y) Mean duration of vulvar symptoms before diagnosis of VC = 30.8 y (range = 0–44 y) Delay in diagnosis of LS in women with VC: 15.3 (vs. 4.4 y)	–Rate of new VC: 2.1% (7/327, 2.8 [6/253] if children excluded)
Jones et al.[23] (2004)	Auckland, New Zealand 1992–2000 Objective: to identify clinical factors that might identify women with VLS who are at increased risk of developing VC Retrospective case-control	$N = 249$ (including a control group with VC [46]) Control group (VLS) $n = 213$; mean age = 63 y; 48% using ultrapotent steroids VC group (and VLS) at enrolment $n = 46$; mean age = 75 y; 45% using ultrapotent steroids Follow-up = up to 8 y Clinical and/or histological (97%)	VC (control group) $n = 1$	–Rate of new VC: 0.5% (1/213) –Overall rate of VC: 18.9% (47/249, cases of VC selected for control)
Renaud-Vilmer et al.[24] (2004)	St Cloud, France 1981–2001 Objective: to analyze the rates of remission, recurrence, and chronic evolution of VLS treated with clobetasol and determine whether this treatment can decrease the risk of malignant evolution Prospective cohort, single center	$N = 77$ (enrolled 83, 6 with VC) Mean age = 59.4 y (range = 30–92 y) Median time of follow-up = 4.7 y (2 mo–19 y) Histological Clobetasol (previous use was criterion of exclusion)	VC $n = 2$	–Rate of new VC: 2.6% (2/77) –Overall rate of VC: 9.6% (8/83)
Naswa and Marfatia et al.[25] (2015)	New Delhi, India Objective: to assess the usefulness of a physician-administered clinical scoring system for the clinical diagnosis and evaluation of VLS Cohort	$N = 35$ (enrolled 36, 1 with VC) Previously untreated Mean age = 56.4 y Mean time of follow-up = 12 mo Clinical and/or histological	VC $n = 0$	–Rate of new VC: 0% (0/35) –Overall rate of VC: 2.8% (1/36)

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TABLE 1. *(Continued)*

Study	Location and period of study Aim of the study Type of study	LS participants Age Follow-up Diagnostic criteria Treatments	Women who developed VC or VIN	Calculated rates
Challenor[26] (2015)	Plymouth, United Kingdom Dec 1, 2012–Nov 30, 2013 Objective: to review the characteristics and care of the cohort of women with VLS Retrospective	*N* = 273 Mean age = 61 y (range = 14–94) Clinical and/or histological (78/273) Topical steroids 242/273, testosterone 4/273, surgery 13/273, no treatment 7/273	VC *n* = 6 Age = 72, 73, 47, 49, 69, 52 y	–Rate of new VC: 2.2% (6/273)
Lee et al.[27] (2015)	Sydney, Australia Jan 2, 2008–Sep 26, 2014 Prospective cohort, single center Objective: To determine the impact of long-term topical corticosteroid in VLS (induction and maintenance of skin texture and color, risk of VC, symptoms, function, and preservation of vulvar architecture, and adverse effects of treatment)	*N* = 507 Mean age (presentation) = 55.4 y (range = 18–86 y) Mean time of follow-up = 4.7 y (range = 2–6.8 y) Control group (noncompliant with topical steroid use) *n* = 150 Intervention group (compliant) *n* = 357 Histological	Control group: VC = 3 and dVIN = 4 Age: 57.8 y (range = 29–76 y) Intervention group VC = 0	–Rate of new VC (overall): 0.6% (3/507) –Rate of new VC (compliant): 0% (0/357) –Rate of new VC (noncompliant): 2.0% (3/150)
Micheletti et al.[28] (2016)	Torino, Italy Nov 1981–Jul 2014 Retrospective Objective: to estimate the neoplastic potential of VLS	*N* = 976 Mean age (diagnosis) = 60 y (range = 8–91 y) Mean time of follow-up = 52 mo (range = 1–331 mo) Clinical (546) and/or histological (430) Cases with cancer at first visit excluded (no. cases not reported)	VC *n* = 26 dVIN = 4 Vulvar HSIL = 4	–Rate of new VC: 2.7% (26/976)
Bleeker et al.[1] (2016)	Amsterdam, the Netherlands 1991–2011 Retrospective Objective: to estimate the incidence of VLS and VC risk in lichen sclerosus women	*N* = 2,875 Mean age = 59.8 (1.6–95.4) y (range = 1.6–95.4 y) Histological (extracted from the Dutch Pathology Registry) Women with previous VC or in <3 mo after the diagnosis of VLS excluded (*n* = 163)	VC *n* = 75 (in 39 preceded by dVIN) Mean time between the first biopsy of LS and VC = 3.3 y (range = 0.27–18.4 y)	–Rate of VC (overall) = 7.8% (238/3,038) –Rate of VC (new) = 2.6% (75/2,875)
Halonen et al.[16] (2017)	Helsinki, Finland 1970–2012 Retrospective Objective: to estimate the risk of different malignancies among women with VLS	*N* = 7,616 Mean follow-up = 8.8 y Histological (extracted from Finnish Hospital Discharge Registry and crossed with the Finnish Cancer Registry data)	VC *n* = 182	–Rate of VC (new): 2.4% (182/7,616)
Meani et al.[29] (2019)	Victoria, Australia Jul 2012–Apr 2016 Retrospective Objective: to determine the incidence of VIN and VC	*N* = 466 (38 excluded because of VIN/VC at enrolment [not specified]) Clinical and/or histological	VC *n* = 1 (age = 77 y, preceded by dVIN) dVIN *n* = 2 (age = 56, 62 y) HSIL *n* = 2 (age = 50, 65 y)	–Rate of VIN/VC (overall): 8.5% (43/504) –Rate of VC (new): 0.2% (1/466)
Corazza et al.[30] (2019)	Ferrara, Italy 1995–2011 Retrospective Objective: to assess the risk of VC development in a cohort of women with VLS in the province of Ferrara, Northern Italy	*N* = 308 Histological (data crossed with the Ferrara Cancer Registry) Women with <6 y between the diagnosis of LS and VC excluded	VC *n* = 7	–Rate of VC (new): 2.3% (7/308)

CIS indicates carcinoma in situ; RR, relative risk.

reduction for the development of cancer.[21–23,26] One did not find benefit,[15] 1 concluded that there is a possible benefit,[24] and 2 considered it effective.[27,29] There was a general agreement that long-term use of topical steroids is safe and improves the symptoms associated with VLS.[15,21,22,24,26,27]

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The 8 studies on VLP included 14,268 women (13,100 from one study[36]), of which 38 (0.3%) developed VC; this rate ranged between 0.1% and 2.3% (see Table 2). The age of the included women ranged between 17 and 90 years, and the follow-up period

TABLE 2. Studies Included in the Systematic Review Involving Women With VLP

Author	Location and period of study Aim of the study	LP participants, age, follow-up Diagnostic criteria	Women who developed cancer	Calculated rates
Kirtschig et al.[31] (2005)	Oxford, United Kingdom 1997–2000 Retrospective Objective: to investigate the course of vulvar VLP, its response do treatments and associated laboratory features	*N* = 44 Clinical (19) and/or histological (25) Topical ultrapotent steroids 44/44	VC *n* = 1 Age = 55 y	–Rate of VC (new): 2.3% (1/44)
Kennedy et al.[32] (2008)	Iowa, United States Jan 1995–Dec 2002 Retrospective Objective: to determine the occurrence of cancer in women after a diagnosis of vulvar erosive VLP	*N* = 113 Mean age = 50 y (range = 19–81 y) Mean time of follow-up = 5 y Clinical and/or histological	VC *n* = 1 Age = 37 y	–Rate of VC (new): 0.9% (1/113)
Santgoets et al.[33] (2010)	Rotterdam, the Netherlands Retrospective May 1995–Dec 2002	*N* = 95 Median age = 55 y (range = 24–80) Most treated with topical steroids; systemic treatment not used Histological (72 [75.8%], cases with typical clinical presentation, despite a nondiagnostic biopsy were included)	VC *n* = 2	–Rate of VC (new): 2.1% (2/95)
Regauer et al.[34] (2016)	Graz, Austria 2004–2016 (?) Retrospective Objective: to report about the diagnostic and therapeutic challenges of HPV-induced squamous intraepithelial lesion in patients with VLP	*N* = 584 Follow-up = 2 mo–20 y	VC *n* = 10 (1 preceded by HSIL [age = 54 y] and 9 by dVIN) HSIL *n* = 7 (age = 23, 39, 50, 54, 61, 66, 60 y) dVIN *n* = 16	–Rate of VC (new): 1.7% (10/584)
Fahy et al.[35] (2017)	Rochester, United States Jan 1997–Dec 2015 Retrospective Objective: to review clinical presentation and treatment of patients who received a diagnosis of VLP	*N* = 100 Mean age = 60.3 ± 12.3 y Mean follow-up = 24 mo (range = 1–165 mo) All treated with topical steroids (different potencies) Histological	VC *n* = 2 VIN (in situ squamous cell carcinoma) *n* = 1	–Rate of VC (new): 2.0% (2/100) –Rate of "VIN" (new): 1.0% (1/100)
Halonen et al.[36] (2018)	Helsinki, Finland 1969–2012 Retrospective Objective: to estimate the risk of different cancers among women previously diagnosed for VLP	*N* = 13,100 Histological (extracted from Finnish Hospital Discharge Registry and crossed with the Finnish Cancer Registry data)	VC *n* = 18	–Rate of VC (new): 0.1% (18/13,100)
Kherlopian et al.[10] (2020)	Sydney, Australia Jan 2018–Dec 2019 Objective: to characterize the prevalence of vulvar malignancy in a population of patients with biopsy-proven VLP	*N* = 105 Mean age = 60.6 ± 1.3 y Mean time of follow-up = 36.3 ± 3.4 mo Histological All treated with topical steroids (some also with other options)	VC *n* = 2 (at 19 and 24 mo of follow-up, age = 76 and 79 y) dVIN *n* = 1 (at 5 mo of follow-up, age = 66 y)	–Rate of VC (new): 1.9% (2/105) –Rate of dVIN (new): 0.9% (1/105)
Lyra et al.[37] (2021)	Porto, Portugal Jan 2008–Dec 2018 Retrospective Objective: to assess the risk of VC and precursors in a cohort of women with vulvar VLP	*N* = 127 Mean age = 59.0 ± 2.9 y (range = 17–90 y) Mean time of follow-up = 3.9 ± 0.5 y (range = 1–11 y) Clinical (108/127) and/or histological (19/127) Topical ultrapotent steroids 112/127, calcineurin inhibitors 10/127, retinoids 2/127, systemic steroids 1/127, methotrexate 4/127, surgery 1/127	VC *n* = 2 (preceded by vulvar HSIL, age = 65 and 74 y) HSIL *n* = 3	–Rate of VC (new): 1.6% (2/127)

CIS indicates carcinoma in situ.

ranged from 2 months to 20 years. One large study involving national databases reported a 0.1% (18/13,100) rate of VC in women with VLP and concluded that they had an increased risk for VC (SIR = 1.99 [1.18–3.13]).[36]

The development rate of dVIN was reported in 2 studies; the combined rate was 2.5% (17/689).[10,34] Vulvar HSIL detection was reported in 2 studies, yielding a combined rate of 1.4% (10/711). In one study, the development of "in situ squamous cell carcinoma" without further specification was reported in 1 of 100 women.[35] In another study, the diagnosis of VC was preceded by that of dVIN (9/10 cases) and HSIL (1/10 cases).[34] In yet another publication, the 2 cases of VC that developed during follow-up were preceded by vulvar HSIL.[37] The development of dVIN or VC was systematically associated with severe treatment-resistant disease in one study (2 cases of VC and 1 case of dVIN).[10]

DISCUSSION

These studies confirm an increased risk of VC in women with VLS, and it is suggested for those with VLP. In those with VLS, there was a peak of increased risk in the first 1–3 years after the diagnosis. The risk increased with age. Treatment with ultrapotent topical steroids seems to reduce VC risk and control symptoms. Women with a diagnosis dVIN have an increased risk for VC, but it is an uncommonly diagnosed lesion. Treatment and regular life-long follow-up of women with VLS and VLP are recommended, regardless of their symptoms or anatomical changes.

The life-long risk of VC in the general population is less than 0.5%. In this systematic review, the risk of *de novo* development of VC in women with VLS was 2.2%; the realistic risk must be higher, as these women were usually not followed up on for the rest of their lives. When women with previous or current VC were considered, in which a 4.0% risk was calculated, it remained a poor estimate because in many studies, we could not determine how many had the condition and studies were not clear about when the patients developed VC, the etiologies, and whether all included cancers are squamous. It is not clear whether comorbid VLS/VLP cases were excluded. It was also difficult to compare data from different study types. The follow-up data were inadequate. The larger studies, based on databases, included only cases confirmed by biopsy, whereas the diagnosis is often clinical; therefore, even these studies do not provide a definite answer.[1]

The preinvasive lesion associated with VLS is dVIN,[17] which is usually associated with TP53 gene mutation. Vulvar HSIL is HPV positive and p16 positive in approximately 95%, while dVIN is usually HPV and p16 negative, and usually p53 positive. There are 3 types of p53 staining patterns—wild type, basal overexpressed, and null. In these studies, the number of reported dVIN cases was low, possibly because of the failure in diagnosis by clinicians and/or pathologists, inadequate localization of biopsy sites, different histological classifications, and, probably, a short latency time to invasion.[13,17,33,38] It is likely that with proper education and awareness of women with vulvar dermatoses, they will seek care when they notice changes, symptoms worsen, change, or stop responding to treatment, thus increasing the diagnosis of VIN. Increased physicians awareness will lead to use of immunohistochemistry and specific criteria for biopsy, so that the diagnosis will be made more often. Nearly all VC cases are associated with either dVIN or HSIL, but detection and treatment of precursors are variable.

In 2 studies, there was a perceived increased risk in the first years after a histological diagnosis of VLS.[16,30] These findings must be considered with caution, as it may be biased: it is possible that a biopsy was performed because of a suspicious lesion, poor control of symptoms, or even cancer-associated symptoms. It is possible that in some cases, dVIN was already present, but missed, because it is challenging (ie, basaloid dVIN) or that it developed and progressed to VC in a short time.[17,38] Some studies have shown that up to one fourth of all VIN may be misclassified.[17]

The use of ultrapotent topical steroids has become the standard treatment for VLS in the last decades, despite different protocols on type and formulation of the steroids used, and treatment duration.[39] A positive effect on symptoms, histology, and occasionally signs[21,22] was observed. Given the currently available data, this treatment should be recommended to all women with VLS, regardless of their symptoms, at least once a week.[40] The growing but unsubstantiated recommendation to replace the use of topical steroids by LASER, stem cells, or platelet-rich plasma should be mitigated, because cancer risk reduction for these approaches has not been shown.[41–43]

There are insufficient data available regarding development of VC in women with VLP. From the few available, we found that the associated risk of developing cancer was lower than that for VLS: 0.3% with VLP and 2.2% with VLS. However, follow-up was very limited. A retrospective case series, in which all lesions were evaluated for the overexpression of p53 and p16, as well as for the presence of HPV, documented that 9 of 10 women with VC had a previous diagnosis of dVIN.[34] In another one, the 3 women with VLP who developed dVIN or VC had poor symptom control and resistance to treatment.[10]

The favorable effect of treatment of VLP by topical steroids on symptoms and of reduction of VC has not yet been substantiated. Although Preti et al.[3] showed an increased risk of relapse of vulvar HSIL after adequate treatment in this population, another study pointed out that all the women who developed dVIN/VC with VLP had severe disease and responded poorly to treatment.[10] While the number of reported cases of vulvar HSIL in this population was small, the recurrent erosions of the vulvar skin, along with the long-term use of topical steroids, may be factors that increase the risk of HPV infection and persistence. However, these women should not be denied adequate topical corticosteroid treatment.[33] Administering HPV vaccination[44] should be considered in the early phase following the detection of the disease, especially in severe disease, which may require systemic immunosuppressants.

In contrast to VLS, it cannot be assumed that adequate treatment of VLP and follow-up significantly decrease the risk of VC. Our findings stress once again that there is a significant risk of VC in women with vulvar dermatoses, although its true magnitude remains unknown. A conservative estimate points to a risk of 5.5 fold if considering only new cases or of 8 fold if women with a previous diagnosis of VC are considered.

This study has several inherent limitations, given the heterogeneity of the protocols and objectives of the studies, diagnostic criteria, and change in histological classification during the last decades. Despite the accepted uniform classification of VC precursor lesions and diagnostic recommendations, established by the International Society for the Study of Vulvovaginal Disease, there are still articles using ambiguous and potentially confusing classifications.[7,38] Most studies failed to distinguish whether VC was associated or not with HPV infection. Vulvar experts usually do not obtain a vulvar biopsy from most cases in clinical practice, so the distinction between VLS and VLP is not always straightforward, especially after treatment. Furthermore, both conditions can be present in the same woman. The follow-up periods were very different across the different studies, and in general, the risk of developing cancer or premalignant lesions is expected to increase with the duration of observation. In the studies in which follow-up time was mentioned, it was usually unknown for how long the woman had VLS/VLP; in most cases, only the date of the diagnosis was known. Some studies included children, which are at a significantly lower risk of developing cancer during the study period. However, data extraction was not accurate in these

studies.[15] Those who attend specialized clinics and undergo biopsies likely have more severe VLS or VLP than those attending community settings. Conclusions could not be made regarding asymptomatic untreated women with VLS or VLP, which are often not diagnosed and thus not followed up in specialized clinics because of the lack of referral.

An effort should be made to stratify the risk of each patient to establish who can safely be discharged for their primary care physician and who can benefit from follow-up in specialized clinics.[8]

CONCLUSIONS

Vulvar lichen sclerosus is associated with an increased risk of VC, which can probably be reduced by the regular and life-long use of ultrapotent topical steroids. Vulvar cancer, dVIN, and vulvar HSIL occurred in 2.2% (314/14,030), 1.2% (50/4,175), and 0.4% (2/460), respectively. The risk seems to increase throughout life and risk factors other than older age, and the presence of VIN could not be identified. Vulvar lichen planus also seems to be associated with an increased risk of VC, but it is still unclear whether it occurs through the pathway of dVIN—the HPV independent pathway, or HSIL—the HPV associated one. Until further data are available, treatment and life-long follow-up must be considered for women with VLP.

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