Lichen Sclerosus: Incidence and Risk of Vulvar Squamous Cell Carcinoma
Maaike C.G. Bleeker1, Pascal J. Visser2, Lucy I.H. Overbeek3, Marc van Beurden4, and Johannes Berkhof5

Abstract

Background: The association between lichen sclerosis and vulvar squamous cell carcinoma (VSCC) has long been recognized, but large epidemiologic studies are lacking.

Methods: Data of women diagnosed with vulvar pathology in the Netherlands were retrieved from the Dutch Pathology Registry. All vulvar pathology reports of this historical cohort were reviewed to construct a research database, including 3,038 women with lichen sclerosis diagnosed between 1991 and 2011. The incidence rate of lichen sclerosis and the cumulative incidence of VSCC among women with lichen sclerosis were estimated.

Results: Between 1991 and 2011, the incidence rate of lichen sclerosis increased from 7.4 to 14.6 per 100,000 woman-years. The median age at time of lichen sclerosis diagnosis was 59.8 years and the cumulative VSCC incidence was 6.7%. The 10-year VSCC incidence in women with lichen sclerosis was associated with concurrent vulvar intraepithelial neoplasia (VIN; 18.8% in women with VIN and 2.8% in women without VIN) and age at time of lichen sclerosis diagnosis (5.9% in women of ≥70 years, 3% in women between 50 and 70 years, and 1.8% in women <50 years). The effects of presence of VIN and age remained significant in adjusted Cox regression analysis.

Conclusion: This historical cohort showed a nearly 100% increase in incidence of lichen sclerosis between 1991 and 2011. Concurrent VIN and age ≥70 years at time of lichen sclerosis diagnosis are important risk factors for vulvar cancer development.

Impact: The incidence of lichen sclerosis is rising and special attention is needed in particular in women with concurrent VIN because of their high risk of cancer. Cancer Epidemiol Biomarkers Prev; 25(8): 1224–30. ©2016 AACR.

Introduction

The incidence rate of vulvar cancer is about 2.4 to 3.4 per 100,000 woman-years and has been rising by 20% to 55% during the past decades (1–6). In the Netherlands, the incidence rate of vulvar cancer increased from 2.2 in 1990 to 3.4 per 100,000 woman-years in 2014 (3). Vulvar squamous cell carcinoma (VSCC) accounts for about 90% of all vulvar cancers (4). Although the etiology of VSCC is not yet fully understood, it is recognized to be heterogeneous. It has been estimated that at least 25% of VSCC can be attributed to infection with human papillomavirus (HPV) while other important risk factors include vulvar inflammatory conditions like lichen sclerosis (7, 8). The rise in the absolute number of vulvar cancer cases has even been more pronounced due to aging of the population.

Attempts to reduce vulvar cancer should focus on adequate recognition and treatment of precursor lesions including lichen sclerosis. High-grade vulvar intraepithelial neoplasia (VIN) is considered as the precursor lesion of VSCC and can be categorized into HPV-induced or usual VIN (uVIN) and HPV-independent or differentiated VIN (dVIN), the latter often being associated with lichen sclerosis. Compared with uVIN, dVIN is not commonly diagnosed as a solitary diagnosis, partly because the clinical presentation is less characteristic than uVIN. In addition, histopathologic features overlap with features that can be seen in reactive disorders with atypia confined to the basal layers resulting in missed diagnoses of dVIN (9). Another possible explanation for the fact that uVIN is more commonly diagnosed than dVIN is that the interval between uVIN and HPV-induced VSCC is thought to be much longer than the interval between dVIN and HPV-independent VSCC (10, 11). It has been conjectured that dVIN can develop from lichen sclerosis and that the presence of both strongly increases the cancer risk. A supportive observation is that both dVIN and lichen sclerosis are observed adjacent to VSCC in 25% to 65% of the cancer cases (12–15). Although the association between lichen sclerosis and VSCC has long been recognized, literature on the incidence of lichen sclerosis is lacking and studies on VSCC risk in women with lichen sclerosis are scant. Our aim was to estimate the incidence of lichen sclerosis and VSCC risk in lichen sclerosis women. Vulvar pathology data were retrieved from the Dutch Pathology Registry to identify an historical cohort of women including 3,038 women diagnosed with lichen sclerosis between 1991 and 2011 in the Netherlands.
Lichen Sclerosus: Incidence and Vulvar Cancer Risk

Materials and Methods

Study design, data collection, and study population

For this study, women diagnosed with lichen sclerosus between 1991 and 2011 were selected from a large historical cohort. All vulvar pathology reports of women with lichen sclerosus, VIN, and/or VSCC diagnosed until June 2011 at one of the 23 pathology laboratories located in the provinces Noord-Holland and Flevoland were reviewed to construct a study database of this historical cohort. The provinces Noord-Holland and Flevoland are situated in the North-West of the Netherlands and comprise about 18% of the Dutch population. The pathology reports were extracted from PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands (in short the Dutch Pathology Registry). Every abstract transferred to histopathology and cytopathology in the Netherlands (in short extracted from PALGA, the nationwide network and registry of about 18% of the Dutch population. The pathology reports were situated in the North-West of the Netherlands and comprise about 18% of the Dutch population. The pathology reports were extracted from PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands (in short the Dutch Pathology Registry). Every abstract transferred to PALGA contains encrypted patient identification data, the conclusion of the pathology report (free text), and a coding system, based on standard pathology terminology, including at least codes for topography (i), type of material (ii) and diagnosis (iii) that are automatically translated to SNOMED codes (16). Only patients with vulvar lichen sclerosus, VIN, and/or VSCC in one of the pathology laboratories within the provinces Noord-Holland and Flevoland were retrieved from PALGA and evaluated for eligibility (see Supplementary Table S1 for specified search terms).

Of these patients, pathology reports of the vulvar region (including the labia majora, labia minora, clitoris, and perianal region) were obtained and for each report the free text of the conclusion was reviewed to categorize the diagnosis correctly. A total of 16,237 pathology reports of 5,697 women were reviewed to categorize women with lichen sclerosus, VIN, and VSCC. As PALGA reached nationwide coverage in 1991, only women with lichen sclerosus diagnosed thereafter were selected for this study. Diagnoses of lichen sclerosus and possible lichen sclerosus were both categorized as lichen sclerosus. Possible lichen sclerosus included cases with interface dermatitis that could fit with an early phase of lichen sclerosus. Women with lichen sclerosus were excluded from the analyses when a history with VSCC was established. It should be noted that a history of VSCC is difficult to establish because lichen sclerosus often remains undiagnosed for a period of time. Therefore, a practical definition of history of VSCC was used, namely that the date at time of the first histologic diagnosis of VSCC was at least 3 months earlier than the date at time of the first histologic diagnosis of lichen sclerosus.

Statistical analysis

Incidence of lichen sclerosus. The crude incidence of lichen sclerosus was calculated from the number of women diagnosed with lichen sclerosus and the total number of woman-years in Noord-Holland/Flevoland (as available at tables of Statistics Netherlands; ref. 17). To calculate the incidence of lichen sclerosus by age, age-specific strata of 5 years were used (0–4 years, 5–9 years etc.). To evaluate the incidence over time, the calendar years were stratified into the periods 1991–1995, 1996–2000, 2001–2005, and 2006–2011. The European Standard Population for women (2013) was used to calculate the European Standardized Rate (ESR).

Risk of VSCC in women with lichen sclerosus. The incidence rate of VSCC per 100,000 woman-years at risk was calculated among women with lichen sclerosus. The Kaplan–Meier method was used to adjust for censoring. The begin date was defined as the date of the first histologic diagnosis of lichen sclerosus and the end date was defined as the date of VSCC diagnosis. For women that did not develop VSCC, the end date was set equal to the earliest date of either the expected date of death at time of the last pathology report or the date of data extraction from the PALGA database (i.e., June 22, 2011). The expected date of death was based on national age-dependent life expectancy tables of Statistics Netherlands at time of the last pathology report (17). When the interval between the diagnoses of lichen sclerosus and VSCC was shorter than 3 months, VSCC was assumed to be prevalent at time of diagnosis lichen sclerosus and these women were excluded in the VSCC risk calculations. Kaplan–Meier analyses were repeated setting this threshold at 6 months. Stratified Kaplan–Meier analyses were performed to examine the effect of VIN at baseline (either VIN present at baseline or VIN not present at baseline) and for age groups at first lichen sclerosus diagnosis (<50 years, 50–70 years, or ≥70 years). Adjusted Cox regression analyses were performed to analyze independency of risk factors.

Median age in different strata was compared by Mann–Whitney tests. The levels of statistical significance were set at 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc.).

Results

Incidence of lichen sclerosus

Between 1991 and 2011, 3,038 women were diagnosed with histology proven lichen sclerosus within the provinces Noord-Holland/Flevoland in the Netherlands. The median age at first lichen sclerosus diagnosis was 59.8 years (range 1.6–95.4 years). Over time, the median age of lichen sclerosus diagnosis remained stable, respectively 60.9, 59.3, 59.3, and 59.9 years in the calendar periods 1991–1995, 1996–2001, 2001–2005, and 2006–2011.

The crude incidence rates and ESRs for lichen sclerosus are presented in Table 1. Between 1991 and 2011, the incidence rate of lichen sclerosus was 10.4 per 100,000 woman-years with the highest incidence rate of 28.6 per 100,000 woman-years achieved between 65–69 years of age. From 1991 to 2011, the incidence rate of lichen sclerosus diagnoses increased from 7.4 to 14.6 per 100,000 woman-years. The ESR showed a similar trend. Between 1991 and 2011, the ESR was 11.9 per 100,000 woman-years: 8.8 in 1991–1995, 9.5 in 1996–2000, 11.5 in 2001–2005, and 16.0 in 2006–2011.

Incidence of VSCC in women with lichen sclerosus

To assess the incidence rate of VSCC in women with lichen sclerosus, 163 women with lichen sclerosus were excluded because of prevalent VSCC (i.e., the interval to VSCC was less than 3 months), leaving 2,875 women and a total of 22,088.9 woman-years available for analyses. In total 75 (2.6%) women developed incident VSCC at a median time of 3.3 years (range 0.27–18.4 years) after the lichen sclerosus diagnosis. The incidence rate of VSCC was 339.9 per 100,000 woman-years of lichen sclerosus.

The cumulative incidence of VSCC in women with lichen sclerosus is presented in Figs. 1 and 2. Kaplan–Meier analyses showed a cumulative incidence of VSCC in women with lichen sclerosus of 2.1% [95% confidence interval (CI), 1.5%–2.7%], 3.3% [95% CI, 2.5%–4.1%], 4.1% [95% CI, 3.2%–5.1%], and 6.7% [95% CI, 4.0%–9.4%] after 5, 10, 15, and 20 years of follow-up, respectively (Fig. 1).
When the threshold for the interval between lichen sclerosus and VSCC was set to 6 months for incident VSCC, results were very similar, that is, 71 of 2,871 (2.5%) developed incident VSCC. Similarly, Kaplan–Meier analyses revealed a cumulative incidence of VSCC in women with lichen sclerosus of 6.6% after 20 years of follow-up.

The 10-year cumulative incidence of VSCC in women with lichen sclerosus was significantly higher in lichen sclerosus women who had concurrent VIN at baseline compared with women without VIN at baseline (18.8%; 95% CI, 9.2%–28.4% and 2.8%; 95% CI, 2.0%–3.6%, respectively, log rank \( P < 0.001; \) Fig. 2A).

Considering only lichen sclerosus women with VIN, the age at first lichen sclerosus diagnosis in women without VSCC (median 59.1 years, range 1.6–95.4) was lower than the age at first lichen sclerosus diagnosis in women with VSCC, including both prevalent and incident cases of VSCC (median 71.0 years, range 30.0–92.3, \( P < 0.001; \) Table 3) or including only women with incident VSCC (median 64.4 years, range 30.0–88.7 years; \( P = 0.004 \)). As VSCC was not observed in women diagnosed with lichen sclerosus under the age of 30 years, analyses were repeated in women of 30 years or older (\( n = 2,648 \)) yielding comparable results.

Considering only lichen sclerosus women with VSCC, the age at first lichen sclerosus diagnosis was higher among women with prevalent VSCC (median 75.0 years, range 34.1–92.3) compared with women with incident VSCC (median 64.4 years, range 30.0–88.7 years; \( P = 0.001 \)). Similarly, the age at VSCC was higher among lichen sclerosus women with prevalent VSCC (median 75.0 years, range 34.6–92.3 years) compared with women with incident VSCC (median 68.8 years, range 34.7–89.5 years; \( P = 0.001 \)).

### Discussion

In this historical cohort, an incidence rate of 10.4 lichen sclerosus cases per 100,000 woman-years was observed between 1991 and 2011. To our knowledge, literature on the incidence of lichen sclerosus in the general population is virtually absent. The best data to reflect our results are described in a lichen sclerosus review published in 1999 by Powell and Wojnarowska who refer to an unpublished study on the incidence of lichen sclerosus in a cohort of 17,000 women with long-term follow-up (18). They describe a positive relation between age and lichen sclerosus and observed an incidence rate of histology proven lichen sclerosus of 14 per 100,000 woman-years in women between the age of 50 to

### Table 1. Incidence rate of lichen sclerosus (LS) per 100,000 woman-years between 1991 and 2011

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>—</td>
<td>—</td>
<td>0.2</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>5–9</td>
<td>0.8</td>
<td>1.4</td>
<td>1.4</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>10–14</td>
<td>0.3</td>
<td>0.3</td>
<td>0.0</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>15–19</td>
<td>0.5</td>
<td>0.0</td>
<td>1.3</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>20–24</td>
<td>1.1</td>
<td>0.9</td>
<td>1.9</td>
<td>3.5</td>
<td>1.9</td>
</tr>
<tr>
<td>25–29</td>
<td>2.6</td>
<td>3.5</td>
<td>4.3</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>&lt;30</td>
<td>1.0</td>
<td>1.2</td>
<td>1.6</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>30–34</td>
<td>3.4</td>
<td>4.5</td>
<td>5.5</td>
<td>5.5</td>
<td>4.7</td>
</tr>
<tr>
<td>35–39</td>
<td>5.2</td>
<td>4.6</td>
<td>4.5</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>40–44</td>
<td>7.2</td>
<td>5.5</td>
<td>6.0</td>
<td>9.8</td>
<td>7.5</td>
</tr>
<tr>
<td>45–49</td>
<td>8.9</td>
<td>9.0</td>
<td>9.3</td>
<td>11.0</td>
<td>9.7</td>
</tr>
<tr>
<td>50–54</td>
<td>6.0</td>
<td>5.8</td>
<td>6.2</td>
<td>8.5</td>
<td>6.7</td>
</tr>
<tr>
<td>55–59</td>
<td>11.7</td>
<td>12.2</td>
<td>18.7</td>
<td>26.3</td>
<td>18.4</td>
</tr>
<tr>
<td>60–64</td>
<td>17.4</td>
<td>24.4</td>
<td>24.4</td>
<td>54.0</td>
<td>26.5</td>
</tr>
<tr>
<td>65–69</td>
<td>18.5</td>
<td>19.4</td>
<td>23.4</td>
<td>41.4</td>
<td>281</td>
</tr>
<tr>
<td>70–74</td>
<td>20.2</td>
<td>21.7</td>
<td>28.2</td>
<td>40.4</td>
<td>28.6</td>
</tr>
<tr>
<td>75–79</td>
<td>20.7</td>
<td>23.6</td>
<td>29.3</td>
<td>34.2</td>
<td>27.2</td>
</tr>
<tr>
<td>80–84</td>
<td>21.1</td>
<td>24.8</td>
<td>23.2</td>
<td>34.9</td>
<td>26.5</td>
</tr>
<tr>
<td>85–89</td>
<td>17.5</td>
<td>17.1</td>
<td>25.1</td>
<td>33.0</td>
<td>24.1</td>
</tr>
<tr>
<td>90–94</td>
<td>12.2</td>
<td>5.1</td>
<td>19.6</td>
<td>23.9</td>
<td>16.2</td>
</tr>
<tr>
<td>&gt;90</td>
<td>9.2</td>
<td>10.5</td>
<td>9.6</td>
<td>5.4</td>
<td>8.3</td>
</tr>
<tr>
<td>All ages crude incidence</td>
<td>7.4</td>
<td>8.1</td>
<td>10.1</td>
<td>14.6</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Lichen sclerosus women with and without VSCC

The age at first lichen sclerosus diagnosis in women without VSCC (median 59.1 years, range 1.6–95.4) was lower than the age at first lichen sclerosus diagnosis in women with VSCC, including both prevalent and incident cases of VSCC (median 71.0 years, range 30.0–92.3, \( P < 0.001; \) Table 3) or including only women with incident VSCC (median 64.4 years, range 30.0–88.7 years; \( P = 0.004 \)). As VSCC was not observed in women diagnosed with lichen sclerosus under the age of 30 years, analyses were repeated in women of 30 years or older (\( n = 2,648 \)) yielding comparable results.

Considering only lichen sclerosus women with VSCC, the age at first lichen sclerosus diagnosis was higher among women with prevalent VSCC (median 75.0 years, range 34.1–92.3) compared with women with incident VSCC (median 64.4 years, range 30.0–88.7 years; \( P = 0.001 \)). Similarly, the age at VSCC was higher among lichen sclerosus women with prevalent VSCC (median 75.0 years, range 34.6–92.3 years) compared with women with incident VSCC (median 68.8 years, range 34.7–89.5 years; \( P = 0.001 \)).
59 years (the oldest age group for which were data available). We found a comparable incidence rate of lichen sclerosus, ranging from 11.7 to 24.4 lichen sclerosus cases per 100,000 woman-years between 50 and 59 years of age in the calendar period up to the year 2000 (thereby excluding our data in the calendar periods after the publication date of this review).

Studies on lichen sclerosus are further complicated as referred patients may be seen by various specialists including dermatologists, gynecologists, urologists, geriatrics, and pediatricians. Estimates in hospital referrals range from 1 to 17 cases of lichen sclerosus per 100,000 patients (18–20). Studying the prevalence of lichen sclerosus in a general gynecology practice, 28 of 1,675 (1.7%) women were diagnosed with lichen sclerosus at a mean age of 52.6 years of whom at least one third were asymptomatic (20). Although most cases of lichen sclerosus present in the genital area (i.e., 85%–96% of the cases) and in women (female to men ratio varies between 10:1 and 6:1; refs. 18, 21), it should be noted that both extragenital and male lichen sclerosus cases were not included in our study.

From 1991 to 2011, the incidence rate of histology-proven lichen sclerosus nearly doubled from 7.4 per 100,000 woman-years between 1991 and 1995 to 14.1 per 100,000 woman-years between 2006 and 2011. This striking increase might be explained by less hesitancy to visit the general practitioner and by an increased biopsy rate during the study period. Of note, patients with clinically diagnosed lichen sclerosus that were not biopsied were not included in our study. This could bias the results in particular in the lowest age groups, as clinicians are more reluctant to biopsy children suspected for lichen sclerosus, not only because of the physical burden of the biopsy procedure but also because of their low cancer risk. This might also affect the median age of lichen sclerosus in the whole study cohort although the median is considered a fairly robust measure of central tendency. A biopsy of a lesion suspected for lichen sclerosus is generally recommended, not only to rule out (pre)malignancy but also to differentiate lichen sclerosus from other vulvar dermatoses (18, 22). Another explanation for possible underestimation of the lichen sclerosus incidence could lie in the possibility that a histology-proven lichen sclerosus might not have been coded as such by pathologists. Instead, codes like inflammation or reactive changes could have been used, resulting in missed cases of lichen sclerosus.

A 20-year VSCC incidence of 6.7% was observed in our historical cohort. An association between lichen sclerosus and VSCC has long been recognized. Carlson and colleagues, reviewed the published literature and reported a pooled proportion of 4.5% (140/3,093) VSCC arising in lichen sclerosus (14). When including only studies of more than 100 lichen sclerosus cases, a pooled proportion of 4.0% was estimated. In comparison, in our study, the proportion of VSCC cases was 2.6% (75/2,875). Most studies included in the review of Carlson were retrospective and case series were often poorly defined. In our study, in all women the diagnosis of lichen sclerosus was histology proven. Moreover, women with lichen sclerosus in whom VSCC was diagnosed within 3 months after the lichen sclerosus diagnosis were excluded in the analyses as we believe that this group represents women with prevalent VSCC that visit a doctor primarily because of cancer and not for complaints of lichen sclerosus. In fact, in 163 of the 238 (68.5%) lichen sclerosus women with VSCC presented with prevalent VSCC. In this latter group, most likely, lichen sclerosus was present prior to VSCC but remained undiagnosed because of lack of serious symptoms and/or lack of patients' need to visit a doctor. Compared with women with prevalent VSCC, the age at lichen sclerosus diagnosis was significant lower in women with incident VSCC. Similarly, the age at VSCC was significantly higher in women with prevalent VSCC compared with women with incident VSCC. To obtain more insight in the clinical relevance of prevalent versus incident VSCCs, further studies are needed, for instance on the association with FIGO stage at the time of VSCC diagnosis.

Of interest is the finding that lichen sclerosus women with concurrent VIN had a 10-year VSCC risk of 18% compared with 3% in lichen sclerosus women without VIN. Although the
sequence of lichen sclerosus-VIN-VSCC could only be established in a minority of lichen sclerosus cases that developed VSCC, this does not necessarily mean that other patients did not progress via VIN. The role of VIN is further supported by the observation that 39 of the 75 women (52%) included in the cancer risk analyses were diagnosed with VIN as well. This proportion is likely to be a conservative estimate due to underreporting of VIN in pathology reports of VSCCs. Of note, studies in which VSCC cases were
Risk factors for cancer development in women with lichen sclerosus remain largely unknown. Unknown clinical aspects include response to therapy (corticosteroids), genetic predisposition, immune status, and smoking. Certain (epi)genetic events in lichen sclerosus might be involved in carcinogenesis but data in literature on this topic are lacking. To summarize, many aspects of HPV-negative vulvar carcinogenesis, sequencing lichen sclerosus-VIN-VSCC, remain unclear because lack of structural studies. As long as clinicopathologic characteristics are not able to stratify lichen sclerosus at high or low risk for VSCC, it seems useful to control women with lichen sclerosus and monitor for alterations within areas affected by lichen sclerosus. Given the higher risk on VSCC, our results implicate that monitoring should be intensified in lichen sclerosus women with concurrent VIN or women at higher age.

Lack of attention for vulvar pathologies in elderly women might explain the decreased incidence of lichen sclerosus after the age of 80 years, as observed in our study. In a study of Leibovitz, who studied 96 women in an elderly nursing home at a mean age of 82 years, one-third of the women had vulvovaginal pathologies and 3% had lichen sclerosus (25). Therefore, special attention in vulvar care might be needed in elderly women, especially when taking into account that the incidence of VSCC is considerably higher in women diagnosed with vulvar lichen sclerosus after an age of 70 years compared with women diagnosed with lichen sclerosus at younger age groups. A higher risk of VSCC in elderly age groups was also found by others (23).

In conclusion, this historic cohort study showed a doubling in lichen sclerosus incidence from 1991 to 2011. The 20 years VSCC risk in women with lichen sclerosus is 6.7% and special attention is needed in lichen sclerosus women with VIN as well as in women diagnosed with lichen sclerosus at younger age groups. A higher risk of VSCC in elderly age groups was also found by others (23).

### Table 2. Prognostic factors for vulvar squamous cell carcinoma (VSCC) in women with lichen sclerosus (LS)

<table>
<thead>
<tr>
<th>Presence of VIN at baseline</th>
<th>Number</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>2,786</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89</td>
<td>7.6 (4.3-13.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

**Table 3. Age at lichen sclerosis (LS) and vulvar squamous cell carcinoma (VSCC) diagnosis**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age at first LS diagnosis</th>
<th>Age at first VSCC diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>LS</td>
<td>3,038</td>
<td>59.8</td>
<td>16-95.4</td>
</tr>
<tr>
<td>Without VSCC</td>
<td>2,800</td>
<td>59.1</td>
<td>16-95.4</td>
</tr>
<tr>
<td>≥30 years</td>
<td>2,648</td>
<td>59.9</td>
<td>30-95.4</td>
</tr>
<tr>
<td>With VSCC</td>
<td>238</td>
<td>71.0</td>
<td>30-92.3</td>
</tr>
<tr>
<td>Prevalent</td>
<td>163</td>
<td>75.0</td>
<td>34-92.3</td>
</tr>
<tr>
<td>Incident</td>
<td>75</td>
<td>88.7</td>
<td>30-92.3</td>
</tr>
</tbody>
</table>

NOTE: Median age of women with LS without VSCC (59.1 or 59.9) versus with VSCC (71.0), P = 0.001 or <0.001. Median age of women with LS with prevalent VSCC (75.0) versus incident VSCC (64.4), P = 0.001. Median age of women with LS without VSCC (59.1 or 59.9) versus incident VSCC (64.4), P = 0.004 or P = 0.0029. Median age of women with incident VSCC (68.8) versus prevalent VSCC (75.0), P = 0.001. Including only women of 30 years and older.
above the age of 70 years as these women have an increased risk for VSCC.

Disclosure of Potential Conflicts of Interest
J. Berkhof is a consultant/advisory board member for Merck, Roche, and GSK. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Conception and design: M.C. Bleeker, L.I.H. Overbeek, M. van Beurden
Development of methodology: M.C. Bleeker, L.I.H. Overbeek, M. van Beurden, J. Berkhof
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.C. Bleeker, P.J. Visser, L.I.H. Overbeek, M. van Beurden
Study supervision: M.C. Bleeker, M. van Beurden

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 15, 2016, revised April 21, 2016; accepted May 11, 2016. Published OnlineFirst June 2, 2016.

References
9. van de Nieuwenhof HP, Bulten J, Hollema H, Dommerholt RG, Massuger LF, van der Zee AG, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions previously diagnosed as lichen sclerosis, which have progressed to vulvar squamous cell carcinoma. Mod Pathol 2011;24:297–305.
Lichen Sclerosus: Incidence and Risk of Vulvar Squamous Cell Carcinoma


Updated version Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-16-0019

Supplementary Material Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2016/06/02/1055-9965.EPI-16-0019.DC1

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/25/8/1224. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.