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Lichen sclerosus and risk of cancer

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Malignant potential of *lichen sclerosus* (LS) has been suspected, but evidence is sparse. We used the population-based Finnish Cancer Registry data to further study this connection.

We identified all women with the diagnosis of LS ($n = 7,616$) listed in the Finnish Hospital Discharge Registry from 1970 to 2012. The cohort was followed through the Finnish Cancer Registry for subsequent cancer diagnoses until 2014. Standardized incidence ratios (SIRs) were calculated for different cancers by dividing the observed numbers of cancers by expected ones. The expected numbers were based on national cancer incidence rates.

During the follow-up period, we found 812 cancers among patients with LS (SIR: 1.13, 95% CI 1.05–1.21). LS was associated with an increased risk of vulvar (182 cases, SIR: 33.6, 95% CI 28.9–38.6) and vaginal cancer (4 cases, SIR: 3.69, 95% CI 1.01–9.44). The risk of cancers of the uterine cervix and lung was significantly decreased.

LS is associated with an increased risk for vulvar and vaginal cancer. These data are important when designing the care of women diagnosed with LS.

Lichen sclerosus (LS) is a chronic disease of the skin. It is an inflammatory condition with an unknown but probably autoimmune etiology. LS mainly affects the skin of the anogenital region, but is also seen on extragenital skin locations in up to 20% of patients with the anogenital disease.[1–4] Of all LS cases, 6–15% are manifested on extragenital locations only.[3,4] There are also case reports of LS affecting the mucosal surface of the oral cavity.[5] Other mucosal sites are usually spared, but there are at least two case reports of the disease affecting the mucosa of vagina.[6,7] The diagnosis of LS can be made clinically, but is often confirmed by histology.

LS is estimated to affect 0.1–0.3% of new patients in a general hospital patient population[4] and 1.7% of patients referred to general gynecological practice.[8] Most patients affected by LS are postmenopausal, but there is also a peak in incidence among prepubertal girls.[2,4,9]

Malignant potential of LS has been suspected. There is an association with vulvar LS and subsequent vulvar squamous cell carcinoma (SCC); the estimated risk of developing vulvar SCC in the areas affected by LS is up to 5%.[1,2,4,10–12] In contrast, extragenital LS does not seem to be associated with malignant transformation.[13,14]

The aim of this study was to estimate the risk of different malignancies among women previously diagnosed for LS. We paid special attention to cancers of the body parts where LS is diagnosed (*i.e.*, genital organs, oral cavity and extragenital skin). In addition, we counted the risk for three of the leading cancers of women among LS patients (*i.e.*, breast, colon and lung cancer).

Material and Methods

In Finland, diagnoses from health care facilities are collected in the Hospital Discharge Register (HDR) (https://www.thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care). All women with an inpatient public or private hospital episode with a primary or secondary diagnosis of LS from 1970 through 2012 were identified in the HDR. We also had the same data from public hospital outpatient care from 1998 until 2012. The women were identified by using unique personal identity codes, and they were included in the cohort from the first available inpatient or outpatient hospital episode with a diagnosis of LS. The LS diagnoses were specified according to the International

Key words: lichen sclerosus, vulvar cancer, cancer risk

Abbreviations: CIN: cervical intraepithelial neoplasia; CI: confidence interval; dVIN: differentiated vulvar intraepithelial neoplasia; HDR: Hospital Discharge Register; HPV: human papillomavirus; ICD: International Classification Of Diseases; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; LS: lichen sclerosus; SCC: squamous cell carcinoma; SIR: standardized incidence ratio; THL: National Institute For Health And Welfare; VIN: vulvar intraepithelial neoplasia

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What's new?

Does it or doesn't it? Evidence is scant on whether the skin condition lichen sclerosus leads to cancer. These authors conducted the largest study to date, looking at 7,600 patients for nearly a decade. Among these patients, 800 cancer cases arose. Analysis showed that lichen sclerosus does increase one's risk of developing vulvar or vaginal cancer, but decreases the risk of cervical cancer, although the numbers were few due to the rarity of LS and these cancers.

Classification of Diseases (ICD) coding system. During the study period, three different revisions of the coding system have been in use in Finland: ICD-8 in 1969–1986, ICD-9 in 1987–1995 and ICD-10 since 1996. The following diagnosis codes were used: 701.01 *Lichen sclerosus et atrophicus* (ICD-8), 7010B *Lichen sclerosus et atrophicus* (ICD-9) and L90.0 *Lichen sclerosus* (ICD-10).

The Finnish Cancer Registry includes information on cancers diagnosed in Finland since 1953. More than 99% of all cancer cases are reported to the Registry.[15] The records of female patients with the diagnosis of LS were linked with diagnosed cancers from the Finnish Cancer Registry using unique personal identity codes. The cancers were classified according to the International Classification of Diseases for Oncology (ICD-O-3), and we also separated vulvar SCC using the morphology code of ICD-O-3. The topographical code for vulvar SCC used was C51 and behavior code was 3. The morphology codes used were either only 8070 Squamous cell carcinoma, NOS or 805–808 Squamous cell neoplasms. Follow-up for cancer started at time of first hospital or outpatient visit with diagnosis for LS and ended at death, first emigration or on December 31, 2014, whichever was first. Dates of emigration and death were received from the Finnish Population Information System (http://vrk.fi).

The numbers of observed cancers and person-years at risk were counted by five-year age groups, by calendar periods and by follow-up periods (<1 year, from 1 to <5 years and 5 years or more since the beginning of follow-up). The expected numbers of cases were calculated by multiplying the number of person-years in each stratum by the corresponding incidence among women in Finland. The Standardized Incidence Ratio (SIR) was calculated by dividing the number of observed cases by the number of expected cases. The 95% confidence intervals (95% CI) for the SIRs were based on the presumption that the number of observed cases followed a Poisson distribution. The absolute excess risk was calculated by using the following equation: (observed cases − expected cases)/person-years.

National Institute for Health and Welfare (THL) gave permission for data linkages between the different registers (THL/1440/5.05.00/2013) as required by legislation.

Results

A total of 7,616 women with LS were included in our study. Most patients diagnosed with LS were postmenopausal (Table 1). The number of outpatients was 6,998 (91.8%) and inpatients 618 (8.1%). The results are presented here combined, because there was no marked difference in cancer risk estimates between the patients diagnosed in inpatient or outpatient setting.

Table 1. Age distribution of the women, whole study period

Age	Persons (%)	Person-years (%)
0–9	204 (2.7)	697.8 (1.0)
10–19	117 (1.5)	1,736.8 (2.6)
20–29	200 (2.6)	1,446.2 (2.2)
30–39	365 (4.8)	2,406.7 (3.6)
40–49	762 (10.0)	5,246.1 (7.8)
50–59	1,587 (20.8)	10,659.7 (15.9)
60–69	1,995 (26.2)	17,159.8 (25.6)
70–79	1,709 (22.4)	16,981.5 (25.3)
80–84	439 (5.8)	6,360.7 (9.5)
≥85	238 (3.1)	4,395.8 (6.6)
Total	7,616 (100)	67,091.1 (100)

Age of persons defined in the beginning of follow-up, person-year calculations based on dynamic age.

During the follow-up of 67,091 person-years, a total of 812 cancers were found among women with LS (Table 2). The expected number was 718 resulting in a SIR of 1.13 (95% CI 1.05–1.21).

We found a significantly increased risk for vulvar cancer among women with LS (SIR 33.6, 95% CI 28.9–38.6) (Table 2). Of these, 88% ($n = 160$) were histologically of SCC type (topographical code 8070), and the SIR for vulvar SCC was 40.3 (95% CI 36.3–46.7). The risk for vulvar cancer was highest during the first year of follow-up (SIR 140, 95% CI 108–177) (Table 3). The risk remained elevated in the group with a follow-up between 1 and 5 years (SIR 23.4, 95% CI 17.1–31.3). Most cancer cases occurred in the group with a follow-up of more than 5 years (SIR 23.2, 95% CI 18.1–29.3).

The SIR for vulvar cancer was the highest among women in their 30s (SIR 385, 95% CI 122–928), it gradually lowered in the older age groups, and was at its lowest in the group of women over 80 years (SIR 23.7, 95% CI 17.9–30.9) (Table 4). However, the absolute excess risk was lowest in the age group of women of 30–39 years (166/100,000 person-years) and increased with age (Table 4). Among women aged 80 years or more, it was 463/100,000 person-years.

The risk for vaginal cancer was also significantly elevated (SIR 3.69, 95% CI 1.01–9.44) (Table 2). Three of the four vaginal cancer cases were diagnosed more than 5 years after the beginning of follow-up (SIR 5.08, 95% CI 1.05–14.8).

Table 2. Observed (Obs) and expected (Exp) numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) among women with diagnosis of *lichen sclerosus* during 1970–2014

Cancer site	Obs	Exp	SIR	95% CI
All sites	812	717.9	1.13	1.05–1.21
Lip	-	2.04	0.00	0.00–1.81
Tongue	3	2.70	1.11	0.23–3.24
Oral cavity	13	11.3	1.15	0.61–1.96
Colon	40	50.5	0.79	0.57–1.07
Lung, trachea	28	43.2	0.65	0.43–0.93
Skin, nonmelanoma	32	40.7	0.79	0.54–1.10
Breast	170	194.5	0.87	0.75–1.01
All female genitals	253	83.3	3.04	2.67–3.42
Cervix uteri	-	5.23	0.00	0.00–0.70
Corpus uteri	41	43.5	0.94	0.68–1.27
Ovary	21	23.4	0.90	0.56–1.37
Vagina	4	1.08	3.69	1.01–9.44
Vulva	182	5.42	33.6	28.9–38.6

Table 3. Observed (Obs) and expected (Exp) numbers of vulvar cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) among women with diagnosis of *lichen sclerosus*. Vulvar cancer cases divided into categories according to follow-up time of LS before diagnosis of cancer

Follow-up in years	Obs	Exp	SIR (95% CI)
<1	67	0.48	140 (108–177)
1–4.99	45	1.92	23.4 (17.1–31.3)
>5	70	3.02	23.2 (18.1–29.3)
Total	182	5.42	33.6 (28.9–38.6)

There was a reduced risk for cervical cancer with no observed cases vs. 5.23 expected cases. The risk of uterine or ovarian cancer was not increased (Table 2).

Although LS is also found on the mucosal surface of the oral cavity and on extragenital skin, we did not find an increased risk of cancers in these body parts (Table 2). We found a significantly decreased risk of lung cancer (SIR 0.65, 95% CI 0.43–0.93). The risks for breast and colon cancers were lower than in the reference population, though not significantly so (Table 2).

Discussion

We found that patients diagnosed with LS have a significantly elevated risk for developing vulvar cancer. The vast majority of these cancers consisted of SCC, and the SIR for this histological subgroup did not differ from the SIR for the whole group. The risk of vulvar cancer was especially high during the first year of follow-up. The patients with close diagnosis of LS and subsequent cancer probably sought medical care because of symptoms of cancer instead of symptoms of LS. However, the risk of vulvar cancer among patients with LS remained elevated through the whole follow-up period, suggesting a true association.

Table 4. Observed (Obs) and expected (Exp) numbers of vulvar cancer cases standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) and absolute excess risk (AER) among women with diagnosis of *lichen sclerosus* during 1970–2014 in different age groups

Age	Obs	Exp	SIR (95% CI)	AER per 100,000 person years
30–39	4	0.01	385 (122–928)	166
40–49	11	0.07	157 (82.6–273)	208
50–59	23	0.27	85.2 (55.3–126)	213
60–69	40	0.87	46.0 (33.3–62.0)	228
70–79	52	2.02	25.7 (19.4–33.5)	294
80+	52	2.19	23.7 (17.9–30.9)	463

The SIR of vulvar cancer among LS patients was the highest in the younger age groups due to the fact that the expected number of cancers is low among young women. The SIR decreased with age but was still over 20-fold among the oldest age group of women over 80. The absolute excess risk was the highest among women over 80 years: 460/100,000 person-years.

There was also an increased risk for vaginal cancer among LS patients. This is somewhat unexpected, as LS is traditionally not thought to affect the vaginal mucosa but there are at least two case reports of this phenomenon.[6,7] To our knowledge, this is the first time that such an association has been suggested.

We found that the risk for cervical cancer was significantly decreased among LS patients, a finding that has not been suggested previously. LS may impair patients' sexual life because it can destroy normal anatomy in the vulvar area. Therefore, one might hypothesize that patients with LS are less exposed to human papillomavirus (HPV), a causative agent in cervical cancer. Other explanations could be lower rates of smoking among LS patients (suggested by the decreased SIR of lung cancer known to be strongly related to smoking), and more intensive cervical cancer screening among patients with a gynecological condition that might lead to detection of cervical abnormalities before their progression to cancer.

We did not find an increased risk of any skin cancer type despite the fact that LS manifests occasionally on extragenital skin. Also, the risk for cancer of the oral cavity was not elevated although LS sometimes affects oral mucosa. Unfortunately, we could not stratify our analyses according to anatomic location of the LS because the ICD codes used do not indicate the area of the body of the LS. Because all our patients do not have vulvar LS, this setting probably gives a lower risk estimate of vulvar cancer that would be achieved from a cohort with only genital LS. Also, it is likely that only a minority of our patients has extragenital LS, so possible risks for extragenital malignancies may be hidden.

It is probable that some vulvar LS patients are missing from our cohort because all affected patients do not receive

the diagnosis. This is in part due to the sometimes symptomless character of the disease. Also, some patients may feel embarrassed to discuss symptoms in the vulvar region if not actively asked. The missing patients may suffer from a milder form of LS, which could be less likely to undergo malignant transformation.

The follow-up of our cohort started as early as in 1970 and, therefore, the diagnostic criteria of LS could have been revised over time with newer data possibly being more accurate. The register data available for us did not include information on whether the LS diagnosis was confirmed by biopsy or was based only on the clinical picture. The golden standard is to confirm LS diagnosis by histological biopsy.

Vulvar cancer, vaginal cancer and cervical cancer are rare diseases in Finland. In 2013, vulvar cancer accounted for 0.8%, vaginal cancer for 0.2% and cervical cancer for 1.0% of all cancers of women (www.cancerregistry.fi). The small number of patients with LS and these gynecological cancers has made it difficult to get sufficient data for studying associations between LS and cancer. The strength of our study is the size of the study cohort, comprising >7,600 LS patients with a follow-up of >67,000 person-years. The completeness and quality of the Finnish population-based registers further improves the credibility of our results.[15–17]

Previous studies on the malignancy potential of LS are based mainly on settings of some hundreds of patients at best. In two prospective studies comprising 253 and 211 patients,[2,11] altogether six (2.4%) and three (1.4%) vulvar SCCs were diagnosed after a mean follow-up of 5.4 and 1.7 years, respectively. In a recent study, 2.6% of the 2,875 LS patients developed vulvar SCC at a median time of 3.3 years.[18] In our material, 2.1% of LS patients were diagnosed with vulvar SCC during a mean follow-up of 8.8 years. Difference in length of follow-up of course has an effect of the proportion of LS patients developing vulvar SCC, but also differences in the population characteristics cause incomparability between the studies.

In previous literature, extragenital LS is not presumed to have premalignant potential.[13,14] However, there is a case report of a patient with severe LS affecting the anogenital region, scalp, trunk and legs who subsequently developed SCC in the buttock and shoulder.[19]

Vulvar SCC (HPV independent type) was previously thought to evolve through LS. According to current hypothesis, however, differentiated vulvar intraepithelial neoplasia (dVIN) is considered to be the true precursor of vulvar SCC.[20,21] The challenge is to differentiate dVIN from LS even with histological biopsies. DVIN often arises in the background of LS.[22] In 2011, van de Nieuwenhof *et al.* reassessed biopsies collected from 60 patients with the diagnosis of LS who later developed vulvar SCC.[23] The study hypothesis was that some of the previous LS diagnoses might have actually been dVIN. Indeed, only 30% of LS diagnoses remained unchanged, whereas 42% were reclassified into dVIN.[23]

We did not have information on confounding factors such as smoking, HPV status or diseases such as autoimmune conditions, which might predispose patients to cancer. In this cohort, the risk of tobacco-related lung cancer was decreased suggesting that smoking among LS patients was less common than among women in the general population. If that is true, the SIRs for tobacco-related cancers in our study are biased downward due to confounding by smoking. Smoking is thought to be a predisposing factor for vaginal cancer,[24] and therefore, the SIR for vaginal cancer in our study might be an underestimate. A recent giant UK study comprising of 1.3 million women and 898 vulvar cancers did not detect an association between vulvar cancer and smoking.[25]

Because patients may have initially been diagnosed with LS in the primary care before being referred to hospital and thus appearing in the HDR, the time since LS diagnosis may be underestimated in our analyses. If we had the information on the actual diagnosis date for all LS patients, the SIR estimates would have been larger in the short follow-up categories.

We had no information concerning the management of the LS patients. Clinicians have long suspected that active management of vulvar LS might reduce the risk of malignant transformation. In a recent prospective study,[26] 507 women with vulvar LS were treated with topical corticosteroids in a long-term, regular and tailored fashion. In the group of 357 patients considered compliant, no cases of vulvar SCC occurred during the mean follow-up period of 4.7 years. Of the 150 patients considered only partially compliant, seven (4.7%) developed vulvar SCC or VIN.

We conclude that the diagnosis of LS is strongly associated with an increased risk of vulvar cancer, with this risk remaining elevated throughout the whole follow-up time. We also detected a significantly elevated risk of vaginal cancer and a significantly reduced risk of cervical cancer, this being the first time such associations are suggested. However, because of the rarity of LS and these gynecological malignancies, the number of cancers was small. The risk for other malignancies among LS patients was similar to that seen among the general Finnish female population.

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