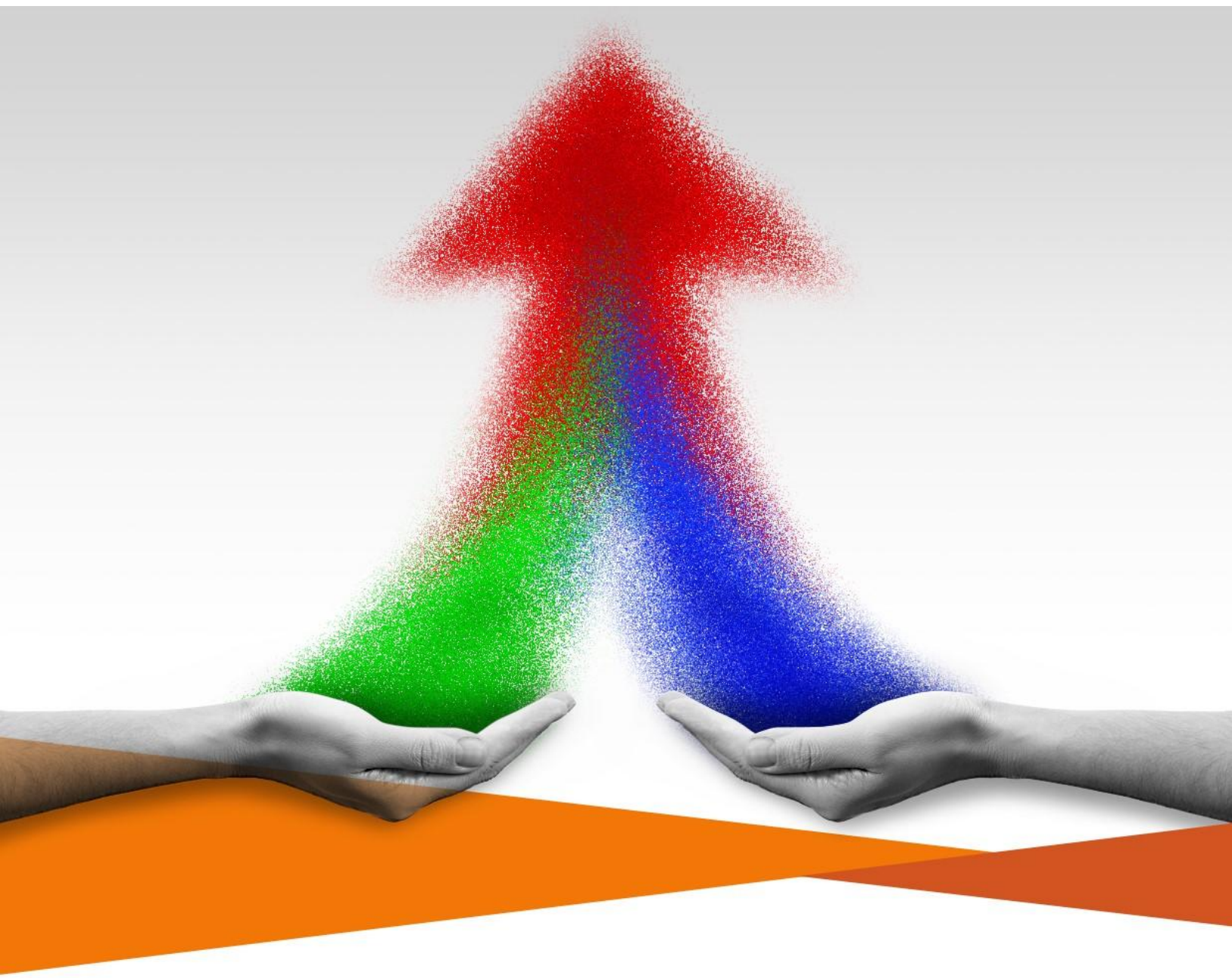

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Cancer risk of *Lichen planus*: A cohort study of 13,100 women in Finland

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The association between *Lichen planus* (LP) and cancer has been under debate for decades. We studied the connection *via* population-based Finnish register data. All women with the diagnosis of LP ($n = 13,100$) were identified from the Finnish Hospital Discharge Registry from 1969–2012. These patients were linked with subsequent cancer diagnoses from the Finnish Cancer Registry until 2014. Standardized incidence ratios (SIRs) were counted for different cancers by dividing the observed numbers of cancers by expected numbers, which were based on national cancer incidence rates. In total, 1,520 women with LP were diagnosed with cancer (SIR 1.15, 95% confidence interval [CI] 1.09–1.20). LP was associated with an increased risk of cancer of lip (SIR 5.17, 95% CI 3.06–8.16), cancer of tongue (SIR 12.4, 95% CI 9.45–16.0), cancer of oral cavity (SIR 7.97, 95% CI 6.79–9.24), cancer of esophagus (SIR 1.95, 95% CI 1.17–3.04), cancer of larynx (SIR of 3.47, 95% CI 1.13–8.10) and cancer of vulva (SIR 1.99, 95% CI 1.18–3.13). The risk of cancer was not increased in other locations where LP manifests (pharynx and skin). Patients with diagnosed LP have an increased risk of developing cancer of lip, tongue, oral cavity, esophagus, larynx and vulva. These data are important when considering treatment and follow-up of patients with LP diagnosis.

Cancer Epidemiology

Introduction

Lichen planus (LP) is a chronic, inflammatory disease of the skin and mucous membranes. The etiology of the disease remains uncertain, but evidence points to autoimmune factors.

The prevalence of LP is unknown because of the diverse clinical picture of the disease. On the skin, LP most often manifests on the flexor surfaces of wrists, lower trunk and lower limbs. It is rarely seen in skin appendages such as nails or scalp. The mucosal site most often affected is that of the oral cavity, but the dermatosis is also seen in the mucous membranes of the genitalia and rarely the esophagus, pharynx, larynx or the conjunctiva.

The estimated prevalence of cutaneous LP among Swedish women in the 1960s was 0.1%,[1] and the prevalence of oral LP in the 1970s among Swedish women was 2.2%.[2] The prevalence of genital LP is probably less. In a study from a specialized vulvar clinic, 3.7% of biopsied patients were diagnosed with vulvar LP.[3] In literature, esophageal, laryngeal and vaginal LP are mainly represented in case reports.[4–7] It is possible for LP to affect different mucosal or both mucosal and cutaneous sites simultaneously or sequentially.[8,9]

There seems to be an association with oral LP and oral squamous cell carcinoma (SCC).[10] There are also reports of vulvar SCC developing in vulvar LP.[11–14] The cutaneous form of LP is not considered to be associated with cancer risk.[15]

The aim of our study was to estimate the risk of different cancers among women previously diagnosed for LP. Special attention was paid to cancers of the areas of the body where LP manifests (*i.e.*, oral cavity, larynx, esophagus, vulva, vagina and skin). Standardized incidence ratios (SIRs) were also counted for the leading cancers of women (*i.e.*, breast, colon and lung cancer).

Materials and Methods

The data for our study were collected from national registries in Finland. The patient was recognized in different registries using a personal identity code assigned to all Finnish citizens.

Key words: *Lichen planus*, cancer risk, oral cancer, vulvar cancer
Abbreviations: CI: confidence interval; HDR: hospital discharge register; ICD: International Classification of Diseases; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; LP: *Lichen planus*; SCC: squamous cell carcinoma; SIR: standardized incidence ratio; THL: National Institute for Health and Welfare; WHO: World Health Organization
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What's new?

Lichen planus **(LP) is a chronic disease of the skin and mucous membranes that is likely autoimmune in origin. Owing to its inflammatory nature, it is also suspected of causing certain cancers. Whether LP possesses malignant potential, however, remains uncertain. Here, in a cohort of 13,100 women diagnosed with LP between 1969 and 2012 in Finland, some 1,520 were eventually diagnosed with cancer. Malignancies with significant increases in incidence in LP patients included those of the lip, tongue, oral cavity, esophagus, larynx and vulva. The findings suggest that LP patients could benefit from multidisciplinary approaches to care.**

The hospital discharge register (HDR) includes data of all inpatient diagnoses since 1969 and of outpatient diagnoses from public hospitals since 1998. The diagnoses made in primary care or in private outpatient units are not included. In the HDR, the diagnoses are classified according to the International Classification of Diseases (ICD) coding system: ICD-8 between 1969 and 1986, ICD-9 between 1987 and 1995 and ICD-10 since 1996. All women with a primary or secondary diagnosis code for LP were identified in the HDR from 1969 to 2012. The following diagnosis codes were used: 697 Lichen, 697.00 Lichen ruber planus, 697.98 Lichen alius definitus, 697.99 Lichen NUD (ICD-8), 697 Lichen, 6970 A Lichen ruber planus, 6970B Lichen ruber verrucosus, 6978X Lichen alius definitus, 6979X Lichen NUD (ICD-9), L43 Lichen ruber planus, L43.0 Lichen ruber planus hypertrophicus, L43.1 Lichen ruber planus bullosus, L43.3 Lichen planus subacutus, Lichen planus trophicus, L43.8 Alius Lichen planus specificatus and L43.9 Lichen planus non-specificatus (ICD-10).

The Finnish Cancer Register includes information on diagnosed cancers in Finland since 1953. The information included is highly reliable since over the decades >99% of cancers have been reported to the Registry.[16] The cancers are classified according to the International Classification of Diseases for Oncology (ICD-O-3) system. The records of women with a diagnosis of LP from the HDR were linked with diagnosed cancers from the Finnish Cancer Registry by using the women's personal identity codes. The follow-up for subsequent cancer started from the first inpatient or outpatient hospital diagnosis of LP and ended at death, first emigration or on December 31, 2014, whichever was first. The dates on emigration and death were collected from the Finnish Population Information System.

The numbers of observed cancers and person-years at risk among LP patients were calculated by 5-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 numbers of expected cancers were calculated by multiplying the number of person-years in each stratum by the corresponding incidence among women in Finland. The SIRs were calculated as the ratios of observed to expected numbers of cancers. The 95% confidence intervals (95% CI) for the SIRs were based on the presumption that the number of observed cases follows a Poisson distribution.

The permission to use and merge register data for our study was given by the National Institute for Health and Welfare (THL) (THL/1440/5.05.00/2013) as required by legislation.

Results

In total, 13,100 women with LP (140,179 person-years) were included in the study cohort. Most patients were diagnosed with LP in their perimenopausal or postmenopausal years (Table 1). The number of patients diagnosed in inpatient setting was 2,089 (15.9%) and in outpatient setting was 11,011 (84.1%). We combine the results as the cancer risk estimates are same for inpatient and outpatient groups.

During the whole follow-up, 1,520 cancers were detected among women with a diagnosis of LP, whereas the expected number was 1,326. The SIR for any cancer was 1.15 (95% CI 1.09–1.20) (Table 2).

The risks of cancers of the oral mucosa, esophagus and larynx were significantly elevated. The SIR for cancer of lip was 5.17 (95% CI 3.06–8.16), for cancer of tongue 12.4 (95% CI 9.45–16.0) and for cancer of oral cavity 7.97 (95% CI 6.79–9.24). The SIR for cancer of esophagus was 1.95 (95% CI 1.17–3.04) and for cancer of larynx 3.47 (95% CI 1.13–8.10) (Table 2).

The SIRs for these cancers were highest during the first year of follow-up but remained elevated even with longer follow-up times (Table 3).

We also found an elevated risk of vulvar cancer among LP patients (SIR 1.99, 95% CI 1.18–3.13). This risk was also at its highest with a follow-up of less than a year (SIR 8.27, 95% CI 2.69–19.3) and remained significant with follow-up between one and five years (SIR 2.74, 95% CI 1.10–5.65) (Table 3).

The risk of vaginal cancer was not elevated with only two observed and 1.92 expected cases (Table 2).

Although LP often affects the skin, the risk of cancer of the skin was not elevated (SIR 1.25, 95% CI 0.99–1.57). The risks of lung cancer, colon cancer and breast cancer were the same as in the reference population (Table 2).

Discussion

We found that patients with a diagnosis of LP have a significantly elevated risk of developing cancer of lip, tongue, oral cavity, esophagus and larynx. The risks were highest during the first year of follow-up suggesting that these patients sought medical advice because of symptoms of cancer, not because of LP. The risks remained elevated even with longer follow-up thus suggesting a true association between LP and cancer.

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

Age	Persons (%)	Person–years (%)
0–9	51 (0.4)	181.6 (0.1)
10–19	161 (1.2)	933.6 (0.7)
20–29	444 (3.4)	2,963.1 (2.1)
30–39	951 (7.3)	6,808.1 (4.9)
40–49	1,999 (15.3)	15,339.7 (10.9)
50–59	3,748 (28.6)	31,631.2 (22.6)
60–69	3,279 (25.0)	38,911.1 (27.8)
70–79	1,901 (14.5)	29,357.1 (20.9)
80–84	407 (3.1)	8,552.4 (6.1)
≥85	159 (1.2)	5,501.1 (3.9)
Total	13,100 (100)	140,179.0 (100)

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

Table 2. Observed (Obs) and expected (Exp) numbers of cancer cases and SIRs with 95% CIs among women with diagnosis of LP during 1969–2014

Cancer site	Obs	Exp	SIR	95% CI
Any site	1,520	1,326	1.15	1.09–1.20
Lip	18	3.48	5.17	3.06–8.16
Tongue	59	4.75	12.4	9.45–16.0
Oral cavity	163	20.5	7.97	6.79–9.24
Pharynx	5	3.49	1.43	0.47–3.34
Esophagus	19	9.75	1.95	1.17–3.04
Larynx, epiglottis	5	1.44	3.47	1.13–8.10
Lung, trachea	82	76.4	1.07	0.85–1.33
Skin, non-melanoma	75	59.8	1.25	0.99–1.57
Colon	72	86.7	0.83	0.65–1.04
Breast	368	391	0.94	0.85–1.04
All female genitals	161	160	1.01	0.86–1.16
Cervix	6	11.7	0.51	0.19–1.11
Uterus	79	82.9	0.95	0.75–1.18
Ovary	46	46.2	1.00	0.73–1.32
Vagina	2	1.92	1.04	0.13–3.76
Vulva	18	9.07	1.99	1.18–3.13

Table 3. Observed (Obs) and expected (Exp) numbers of cancer cases and SIRs with 95% CIs among women with diagnosis of LP, by site and follow-up time since the first known LP diagnosis

Cancer site	Follow-up (years)	Obs	Exp	SIR (95% CI)
Lip	<1	5	0.23	22.0 (7.13–51.2)
	1–4.99	6	0.92	6.54 (2.40–14.2)
	≥5	7	2.34	2.99 (1.20–6.16)
	Total	18	3.48	5.17 (3.06–8.16)
Tongue	<1	17	0.35	48.8 (28.5–78.2)
	1–4.99	18	1.43	12.6 (7.47–19.9)
	≥5	24	2.98	8.06 (5.17–12.0)
	Total	59	4.75	12.4 (9.45–16.0)
Oral cavity	<1	37	1.47	25.1 (17.7–34.6)
	1–4.99	51	6.04	8.44 (6.28–11.1)
	≥5	75	12.9	5.80 (4.56–7.26)
	Total	163	20.5	7.97 (6.79–9.24)
Esophagus	<1	2	0.68	2.93 (0.35–10.6)
	1–4.99	4	2.76	1.45 (0.39–3.70)
	≥5	13	6.31	2.06 (1.10–3.52)
	Total	19	9.75	1.95 (1.17–3.04)
Larynx, epiglottis	<1	1	0.12	8.53 (0.22–47.5)
	1–4.99	1	0.45	2.21 (0.06–12.3)
	≥5	3	0.87	3.45 (0.71–10.1)
	Total	5	1.44	3.47 (1.13–8.10)
Vulva	<1	5	0.60	8.27 (2.69–19.3)
	1–4.99	7	2.55	2.74 (1.10–5.65)
	≥5	6	5.91	1.01 (0.37–2.20)
	Total	18	9.07	1.99 (1.18–3.13)

The risk of vulvar cancer was also elevated among LP patients. Again, the risk was highest with follow-up of less than a year, but remained elevated among the group of LP patients with a follow-up between 1 and 5 years. The risk of vaginal cancer was not found to be elevated with only two observed cancer cases.

The ICD codes available for us unfortunately did not allow stratification of the analyses according to the location of LP, which is a limitation of our study. Therefore, we cannot ascertain whether cancer developed in the same area as previous LP. Most likely the majority of our patients suffer from cutaneous or oral LP or they have multiple sites of disease involvement. It can be assumed that the SIRs for vulvar, vaginal, pharyngeal, esophageal and laryngeal disease would be higher than those shown in our results, if we could have studied patients with LP located only in those sites.

In literature, cutaneous LP is not thought to undergo malignant transformation,[15] although there are case reports of SCC developing in cutaneous LP.[17] Evidence on the malignancy potential of vulvar LP is weak, based mainly on case reports.[18–22] In the only prospective study comprised of 114 patients with vulvar LP followed for a mean of 72 months, one patient developed a subsequent vulvar SCC.[11] The diagnosis of laryngeal or esophageal LP is rare, and the possible malignant potential of LP on these locations is unknown.[4–6] In our study, the risk of esophageal cancer was highest with follow-up of 5 years or more. Therefore, LP patients should be informed to seek medical attention if any esophageal symptoms develop later in life.

In previous literature, malignant transformation of oral LP has been documented in prospective and retrospective studies, but still the premalignant potential of the disease remains controversial. The main problem with interpreting results lies in the heterogeneity of diagnostic criteria used for LP. Also, there are differences of study inclusion criteria, follow-up length and information on exposure to different oral carcinogens. The most recent systematic review included 16 studies with a total of 7,806 patients with oral LP. The age of the patients ranged between 30 and 89 years and the follow-up between 0 and 312 months. In total 85 of the patients developed oral SCC resulting in 1.09% overall rate of malignant transformation.[10]

Even with reliable register data, it is likely that some patients with LP are missing from our cohort. Sometimes the disease is entirely symptom-free and the patient goes undiagnosed. On the other hand, patients with vulvar LP might be too embarrassed to discuss of vulvar symptoms with physicians, if not actively asked. The LP of these patients may be milder and thus have smaller pre-malignant potential than that of symptomatic patients seeking medical attention.

The diagnosis of LP may be inaccurate in some cases, which is a limitation of our study. The diagnosis may be done clinically, histologically or both. The gold standard is a combination of the two for oral LP as recommended in the diagnostic criteria created by the World Health Organization (WHO) in 1978 with later modifications in 2003 by van der Meij *et al.*[23,24] For vulvar LP, experts from the International Society for the Study of Vulvovaginal Disease and the British Society for the study of Vulval Disease stated in 2013 that the diagnosis may be carried out clinically, but biopsy is necessary when the diagnosis is not obvious.[25]

Register data give no details as to how diagnoses were made. The clinical picture may be mistaken for, for example, leukoplakia, *Lichen sclerosus* or differentiated vulvar intraepithelial neoplasia or other conditions that may have different malignant potential than LP. If there were a large number of misdiagnosed persons in our current LP cohort, this would bias the SIR estimates. However, we do not see biased SIR estimates in our data.

The cancers with excess risk observed in our study are rare in Finland: in 2013, lip cancer accounted for 0.2%, tongue cancer 0.3%, oral cancer 0.5%, esophageal cancer 0.5%, laryngeal cancer 0.1% and vulvar cancer 0.8% of all cancers of women (cancerregistry.fi). Due to the rarity of LP and these cancers, there are no strong earlier findings related on the risk of these cancers in LP patients. Relative to previous literature, our cohort of LP patients is large with 13,100 women and 140,000 person-years. Also, the Finnish registries are unique in their completeness and quality.[16,26,27]

Another limitation of our study is not having information on confounding factors, such as smoking, alcohol consumption, human papilloma virus (HPV) infection or autoimmune or other diseases. In our study, the incidence of tobacco-related lung cancer was the same as in the reference population suggesting that smoking does not cause significant confounding in our results.

Alcohol is a risk factor for cancers of the oral cavity, pharynx, larynx and esophagus,[28] all of which showed increased risk in our study. In studies of patients with oral LP, the patients have not consumed alcohol more than people in general.[29–33] In a British study, patients with oral LP and oral SCC consumed alcohol less than patients with oral SCC in the absence of oral LP.[34] Thus, one can assume that alcohol consumption in our cohort should not be higher than in the reference population and hence not confound the risk estimates of alcohol-related cancer types upwards.

LP is typically treated with topical corticosteroids based on clinical experience. Rare options include systemic corticosteroids, topical calcineurin inhibitors or systemic immunosuppressants (*e.g.*, azathioprine, methotrexate or ciclosporin). Data on treatment of LP patients in our cohort was not available. The effect of LP treatment on the possibility of malignant progression is sparsely studied. In three follow-up studies from Italy with 402, 808 and 327 patients with oral LP, treatment with local or systemic steroids and antimycotics did not seem to affect the risk of malignant transformation.[32,35,36] For *L. sclerosus*, another dermatosis affecting genital skin, there are some recent data suggesting that topical corticosteroids may reduce risk of malignant transformation.[37]

We conclude that the diagnosis of LP is significantly associated with an increased risk of cancer of lip, tongue, oral cavity, esophagus, larynx and vulva. The risk of other cancers did not differ from that of the general Finnish female population. Due to the multisystem character of the disease, a multidisciplinary approach to treatment and follow-up should be adapted.

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