Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Association between oral leukoplakia and risk of upper gastrointestinal cancer death: A follow-up study of the Linxian General Population Trial

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Keywords
Follow-up study; oral leukoplakia; upper gastrointestinal cancer.

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Received: 28 June 2017;
Accepted: 27 July 2017.

doi: 10.1111/1759-7714.12501

Thoracic Cancer **8** (2017) 642–648

Abstract

Background: This study was conducted to explore the association between oral leukoplakia (OL) and the risk of upper gastrointestinal cancer death in the Linxian General Population Trial Cohort.

Methods: A prospective cohort study of the Linxian General Population Trial Cohort was performed. Participants with OL were treated as an exposed group, and the remainder was selected as a control group. All subjects were followed monthly by village health workers and reviewed quarterly by the Linxian Cancer Registry. Hazard ratios (HRs) and 95% confidence interval (CIs) were evaluated using proportional hazard and proportional subdistribution hazard models, respectively.

Results: Over a median of 27 years of observation, 29 476 subjects were followed-up. A total of 17 473 deaths occurred, including 2345 esophageal squamous cell carcinoma (ESCC), 1139 gastric cardia carcinoma, and 506 gastric non-cardia carcinoma deaths. Significant increased ESCC mortality was observed in subjects with OL (exposed 9.66% vs. unexposed 7.39%; $P < 0.0001$). Furthermore, subjects with OL had a 22% higher risk of death from ESCC (HR 1.22, 95% CI 1.10–1.34; $P = 0.0001$) after adjusted covariates. In subjects aged ≤52 at the baseline, OL was significantly associated with an elevated risk of ESCC mortality (HR 1.32, 95% CI 1.13–1.54; $P = 0.0005$). No significant associations were observed for gastric cardia carcinoma and non-cardia carcinoma mortality.

Conclusions: OL may increase the risk of ESCC mortality, especially in the younger population. These associations should be investigated in further studies.

Introduction

Oral leukoplakia (OL) is the most potentially malignant lesion of the oral cavity.[1,2] The World Health Organization defines leukoplakia as "A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer."[3,4] Estimates of the global prevalence of OL range from 0.5% to 3.46% in various populations and geographical areas.[5] Previous reports have indicated a pooled estimated annual rate of OL malignant transformation of 1.36% (95% confidence interval [CI] 0.69–2.03%).[5,6] About 70–90% of OL is related to smoking and areca nut use, either alone or in combination, and there is a direct relationship between the frequency and duration of cigarette, pipe, or cigar smoking and OL prevalence.[7–10]

Cancers of the upper gastrointestinal tract (UGIs) remain a significant cause of morbidity and mortality.[11,12] In 2012, there were an estimated 456 000 new cases of esophageal cancer and 952 000 new cases of stomach cancer worldwide, ranking as the sixth and fourth leading causes of cancer-related mortality globally.[13] Incidence in China accounted for approximately 49% of the esophageal cancer cases worldwide.[14] In Linxian, China, at the commencement of this study, UGI

cancers were endemic.[15] Mortality of esophageal cancer in Linxian exceeded the Chinese average by 10-fold and the American average (in white men) by 100-fold.[12,16,17]

Oral leukoplakia is common among residents in Linxian. Previous studies in Linxian have shown an association between OL and an increased risk of esophageal squamous cell carcinoma (ESCC), particularly in the younger population.[18] In this study, we investigated associations between OL and risk of ESCC, gastric cardia carcinoma (GCC), and gastric non-cardia carcinoma (GNCC) deaths in the Linxian General Population Trial Cohort.

Methods

Ethics statement

The institutional review boards of the Cancer Institute of the Chinese Academy of Medical Sciences and the United States (US) National Cancer Institute approved the Linxian General Population Nutrition Intervention Trial (NIT) and additional work described here. NIT participants provided written informed consent at enrollment indicating their willingness to participate and their understanding of the procedure and general aim of the study. All participant consent was obtained prior to the survey and all study processes were conducted in accordance with the Declaration of Helsinki.

Study population

Details of the design, intervention agents, conduct, and primary end-point analyses of the NIT have been reported elsewhere.[17,19] In brief, 29 584 eligible healthy individuals aged between 40 and 69 without a history of cancer, debilitating disease, or requirement of daily medication were recruited from four northern communes of Linxian in 1985, a rural county in Henan Province. These individuals were randomly assigned to receive either a vitamin-mineral combination or a placebo according to partial factorial design. The intervention began in March 1986 and ceased in May 1991, however follow-up continued until recently.

Baseline examination

Baseline data including age, gender, smoking, alcohol consumption, and family cancer history were obtained from the questionnaire. Trained local village doctors conducted a brief physical examination including body weight, height, and an oral cavity inspection. Age at baseline and gender were recorded from the subject's ID cards. Smoking was defined as regular cigarette or pipe use for at least six months (including ever and current smokers), and alcohol consumption was defined as any consumption in the previous 12 months (possible responses for drinkers ranged from "several times per year" to "several times per day"). A subject was considered as having a positive family history of cancer if cancer was reported in at least one first-degree relative, including parents, siblings, or offspring. Body weight and height were measured during the physical examination, and body mass index (BMI) was calculated as kg/m^2. After ruling out all other possible causes, such as oral candidiasis and lichen planes, OL was characterized by white spots or patches in the mucous membranes inside the mouth. Participants with a positive history of OL, given that OL was a permanent change to the mucosa, were included in the study.

Follow-up data collection

Local village doctors ascertained cancer mortality and incidence among the trial participants through monthly follow-ups. Less than 1% of the participants were lost to follow-up during the study period. A diagnosis of cancer was made by the local commune and county hospital, and described by a study team that provided clinical and diagnostic services, including endoscopy, cytology, pathology, surgery, and radiology. A joint expert panel of American and Chinese cytology pathologists and radiologists audited more than 85% of the diagnostic material. A diagnosis was made in 95% of cases by endoscopy, surgery, and/or X-ray.[18] All esophageal cancers were ESCC. Cancers in the most proximal 3 cm of the stomach were defined as GCC and those originating elsewhere in the stomach were defined as GNCC.[12]

Statistical analysis

The main outcome of this study was death from ESCC, GCC, or GNCC. Participants were censored at their last known follow-up date, death, or 31 May 2012. χ^2 and *t*-tests were used to compare categorical and continuous variables between the two groups, respectively. Cumulative mortality between the groups was compared using log-rank tests and the Fine and Gray model.[20–22] Hazard ratios (HRs) and 95% CIs were calculated using standard Cox proportional hazard models (PHMs)[23] and proportional subdistribution hazard models (PSHMs),[20,24–26] adjusting for age at baseline (continuous variable), gender (men vs. women), BMI (continuous variable), smoking (yes/no), alcohol consumption (yes/no), tooth loss (yes/no), family cancer history (yes/no), and commune (Yaocun, Rencun, Donggang, and Hengshui [as a reference]). The proportionality assumption was examined using models that allowed time-dependent HRs; no differences in time variables were observed.[23] A possible interaction between OL and basic characteristics was determined using stratified models,[12] such as age at baseline (<52 and ≥52, based on the median age), gender (men vs. women), smoking (yes/no), and alcohol consumption

(yes/no). All *P* values were two-sided and *P* values less than 0.05 were considered statistically significant. Analyses were conducted using SAS version 9.3 service package 4 (SAS Institute, Inc., Cary, NC, USA) and the R software package Version 2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 29 476 individuals were included in the final analysis. At baseline, 7371 participants were confirmed with OL. Baseline characteristics of the study participants are presented according to OL status in Table 1. OL was inversely related to age at baseline, alcohol consumption, family cancer history, commune, BMI, and tooth loss ($P < 0.05$). Smoking was more common in subjects without OL ($P < 0.05$).

Cumulative mortality

During the 27 years of follow-up, 17 473 deaths occurred: 2345 ESCC, 1139 GCC, and 506 GNCC deaths. ESCC deaths accounted for approximately 50% of all cancer deaths. Figure 1 presents the crude cumulative mortality for ESCC (9.66% vs. 7.39%), GCC (4.76% vs. 3.60%), and GNCC (2.21% vs. 1.55%) compared to subjects without OL, respectively.

Estimate of the effect of oral leukoplakia

Crude and adjusted HRs and 95% CIs for the associations between OL and risk of ESCC, GCC, and GNCC death are presented in Table 2. OL was significantly associated with the risk of ESCC mortality (HR 1.17, 95% CI 1.06–1.29 vs. HR_{CR} 1.22, 95% CI_{CR} 1.10–1.34) after adjusting for age, gender, smoking, alcohol consumption, family cancer history, commune, BMI, and tooth loss in both PHMs and PSHMs. However, no significant associations were observed for GNCC (HR 1.05, 95% CI 0.86–1.29 vs. HR_{CR} 1.09, 95% CI_{CR} 0.89–1.33) or GCC (HR 0.96, 95 CI 0.84–1.11 vs. HR_{CR} 0.99, 95% CI_{CR} 0.87–1.14) mortality. We also estimated the adjusted HRs for ESCC, GCC, and GNCC death after stratification by age, gender, smoking, and consumption of alcohol in PHMs. Significant interactions were observed between age ($P < 0.0001$), gender ($P = 0.0006$), smoking ($P = 0.0009$), and ESCC mortality. The associations between OL and ESCC mortality were stronger in young people (HR 1.34, 95% CI 1.15–1.56), non-smokers (HR 1.24, 95% CI 1.08–1.42), and non-drinkers (HR 1.22, 95% CI 1.09–1.37).

Table 1 Baseline characteristics by oral leukoplakia in Linxian General Population Trial Cohort

	Oral leukoplakia		No oral leukoplakia		
Covariates	N	%	N	%	*P**
Age at interview (years, mean ± SD)	51.29 ± 8.69		51.91 ± 8.95		<0.001
Body mass index (kg/m^2, mean ± SD)	21.89 ± 2.30		22.00 ± 2.56		0.002
Gender					<0.001
Male	5591	42.55	7548	57.45	
Female	1780	10.90	14 557	89.10	
Smoking					<0.001
Yes	4473	50.25	4428	49.75	
No	2898	14.09	17 677	85.91	
Drinking					<0.001
Yes	2583	37.33	4336	62.67	
No	4788	21.23	17 769	78.77	
Commune					<0.001
YaoCun	2430	24.48	7496	75.52	
RenCun	1569	26.46	4361	73.54	
DongGang	2054	32.82	4204	67.18	
HengShui	1318	17.90	6044	82.10	
Tooth loss					<0.001
Yes	5082	23.06	16 953	76.94	
No	2289	30.77	5151	69.23	
Family cancer history					<0.001
Yes	2703	26.65	7438	73.35	
No	4668	24.14	14 667	75.86	

*P value derived from χ^2 or two-sample t tests, as appropriate, for categorical and continuous variables. SD, standard deviation.

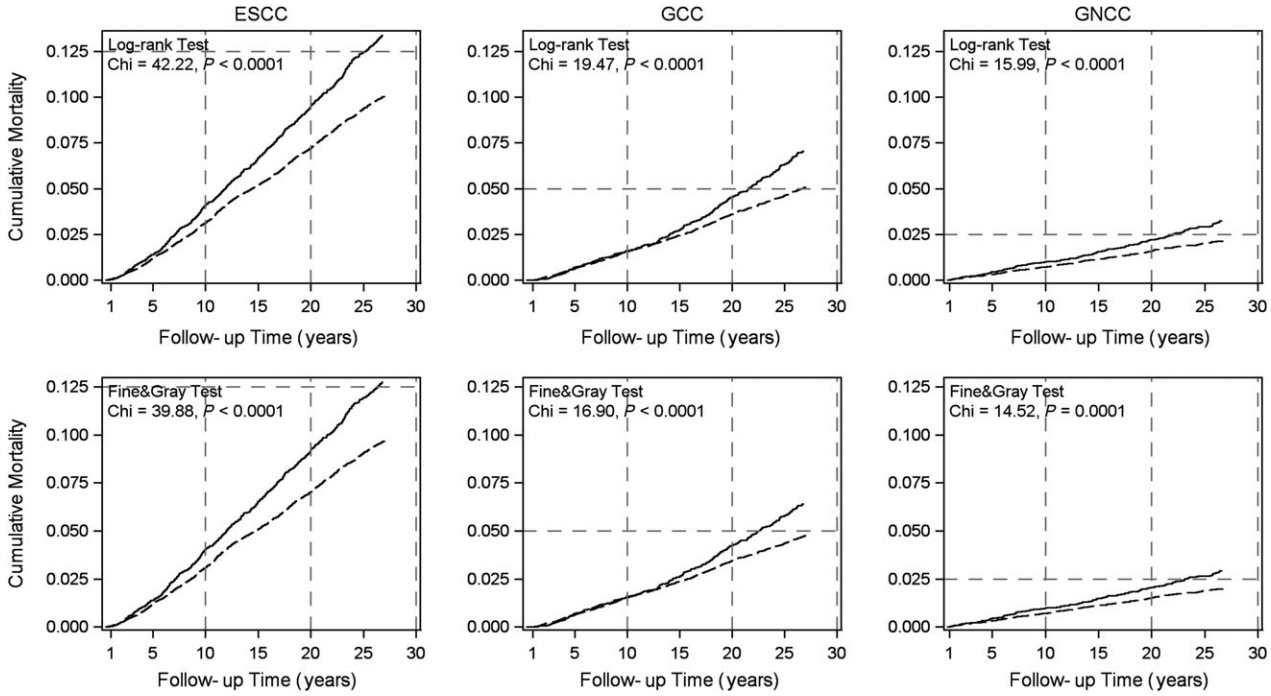

Figure 1 Effect of oral leukoplakia on cumulative mortality caused by esophageal squamous cell carcinoma (ESCC), gastric cardia carcinoma (GCC), and gastric non-cardia carcinoma (GNCC). The first row shows cumulative mortality from Kaplan–Meier estimates; the second row shows cumulative mortality based on a proportional subdistribution hazard model with a Fine and Gray test. Solid lines represent participants diagnosed with oral leukoplakia; dashes represent healthy participants.

The inverse associations were similar in PHMs and PSHMs (Table 3.) However, we found that the associations between OL and risk of ESCC death became stronger in PSHMs with heterogeneity among gender (men: HR_{CR} 1.20, 95% CI_{CR} 1.06–1.35 vs. women: HR_{CR} 1.25, 95% CI_{CR} 1.05–1.48), smoking status (smoker: HR_{CR} 1.16, 95% CI_{CR} 1.01–1.34 vs. non-smoker: HR_{CR} 1.26, 95% CI_{CR} 1.10–1.45) and alcohol consumption status (drinker: HR_{CR} 1.22, 95% CI_{CR} 1.01–1.40 vs. HR_{CR} 1.25, 95% CI_{CR} 1.12–1.40). No significant associations were observed between OL and GNCC or GCC mortality.

Table 3 summarizes the association between OL and risk of UGI death. The results were similar between PHMs and PSHMs. Unilateral OL was associated with a 13% higher risk of ESCC mortality (HR 1.13, 95% CIs 0.99–1.28), whereas the risk in subjects with bilateral OL increased by 32% (HR 1.32, 95% CIs 1.16–1.49), with a statistically significant monotonic trend ($P_{Trend} < 0.0001$). No monotonic trends were observed for GNCC or GCC deaths.

Discussion

This study is the largest prospective analysis to assess the association between OL and risk of UGI death using a proportional subdistribution hazard model in the Linxian General Population Nutrition Intervention Trial Cohort. Overall, we found that subjects with OL had a 22% higher risk of ESCC mortality, especially in the younger population. In addition, we also observed monotonic trends between OL and the risk of ESCC mortality. Previous studies by our team found that subjects with OL had an 18% higher risk of developing ESCC compared to those without OL,[18] comparable with the results of this study, thus our results confirm an association between OL and risk of ESCC death.

In a previous study,[18] we used the Cox proportional hazard model to assess the association between OL and risk of developing ESCC, which is a classical semi-parametric model to fit time-to-event data.[27] We analyzed the cause-specific hazard of each event type separately by applying Cox regression targeting each event type in turn, censoring all other event types.[26] However, if the event of interest in some subjects occurred after they had suffered a different event, Cox regression based on a product-limit method for estimating the survival function may bias the results.[25,28] By contrast, the proportional subdistribution hazard model, a competing risk model, is an extension of classic survival analysis and uses an analysis of time-to-event data for competing events.[20,21,25] Therefore, we used cause-

Table 2 Multivariable HRs and 95% CIs from Cox regression and proportional subdistribution hazard models†

	ESCC			GNCC			GCC		
	N	HR (95% CI)	HR_{CR} (95% CI_{CR})	N	HR (95% CI)	HR_{CR} (95% CI_{CR})	N	HR (95% CI)	HR_{CR} (95% CI_{CR})
Crude	**2345**	**1.34 (1.23–1.46)**	**1.32 (1.21–1.44)**	506	**1.46 (1.21–1.76)**	**1.43 (1.19–1.72)**	1139	**1.33(1.17–1.51)**	**1.30 (1.15–1.48)**
Age- and gender-adjusted	—	**1.27 (1.16–1.40)**	**1.31 (1.19–1.44)**	—	1.10 (0.90–1.34)	1.12 (0.92–1.36)	—	1.01 (0.89–1.16)	1.03 (0.90–1.18)
Fully adjusted	—	**1.17 (1.06–1.29)**	**1.22 (1.10–1.34)**	—	1.05 (0.86–1.29)	1.09 (0.89–1.33)	—	0.97 (0.84–1.11)	0.99 (0.87–1.14)
Age									
<52 years	**970**	**1.34 (1.15–1.56)**	**1.32 (1.13–1.54)**	192	1.13 (0.80–1.57)	1.09 (0.78–1.53)	499	1.09 (0.89–1.34)	1.06 (0.87–1.31)
≥52 years	1375	1.06 (0.93–1.20)	1.13 (0.99–1.29)	314	0.99 (0.77–1.30)	1.06 (0.82–1.38)	640	0.87 (0.72–1.05)	0.92 (0.76–1.11)
Gender									
Men	**1155**	**1.14 (1.01–1.29)**	**1.20 (1.06–1.35)**	321	1.07 (0.85–1.35)	1.12 (0.89–1.40)	692	0.95 (0.82–1.12)	0.99 (0.85–1.15)
Women	**1190**	**1.25 (1.05–1.48)**	**1.25 (1.05–1.48)**	185	1.05 (0.66–1.67)	1.03 (0.64–1.64)	447	1.02 (0.76–1.37)	1.01 (0.75–1.36)
Smoking									
Yes	842	1.12 (0.98–1.28)	**1.16 (1.01–1.34)**	232	1.21 (0.93–1.58)	1.25 (0.96–1.64)	478	1.02 (0.85–1.22)	1.06 (0.88–1.27)
No	**1503**	**1.24 (1.08–1.42)**	**1.26 (1.10–1.45)**	274	0.86 (0.61–1.22)	0.88 (0.61–1.25)	661	0.94 (0.72–1.12)	0.91 (0.73–1.14)
Drinking									
Yes	528	1.16 (0.96–1.39)	**1.22 (1.02–1.46)**	128	0.98 (0.68–1.41)	1.06 (0.73–1.53)	306	0.89 (0.70–1.13)	0.92 (0.72–1.17)
No	**1817**	**1.18 (1.05–1.33)**	**1.25 (1.12–1.40)**	378	1.10 (0.86–1.41)	1.16 (0.91–1.47)	833	1.00 (0.84–1.18)	1.04 (0.88–1.22)

†Adjusted for age at baseline, gender, smoking, drinking, body mass index, tooth loss, communes, and family cancer history. A total of 108 participants were excluded from the competing risk analysis because of a lack of baseline characteristic data. Hazard ratio (HR) (95% confidence interval [CI]) indicates the HR based on standard Cox regression model; HR_{CR} (95% CI_{CR}) indicates the HR based on proportional subdistribution hazard model to competing risk. Bold text indicates statistical significance. ESCC, esophageal squamous carcinoma; GCC, gastric cardia carcinoma; GNCC, gastric non-cardia carcinoma.

specific and PSHMs to fit the differences in cumulative mortality between ESCC, GNCC and GCC. In PSHMs, we found that the association between OL and risk of ESCC mortality became slightly stronger when considering the competing events of GNCC and GCC. Figure 1 shows the differences between cumulative mortality based on PHMs and PSHMs. The shift in curves between PHMs and PSHMs represents not only the association of hazards with OL, but also the influence of having a reduced number of individuals remaining at risk with OL as a result of the number of competing events.[29] That is, PHMs overestimated OL effects leading to survival bias,[30] while PSHMs were more accurate in estimating OL effects.

Recent studies have confirmed the strong association between OL and tobacco smoking and alcohol intake.[9,10,31] Some reports have also asserted that smokeless tobacco users are more likely to have poor oral hygiene, leukoplakia, erythroplakia, and tooth loss.[32] Therefore, we conducted stratified analysis by age (52 years, according to the median age at the baseline), gender, smoking, and drinking. We observed that non-tobacco smokers (HR_{CR} 1.26, 95% CI_{CR} 1.10–1.34), tobacco smokers (HR_{CR} 1.16, 95% CI_{CR} 1.01–1.34), non-alcohol drinkers (HR_{CR} 1.25, 95% CI_{CR} 1.12–1.40), and alcohol drinkers (HR_{CR} 1.22, 95% CI_{CR} 1.02–1.46) diagnosed with OL all had higher ESCC mortality rates; however, these results had high heterogeneity, which is inconsistent with our previous study.[18] Further study will be conducted in the future to explore the possible reasons for these inconsistencies.

The progression of OL to carcinoma is unpredictable and relatively infrequent, with an estimated overall risk of less than 2% per year.[3,4,7,33] In addition, a previous study reported that grading of OL was a significant indicator for evaluating malignant transformation risk in patients, and high-risk dysplastic OL was associated with a 4.57-fold (95% CI 2.36–8.84) risk of malignant transformation, compared to low-risk dysplasia.[6] The translation density is much lower than the reported rate. Because the oral cavity is anatomically adjacent to the esophagus and stomach, it is plausible that changes in the cavity could reflect changes in the UGI tract. Evidence from previous studies has suggested that pre-malignant forms of leukoplakia are centered on epithelial dysplasia.[34,35] Some factors have been reported to be associated with OL, including loss of differentiation-related keratins; carbohydrate antigens; epidermal growth factor receptor mutations; alterations in p53 gene expression, H3, and H3.3 histone messenger RNA; high frequency of hypermethylation for p14, p15 and p16; nitric oxide synthase; and nutritive DNA.[36] Furthermore, the role of chronic candidiasis and inflammation infection mechanisms have also been linked to the development of OL,

Table 3 HRs and 95% CIs for association between oral leukoplakia and upper gastrointestinal cancers based on standard Cox regression and proportional subdistribution hazard models

	ESCC				GNCC				GCC			
	HR (95% CI)†	P_{Trend}	HR_{CR} (95% CI_{CR})†	$P_{CR, Trend}$	HR (95% CI)†	P_{Trend}	HR_{CR} (95% CI_{CR})†	$P_{CR, Trend}$	HR (95% CI)†	P_{Trend}	HR_{CR} (95% CI_{CR})†	$P_{CR, Trend}$
Oral leukoplakia		**0.001**		**<0.001**		0.922		0.772		0.838		0.927
No	1.00		1.00		1.00		1.00		1.00		1.00	
unilateral	1.10 (0.97–1.24)		1.13 (0.99–1.28)		1.03 (0.80–1.34)		1.06 (0.81–1.37)		0.95 (0.79–1.13)		0.97 (0.82–1.16)	
Bilateral	**1.26 (1.11–1.42)**		**1.32 (1.16–1.49)**		1.05 (0.81–1.36)		1.10 (0.85–1.41)		0.99 (0.83–1.17)		1.01 (0.85–1.21)	

†Adjusted for age at baseline, gender, smoking, drinking, body mass index, tooth loss, communes, and family cancer history. A total of 108 participants were excluded from the competing risk analysis because of a lack of baseline characteristic data. Hazard ratio (HR) (95% confidence interval [CI]) indicates the HR based on standard Cox regression model; HR_{CR} (95% CI_{CR}) indicates the HR based on proportional subdistribution hazard model to competing risk. Bold text indicates statistical significance. ESCC, esophageal squamous carcinoma; GCC, gastric cardia carcinoma; GNCC, gastric non-cardia carcinoma.

which is associated with UGI cancers.[37] Few studies have assessed the relationship between OL and UGI cancer death with long-term follow-up in a Chinese population.[38–40]

Our study has a number of strengths, including the prospective study design, large number of cancer cases and OL patients, availability of data on potential confounders, long-term follow-up, and proper analysis using proportional subdistribution hazard models. However, there are still some limitations. Firstly, a diagnosis of OL was based on visual inspection by village doctors who were trained but only modestly experienced in diagnosing this disease. Any misclassification could have biased the result toward the null. Secondly, we only used a single assessment of OL at baseline and included subjects with a positive history of OL under the assumption that OL was a permanent change to the mucosa, which could contribute to a misclassification of OL status. Thirdly, unidentified confounders, such as the effects of esophageal cancer screening, could also lead to potential bias.

In summary, in this large prospective cohort study, we found that OL was associated with a significantly increased risk of ESCC mortality, especially in the younger population. The associations we discovered appear biologically plausible, but the mechanisms should be investigated in further studies.

Acknowledgments

We thank the participants and staff of the General Population Trial Cohort Study for their valuable contributions. Participants did not receive compensation, and staff were not compensated outside of their salaries.

Disclosure

No authors report any conflict of interest.

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