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Association between Oral Leukoplakia and Upper Gastrointestinal Cancers: A 28-year Follow-up Study in the Linxian General Population Trial

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Abstract

Background: Oral leukoplakia is a precancerous disorder that is common among residents in Linxian. However, the associations between oral leukoplakia and upper gastrointestinal cancers have not been reported. We investigated the relationships between oral leukoplakia and upper gastrointestinal cancers in the Linxian General Population Trial cohort.

Methods: The Linxian General Population Trial cohort, with 29,584 healthy adults enrolled in 1985 and followed through the end of 2012. With collected baseline data, hazard ratios (HR) and 95% confidence intervals (95% CI) for developing upper gastrointestinal cancers were estimated using Cox proportional hazard models.

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Authors' contribution—JHF and YLQ had all access to the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. YLQ, CCA, SMD and PRT contributed to study the concept and design. JHF, JBW, CXQ and YQZ obtained and analyzed the data. JHF and JBW drafted the report, which was edited by YLQ, CCA, SMD and PRT. All authors have reviewed and approved the final version.

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Trial registration: The trial is registered with ClinicalTrials.gov, NCT00342654

Conflict of interest

None declared.

Ethical approval This study was approved by the Institutional Review Boards of US National Institutes of Health and the Chinese Academy of Medical Science, and all participants gave informed consent for the use of their blood samples and all data.

Results: During 28 years of follow-up, we confirmed a total of 2,924 incident esophageal squamous cell carcinoma (ESCC) cases, 1,644 gastric cardia cancers and 590 gastric non-cardia cancers. Overall, participants with oral leukoplakia had significantly higher risk of developing ESCC (HR=1.18, 95% CI: 1.08, 1.29). Among individuals 52 years old at baseline, oral leukoplakia was associated with elevated risk of ESCC (HR=1.31, 95%CI: 1.15, 1.49). No significant associations were observed for gastric cardia or non-cardia cancers in either all subjects or subgroups.

Conclusions: Oral leukoplakia was associated with increased risk of ESCC, particularly in younger population. Future studies are needed to confirm these findings.

Keywords

oral leukoplakia; esophageal squamous cell carcinoma; gastric cardia carcinoma; gastric non-cardia carcinoma; Linxian General Population Trial

1. Introduction

Esophageal cancer ranked as the 6th leading cause of cancer death worldwide in 2008, causing an estimated 406,000 deaths, while gastric cancer was the 4th, killing 738,000 persons [1]. Nearly 52% of all esophageal cancer and 42% of the world's gastric cancer occur in China [1]. Within Linxian county and the surrounding Taihang Mountain region in north central China, rates of upper gastrointestinal (UGI) cancers are particularly high, and historically have been reported to be responsible for over 20% of all deaths.

The etiology of UGI cancers in Linxian and other high-risk regions remains unclear, but studies have shown a role for numerous dietary deficiencies [2-5] and genetic susceptibility [6-7], and have suggested that environmental carcinogens [8] and thermal damage [9, 10] are also involved. Associations between oral hygiene and UGI cancers have previously been reported by us [11, 12] and others [13, 14]. Oral leukoplakia is an established precursor lesion associated with high risk of oral squamous cell carcinoma [15]. In the 1970s, oral leukoplakia was also reported in a few families with tylosis who also had esophageal squamous cell cancers [16, 17]. Although oral leukoplakia is common in Linxian, little prospective data for the association between oral leukoplakia and UGI cancers are available.

This study aimed to examine the associations between oral leukoplakia and risk of esophageal squamous cell carcinoma (ESCC), gastric cardia carcinoma (GCC) and gastric non-cardia carcinoma (GNCC) in the Linxian General Population Trial cohort in China.

2. Methods

2.1. Study population and data collection

The detailed description of Linxian General Population Trial cohort has been reported in the previous studies [18, 19]. Briefly, the General Population Trial enrolled subjects between 40-69 years old from the general population of four communes in Linxian in 1985. Finally, a total of 29,584 healthy individuals were randomized and received up to four daily vitamin or mineral supplement combinations for 5.25 years, beginning in March 1986. Individuals who

had cancer, debilitating disease, or required daily medications were excluded. All participants were interviewed providing data on age, smoking, alcohol, family history of cancer and other variables, and given a brief physical examination that included an inspection of oral cavity, performed by a village doctor.

Age and sex were recorded from the participants' ID cards. Individuals' weight and height were measured during physical examination and body mass index (BMI) was calculated as weight in kilogram divided by height in meter squared. Smoking was defined as regular cigarette or pipe use for at least six months (including ever and current smokers), and alcohol drinking was defined as any consumption in the previous 12 months (The possible responses for drinkers could range from "several times per year" to "several times per day"). Family history of cancer was considered positive if a cancer was reported in at least one first-degree relative, including parents, siblings or offspring. Oral leukoplakia was characterized by white spots or patches in the mucous membranes inside the mouth after ruling out all other possible causes (such as oral candidiasis and lichen planus).

2.2. Follow up for cancer

During the trial period, village doctors visited all subjects monthly, and an International Endpoints Review Committee consisting of experts in cytology, pathology, surgery, and radiology from the US and China reviewed all endpoints and confirmed 85% of cancer diagnoses based on histology, cytology or x-rays. During the post-trial follow-up, a similar review was performed by Chinese experts. All esophageal cancers were squamous cell carcinomas; gastric cardia cancers were adenocarcinomas that occurred in the proximal three cm of the stomach and gastroesophageal junction; and gastric non-cardia cancers were adenocarcinomas located more distally [20].

2.3. Statistical analysis

We tested the differences of oral leukoplakia prevalence between groups using nonparametric Kruskal-Wallis Test and Chi Square Test. Cox Proportional Hazard Regression Models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI). Potential confounders included age at baseline (continuous variable), sex (men or women), smoking (yes (regular cigarette or pipe use for at least six months) or never), alcohol drinking (yes (any consumption of alcohol in the previous 12 months) or never), BMI (continuous variable), education (never or less than 5 years or primary school or tertiary high school/ higher education or unknown), family history of cancer (positive (defined as reporting a cancer in at least one first-degree relative) or negative) and commune (Rencun, Yaocun, Hengshui or Donggang). Stratification analyses were performed by age at baseline (<52 and ≥52, based on the median age), sex (men or women), smoking (yes or no) and drinking (yes or no). Tests of trend were conducted by assigning individuals' oral leukoplakia numbers as a continuous variable and entering this variable into the models. All analyses were performed using SAS software (version 9.2, SAS Institute Inc. Cary, North Carolina). All tests were two-sided test and the significant level was 0.05.

3. Results

A total of 29,449 individuals were included in the final analysis. At baseline, 7,105 persons were confirmed with oral leukoplakia. During 28 years of follow-up, we identified 2,924 incident ESCC cases, 1,644 GCC cases, and 590 GNCC cases.

Compared with subjects without oral leukoplakia, those with leukoplakia were younger (51.4 vs 52.0 years), were more often male (76.7% vs 34.3%), had a relatively lower median BMI (21.9 vs 22.0 kg/m²), were more likely to have higher education (13.6% vs 7.8%), were more commonly smokers (61.4% vs 20.2%) and drinkers (35.3% vs 19.7%), and were more likely to have a positive family history of cancer (36.5% vs 33.7%). (**Table 1**)

Table 2 presents the associations between oral leukoplakia and risk of all three UGI cancers. We found a significant association between oral leukoplakia and risk of ESCC. Compared with individuals without oral leukoplakia, subjects with leukoplakia had an 18% higher risk of ESCC incidence (HR=1.18, 95% CI: 1.08, 1.29). This significant association was present in both men and women (for men: HR=1.19, 95% CI: 1.06, 1.32; for women: HR=1.19, 95% CI: 1.02, 1.39). There was no statistically significance for gender difference. No significant associations were observed between oral leukoplakia and risk of GCC and GNCC.

In the subgroup analyses, we observed that risk for ESCC was increased for oral leukoplakia in both younger (<52 years) and older (≥ 52 years) age groups, although the HR reached statistical significant only in the younger group (HR=1.31, 95% CI: 1.15, 1.49). Results were also significant for risk of ESCC in both nonsmokers and smokers (HR=1.21, 95% CI: 1.07, 1.37 and HR=1.16, 95% CI: 1.03, 1.32, respectively). For the subgroup analysis by alcohol drinking, results were only significant for risk of ESCC among nondrinkers (HR=1.20, 95% CI: 1.08, 1.34), but not in alcohol drinkers (HR=1.15, 95% CI: 0.97, 1.35). No significant associations were observed for risk of GCC or GNCC in the subgroup analyses. (**Table 2**)

Table 3 summarizes the associations for the number of oral leukoplakia and risk of UGI cancers. Unilateral oral leukoplakia was associated with a 12% higher risk of ESCC (HR=1.12, 95% CI: 1.00, 1.25, $P<0.05$), while risk in subjects with bilateral oral leukoplakia increased by 26% (HR=1.26, 95% CI: 1.12, 1.41), with evidence of a statistically significant monotonic trend ($P_{trend}<0.001$). Neither unilateral oral leukoplakia, bilateral oral leukoplakia nor the trend for the number of oral leukoplakia were significantly associated with risk of GCC or GNCC (all $P>0.05$).

4. Discussion

This is the first prospective study to examine the association between oral leukoplakia and risk of UGI cancers. Overall, a significant association between oral leukoplakia and risk of ESCC was found. Risk for ESCC was increased in men and women alike, and in both younger and older persons, although the association by age group was stronger and statistically significant only in the younger group. We also observed evidence of a significant monotonic trend for the number of oral leukoplakia and risk of ESCC

($P_{trend} < 0.001$). No associations with GCC or GNCC were seen in either all subjects or subgroups.

Several previous studies have reported that oral leukoplakia is a precancerous lesion, with an estimated annual rate of malignant transformation of 1.36%. Both the size and extent of oral leukoplakia are regarded to be risk factors for malignant transformation. Oral cavity is anatomically adjacent to the esophagus and stomach, and it is plausible that changes in the oral cavity could reflect changes in the UGI tract. Oral leukoplakia has been reported to have associations with genetic variants of the phase I xenobiotic metabolism enzyme GSTT1, p53 overexpression[21], and with variants of DNA repair genes[22], and these variants have also shown associations with risk of UGI cancers. In addition, many molecular factors are involved in malignant transformation between oral leukoplakia and cancer. The epidermal growth factor receptor (EGFR) was highly expressed in oral leukoplakia tissue [23, 24], and EGFR expression was also related to tumor stage, metastasis, and poor clinical outcome [25]. Thus several molecular alterations found in oral leukoplakia are similar to those seen in cancer.

Smoking [26] and alcohol drinking [27] have all been related to increased risk of oral leukoplakia, as have deficiencies of beta-carotene [28]. Further, supplementation with vitamin A and beta-carotene [29, 30] and consumption of fresh vegetables have been associated with reduced risk of oral leukoplakia[31]. Risk factors for oral leukoplakia in Linxian are not all similar to those reported from other areas. In Linxian women seldom consume tobacco or alcohol. Despite this, 10% of women had oral leukoplakia. Thus, smoking, and alcohol drinking cannot explain oral leukoplakia in Linxian. Linxian residents have a low socioeconomic status and poor nutritional status as a result of limited intake of fresh vegetables, fruits, meats, and eggs [2]. It seems possible, even likely, that the multiple nutrient deficiencies observed in Linxian contribute to the development of oral leukoplakia. Risk factors for oral leukoplakia in Linxian were also associated with higher risk of ESCC and gastric cancer. Smoking, for example, was related to increased risk of ESCC, GCC, and GNCC in an earlier report from the Linxian General Population Trial cohort [2]. Such shared risk factors suggest potential association between oral leukoplakia and UGI cancers.

As further potential evidence for this association, a previous case series from United Kingdom reported that most ESCC cases had evidence of pre-leukoplakia or leukoplakia in their oral mucosa[17]. Case reports are weak evidence for causality, however, and the present study represents the first analytic epidemiological study to investigate the association between oral leukoplakia and UGI cancers. In our study, oral leukoplakia was associated with risk of ESCC, while no association was seen with GCC or GNCC. From an anatomic perspective, the esophagus is closest to the mouth, the cardia next closest, and the non-cardia farthest. Thus, the associations we observed for oral leukoplakia and UGI cancer sites might be plausible.

This study has several strengths, including the prospective design, large sample size, and long-term follow-up. One limitation was the diagnosis of primary exposure (oral leukoplakia), which was based on visual inspection by village doctors who were trained but only modestly experienced in diagnosing this disease. Inaccurate diagnosis, however, would

more likely have resulted in an over-diagnosis of oral leukoplakia, which should have biased the results towards the null. In addition, we only had single assessment of baseline oral leukoplakia, which could contribute to misclassification of oral leukoplakia status.

In summary, this first prospective study of oral leukoplakia and UGI cancers found that oral leukoplakia was significantly associated with risk of ESCC, especially among younger individuals. Further studies of evaluating the association between oral leukoplakia and UGI cancers are warranted.

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Abbreviations

UGI	upper gastrointestinal
ESCC	esophageal squamous cell carcinoma
GCC	gastric cardia carcinoma
GNCC	gastric non-cardia carcinoma
BMI	body mass index
HR	hazard ratios
95% CI	95% confidence intervals
EGFR	epidermal growth factor receptor

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Research highlights

1. We investigated the associations between oral leukoplakia and UGI cancers.
2. Participants with oral leukoplakia had higher risk of ESCC.
3. Oral leukoplakia was not associated with elevated risk of GCC and GNCC.

Table 1

Baseline demographic characteristics by oral leukoplakia in the Linxian General Population Trial Cohort

	Oral leukoplakia		<i>P value</i>
	Yes	No	
Age (Mean±SD)	51.4±8.7	52.0±8.9	<0.001
Sex, n (%)			
Men	5452 (76.7)	7668 (34.3)	<0.001
Women	1653 (23.3)	14676 (65.7)	
BMI, Mean±SD (kg/m ²)	21.9±2.2	22.0±2.6	0.032
Education level, n (%)			
Never	1982 (27.9)	9831 (44.0)	
Less than 5 years	2753 (38.7)	6430 (28.8)	<0.001
Primary school	1072 (15.1)	2079 (9.3)	
Tertiary high school or higher education	962 (13.6)	1742 (7.8)	
Unknown	366 (4.7)	2263(10.1)	
Smoking, n (%)			
No	2740 (38.6)	17824 (79.8)	<0.001
Yes	4365 (61.4)	4520 (20.2)	
Alcohol drinking, n (%)			
No	4597 (64.7)	17942 (80.3)	<0.001
Yes	2508 (35.3)	4402 (19.7)	
Family history of cancer, n (%)			<0.001
No	4508 (63.5)	14808(66.3)	
Yes	2597 (36.5)	7536(33.7)	

Table 2

Crude and adjusted hazards ratios (HR) and 95% confidence intervals (CI) for the associations between oral leukoplakia and upper gastrointestinal cancers in the Linxian General Population Trial

	ESCC			GCC			GNCC		
	n	HR (95%CI)	<i>P</i> _{interaction}	n	HR (95%CI)	<i>P</i> _{interaction}	n	HR (95%CI)	<i>P</i> _{interaction}
Crude	2924	1.33 (1.23,1.45)	-	1644	1.44 (1.30,1.60)	-	590	1.42 (1.19,1.69)	-
Age- and sex-adjusted	-	1.27 (1.16,1.38)	-	-	1.08 (0.97,1.21)	-	-	1.06 (0.88,1.27)	-
Fully adjusted*	-	1.18 (1.08,1.29)	-	-	1.04 (0.92,1.16)	-	-	1.01 (0.83,1.23)	-
Age									
<52	1344	1.31 (1.15, 1.49)	0.243	734	1.12 (0.94, 1.33)	0.231	250	1.02 (0.76, 1.38)	0.944
52	1580	1.08 (0.95, 1.22)		910	0.96 (0.82, 1.12)		340	1.00 (0.77, 1.29)	
Sex									
Men	1400	1.19 (1.06,1.32)	0.928	1008	1.05 (0.93,1.20)	0.701	367	1.06 (0.86,1.32)	0.473
Women	1524	1.19 (1.02, 1.39)		636	0.97 (0.75, 1.25)		223	0.84 (0.53, 1.35)	
Smoking									
No	1932	1.21(1.07, 1.37)	0.616	952	0.97 (0.81, 1.16)	0.415	329	0.83 (0.59, 1.15)	0.210
Yes	992	1.16 (1.03, 1.32)		692	1.09 (0.94, 1.27)		261	1.16 (0.91, 1.49)	
Alcohol drinking									
No	2244	1.20 (1.08, 1.34)	0.653	1216	1.05 (0.91, 1.21)	0.380	441	1.02 (0.80, 1.28)	0.803
Yes	680	1.15 (0.97, 1.35)		428	0.99 (0.81, 1.21)		149	1.02 (0.72, 1.43)	

Abbreviations: ESCC, esophageal squamous cell carcinoma; GCC, gastric cardia carcinoma; GNCC, gastric non-cardia carcinoma.

* Adjusted for age at baseline, sex, smoking, drinking, BMI, family history of cancer, education, and commune.

Table 3

Hazards ratios (HR) and 95% confidence intervals (CI) for the associations between number of oral leukoplakia and upper gastrointestinal cancers in the Linxian General Population Trial

	ESCC		GCC		GNCC	
	HR (95%CI) *	<i>P</i> _{trend}	HR (95%CI) *	<i>P</i> _{trend}	HR (95%CI) *	<i>P</i> _{trend}
Oral leukoplakia						
No	1.00		1.00		1.00	
Unilateral	<u>1.12(1.00, 1.25)</u>	<u><0.001</u>	0.99(0.85, 1.15)	0.385	1.08(0.85, 1.37)	0.802
Bilateral	<u>1.26(1.12, 1.41)</u>		1.08(0.93, 1.24)		0.95 (0.74, 1.21)	

Abbreviations: ESCC, esophageal squamous cell carcinoma; GCC, gastric cardia carcinoma; GNCC, gastric non-cardia carcinoma.

* Adjusted for age at baseline, sex, smoking, drinking, BMI, family history of cancer, education, and commune.