Risk factors for precancerous lesions of esophageal squamous cell carcinoma in high-risk areas of rural China
A population-based screening study
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Abstract
Although many studies in China have found that environmental or lifestyle factors are major contributors to the etiology of esophageal cancer, most of the patients in the above studies are in the middle and late stages, the early-stage patients account for a small proportion. To clarify the risk/protective factors contributing to early lesions, we conducted the present cross-sectional study. A total of 2925 healthy controls and 402 patients with esophageal precancerous lesions were included in our study by endoscopic examination. Information on risk/protective factors was collected by personal interview, and unconditional logistic regression was used to determine adjusted odds ratios (AORs) by the maximum-likelihood method.

Smoking $>$ 20 pack-years (AOR = 1.48), duration of drinking $>$ 30 years (AOR = 1.40), alcohol consumption $>$ 100 mL/d (AOR = 1.44), gastroesophageal reflux disease (AOR = 1.75), esophagitis (AOR = 1.25), a family history of esophageal cancer (AOR = 1.92), or stomach cancer (AOR = 1.92) were significant risk factors for esophageal precancerous lesions. There was a negative correlation between abdominal obesity and early esophageal cancer and precancerous lesions (AOR = 0.75). In addition, we found that there was a synergistic effect between a family history of esophageal cancer and drinking (AOR = 3.00) and smoking (AOR = 2.90).

Lifestyle risk factors, genetic factors, and upper gastrointestinal diseases are associated with the development of esophageal precancerous lesions. These results highlight the need for primary prevention to reduce the future burden of cancer and other chronic diseases in high-risk areas of rural China.

Abbreviations: AORs = adjusted odds ratios, BMI = body mass index, EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma.

Keywords: cross-sectional study, esophageal precancerous lesions, risk-factors, synergistic effect

1. Introduction
Esophageal cancer, which occurs in the esophageal epithelium, is the eighth most common malignant tumor and the sixth leading cause of cancer-related deaths worldwide. There were more than 572,034 new cases of esophageal cancer in the world in 2018, and more than 508,585 people died of esophageal cancer.\textsuperscript{[1]} The epidemiology of esophageal cancer varies widely across geographic regions, particularly its incidence rate.\textsuperscript{[2–4]} Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are 2 major histological types of esophageal cancer.
While EAC is highly prevalent in many Western countries, ESCC is predominant in China, accounting for over 90% of esophageal cancer cases. ESCC accounts for the majority of esophageal cancer cases worldwide, and the greatest concentration of ESCC cases is located in the “Asian Esophageal Cancer Belt”, which is an area that starts in the Middle East and stretches east to China and north to Russia.

In recent decades, as a result of medical progress and the improvement of living standards, ESCC-induced mortality has decreased significantly in China. Despite the advancements made in cancer management, ESCC remains the fourth most common cancer in both urban and rural areas of China, with the majority of cancer cases concentrated in resource-limited populations and poverty-stricken rural areas. More than 90% of ESCC patients have already progressed to the middle and late stages upon diagnosis. Their quality of life is poor, and the overall 5-year survival rate is less than 20%; on the other hand, early-stage esophageal cancer has a better prognosis, with a 5-year survival rate higher than 80%. Moreover, the exact cause of esophageal cancer is still not very clear, so it is critical to clarify the major risk factors to prevent this lethal disease from progressing to late stages due to their poor prognoses.

The geographic variation in ESCC occurrence in China strongly suggests that environmental or lifestyle factors are major contributors to the etiology of esophageal cancer. Epidemiological studies have shown that smoking and alcohol consumption are important factors for ESCC. A previously reviewed study in Linxian, Henan Province, showed that major risk factors for ESCC are the intake of nitrosamines and their precursors, which are found in pickled vegetables, moldy food, and water. Furthermore, evidence from southern China showed that hot beverages and high-temperature cooking methods might greatly increase the risk of esophageal cancer, and a study in the Chaoshan area, Guangdong Province, found fermented fish sauce to be an important risk factor. Although several epidemiological studies of the risk factors for ESCC have been conducted in China, most of the patients in these studies are in the middle and late stages of the disease, and early-stage ESCC patients account for a small proportion of the participants.

Feicheng is a national pilot region for the “Early detection and treatment of upper gastrointestinal cancer project” in China. Since 2006, with the support of central fiscal subsidies to local special public health funds, endoscopic biopsy with iodine staining has been used for the early diagnosis and treatment of esophageal cancer. Through this project, we screened a large number of patients with esophageal precancerous lesions. To clarify the risk/protective factors for early lesions, we conducted this cross-sectional study.

2. Materials and methods

2.1. Study design and population

Our cross-sectional study was based on data from the “Early detection and treatment of upper gastrointestinal cancer project”. According to the technical scheme, residents aged 40 to 69 were encouraged to undergo a screening for esophageal cancer via an endoscopic examination with Lugol iodine staining and biopsy. We supplemented this project by assessing the participants’ exposure to potential risk factors. The study was approved by the Ethics Committee of the People’s Hospital of Feicheng, and written informed consent was obtained from all participants.

Patients were recruited from the population of individuals with newly diagnosed esophageal precancerous lesions who were screened at the People’s Hospital of Feicheng. The inclusion criteria were as follows: residents who were 40 to 69 years old, pathologically confirmed diagnosis of esophageal precancerous lesions. According to the pathological diagnosis results after endoscopy, patients with mild, moderate, and severe dysplasia were classified as having esophageal precancerous lesions. It is worth mentioning that to ensure the validity of pathological results, endoscopic examination with Lugol’s iodine staining was performed by physicians experienced with endoscopic examinations. Depending on the size of the lesion, a multipoint biopsy examination was performed by 2 pathologists without knowledge of the staining results. The exclusion criteria were as follows: the presence of iodine allergy and hyperthyroidism; concurrent cancer at another organ site, such as stomach cancer or cardia cancer; and a history of cancer.

Given that both groups in our study were from the same village, the participants were similar in terms of education level, economic situation, and occupations but did not have similar lifestyles. All participants who underwent endoscopic examination and received pathological diagnosis confirming the absence of esophageal lesions from June to August were allocated into the control group through the internal control method. The inclusion criteria for controls were the same as those for patients except for the cancer diagnosis. The questionnaire given to controls included the same items as the questionnaire given to patients except for the items asking about esophageal precancerous lesions. From July to August 2016, a total of 5476 individuals who underwent endoscopic examination were approached; 402 patients with esophageal precancerous lesions and 2925 healthy controls participated, and 1149 individuals were eliminated due to inconclusive pathological diagnosis results, incomplete questionnaires, or suspected gastric or cardiac lesions.

2.2. Data collection

Patients were informed about the study by their screening physicians, and then, they were referred to the research center upon receipt of informed consent. Personal interviews were conducted by trained medical care personnel. The interviewers used a structured and validated questionnaire to collect information on demographic characteristics and potential risk factors, such as personal smoking history, alcohol use, medical history, occupational history, and family history of cancer.

Smokers were defined as participants who had smoked for at least 6 months. Smoking history was recorded in terms of pack-years, estimated by multiplying the number of years of smoking by the number of packs of cigarettes smoked per day, such that 1 pack-year = 1 pack of cigarettes per day for a year. Drinkers were defined as participants who had drunk beer, wine, or liquor, and spirits for 6 months in the past. Individuals who had ever drank were further classified according to the total lifetime volume of ethanol consumed in milliliters, which was computed according to the frequency of drinking, type of drinking (beer, wine, or liquor, and spirits), amount of drinking per day, and duration of consumption summed over the whole period of alcohol use. According to the amount of smoking and drinking in the control group, the approximate median value of the control group (20 pack-years for smoking, 100 mL/d for drinking) was selected as the criterion to divide the groups.
The questionnaire was also used to collect information about the history of several medical conditions, such as oral hygiene, gastroesophageal reflux disease, and diabetes. Patients and controls were questioned about the history of cancer among their first- and second-degree relatives. Additional information was collected from those with a positive family history, including the number of family members with cancer, type(s) of cancer, age(s) at cancer diagnosis, and relationship(s) to the study participant. In addition, abdominal obesity (defined as waist circumference ≥ 102 cm in men and ≥ 88 cm in women) was assessed. Each item in the questionnaire was completed in strict accordance with the coding instructions. The data were entered twice to ensure accuracy and then collated into a final database.

2.3. Statistical analysis

EPI-DATA (http://www.epidata.dk/) was used for data entry, and SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina) was used for data analysis. The univariate conditional logistic regression model was used to assess the marginal effects of each factor on the risk for ESCC. In addition, all variables were analyzed through multivariable unconditional logistic regression to calculate adjusted odds ratios and 95% confidence intervals (CIs) and were estimated using maximum likelihood estimation. Moreover, given the good ability to appropriately scale for addressing biologic interactions and public health concerns, we investigated the possible interactions between risk factors through multiple logistic regression models. Both adjusted odds ratios (AORs) were adjusted for age, sex, education, place of residency, and other significant risk factors using the likelihood ratio test. We chose to use additive models rather than multiplicative models to investigate possible interactions between risk factors because the former has a more appropriate scale for addressing biological interactions and public health concerns. All P-values came from the likelihood ratio test comparing nested models and were 2-sided.

3. Results

3.1. The character of study participants

Table 1 presents the distribution of demographic features for study participants who were diagnosed with esophageal precancerous lesions and for healthy controls. A total of 2925 healthy controls and 402 patients with esophageal precancerous lesions were included in the study. A total of 59.20% of the patients were male; this proportion was higher than that among the healthy controls (P < .001). In addition, healthy controls were slightly younger than patients, with a mean difference of 2.24 years (P = .001). Patients also had a lower income level than healthy controls (P = .04). There were no significant differences in job occupation, education level, or registered residence between the esophageal precancerous lesion group and the healthy control group. During statistical analyses, we chose to adjust all demographic factors in the univariate conditional logistic regression model.

Table 2 shows the results for the association between smoking and drinking. The proportion of patients who smoked was 41.79%, which was significantly higher than that of controls (35.71%); the risk of ESCC was 25.6% greater among ever-smokers than among nonsmokers. Compared with nonsmokers, those who smoked unfiltered cigarettes and had smoked more than 20 pack-years had a 73% and 48% higher risk of ESCC, respectively. In terms of drinking, we observed a significant effect of liquor on the elevated risk for esophageal precancerous lesions (AOR = 1.39, 95% CI 1.10–1.74). Overall, heavy drinkers who consumed > 100 mL/d of alcohol and had a drinking history of more than 20 years had a greater risk of ESCC (by 44% and 40%, respectively) than non-drinkers.
3.3. Chronic medical conditions.

Table 3 summarizes the prevalence of several diseases among patients and controls. Good oral hygiene can reduce the risk of esophageal precancerous lesions, but when we control for the confounding effects of other significant risk factors, this protective effect loses statistical significance. The history of gastroesophageal reflux disease and esophagitis lead to a 75% and 25% greater risk of esophageal precancerous lesions, respectively. In addition, our study found that people with abdominal obesity have a 25% lower disease risk than nonobese people. However, we observed no significant correlation between chronic diseases, such as hypertension diabetes, and early-stage esophageal cancer after controlling for the confounding effects of other significant risk factors.

Table 4 shows that a family history of cancer in general and of esophageal cancer in particular was associated with a significantly elevated risk for esophageal precancerous lesions.

### Table 2

Effects of risk factors for ESCC in multivariable logistic regression analysis.

| Study Variables          | Patients | Control | COR (95% CI) | AOR (95% CI) |
|--------------------------|----------|---------|--------------|--------------|
|                          | N        | %       | N            | %            |              |
| Smoke                    |          |         |              |              |              |
| Never                    | 234      | 58.2    | 1681         | 64.3         | 1 (reference) | 1 (reference) |
| Ever                     | 168      | 41.8    | 1044         | 35.7         | 1.29 (1.05–1.60) | 1.26 (1.00–1.578) |
| Smoking type             |          |         |              |              |              |
| Filter type              | 143      | 85.1    | 946          | 90.6         | 1.22 (0.97–1.52) | 1.22 (0.96–1.54) |
| Non-filter type          | 25       | 14.9    | 98           | 9.39         | 2.05 (1.30–3.25) | 1.73 (1.08–2.79) |
| Duration of smoking, pack-years |       |         |              |              |              |
| ≤20                      | 80       | 47.6    | 507          | 48.6         | 1.27 (0.97–1.67) | 1.15 (0.87–1.53) |
| >20                      | 88       | 52.4    | 537          | 51.4         | 1.32 (1.01–1.71) | 1.48 (1.11–1.98) |
| Secondhand smoke         |          |         |              |              |              |
| Never                    | 175      | 43.5    | 1383         | 47.3         | 1 (reference) | 1 (reference) |
| Ever                     | 227      | 56.5    | 1542         | 52.4         | 1.16 (0.94–1.44) | 1.14 (0.91–1.41) |
| Drink                    |          |         |              |              |              |
| Never                    | 226      | 56.2    | 1861         | 63.6         | 1 (reference) | 1 (reference) |
| Ever                     | 176      | 43.8    | 1064         | 36.4         | 1.36 (1.10–1.68) | 1.35 (1.08–1.69) |
| Duration of drinking     |          |         |              |              |              |
| ≤30 yr                   | 62       | 35.2    | 464          | 43.6         | 1.10 (0.82–1.48) | 1.30 (0.95–1.77) |
| >30 yr                   | 114      | 64.8    | 600          | 56.4         | 1.57 (1.23–2.00) | 1.40 (1.08–1.82) |
| Alcohol consumption      |          |         |              |              |              |
| ≤100 ml/d                | 39       | 22.2    | 277          | 26           | 1.16 (0.81–1.67) | 1.11 (0.77–1.61) |
| >100 ml/d                | 137      | 77.8    | 787          | 74           | 1.43 (1.14–1.80) | 1.44 (1.13–1.84) |

* AOR = odds ratio adjusted for sex, age, occupation, education level, registered residence, income, CI = confidence interval.

3.4. Family history of cancer

Table 4 shows that a family history of cancer in general and of esophageal cancer in particular was associated with a significantly elevated risk for esophageal precancerous lesions.

### Table 3

Effects of other medical conditions in multivariable logistic regression analysis.

| Study Variables         | Patients | Control | COR (95% CI) | AOR (95% CI) |
|-------------------------|----------|---------|--------------|--------------|
|                          | N        | %       | N            | %            |              |
| Oral hygiene            |          |         |              |              |              |
| Poor                    | 90       | 22.39   | 505          | 17.27        | 1 (reference) | 1 (reference) |
| good                    | 312      | 77.61   | 2420         | 82.73        | 0.72 (0.56–0.93) | 0.82 (0.63–1.06) |
| GERD                    |          |         |              |              |              |
| No                      | 296      | 73.63   | 2473         | 84.55        | 1 (reference) | 1 (reference) |
| Yes                     | 106      | 26.37   | 452          | 15.45        | 1.96 (1.54–2.50) | 1.75 (1.60–1.96) |
| Hypertension            |          |         |              |              |              |
| No                      | 316      | 78.61   | 2286         | 78.15        | 1 (reference) | 1 (reference) |
| Yes                     | 86       | 21.39   | 639          | 21.85        | 0.97 (0.76–1.26) | 0.88 (0.68–1.14) |
| Diabetes                |          |         |              |              |              |
| No                      | 391      | 97.26   | 2811         | 96.1         | 1 (reference) | 1 (reference) |
| Yes                     | 11       | 2.74    | 114          | 3.9          | 0.69 (0.37–1.30) | 0.61 (0.32–1.19) |
| Esophagitis             |          |         |              |              |              |
| No                      | 210      | 52.24   | 1670         | 57.09        | 1 (reference) | 1 (reference) |
| Yes                     | 192      | 47.76   | 1255         | 43.91        | 1.21 (0.99–1.50) | 1.25 (1.02–1.55) |
| Abdominal obesity       |          |         |              |              |              |
| No                      | 125      | 32.13   | 694          | 25.92        | 1 (reference) | 1 (reference) |
| yes                     | 264      | 67.87   | 1983         | 74.08        | 0.74 (0.59–0.93) | 0.75 (0.59–0.94) |

* AOR = odds ratio adjusted for sex, age, occupation, education level, registered residence, income, CI = confidence interval, ESCC = esophageal squamous cell carcinoma, GERD = gastroesophageal reflux disease.
Compared with the group without a family history, the risk of ESCC increased by 86% and 131% when individuals had fathers or mothers with ESCC, respectively. In addition to esophageal cancer, a family history of gastric cancer is also an important risk factor for esophageal precancerous lesions, leading to an 86% increase in risk. The distribution of other types of cancer, such as intestinal and lung cancer, among first-degree relatives was not significantly different between patients and controls.

3.5. Interactions between risk factors

Table 5 shows the independent and joint effects of cigarette smoking, drinking, and family history of esophageal cancer on esophageal precancerous lesion risk among the participants. After adjusting for other significant baseline factors, we found synergistic relationships between smoking and a family history of esophageal cancer and between drinking and a family history of esophageal cancer. The relative excess risk for patients with a family history of esophageal cancer combined with a history of cigarette smoking or drinking exceeded the sum of the relative excess risk for both risk factors (taking the family history of esophageal cancer and the history of drinking as an example, 3.0 – 1.0 ≥ (1.36 – 1.0) + (1.65 – 1.0)). No significant risk interaction was observed between other risk factors, such as drinking with cigarette smoking, abdominal obesity, or a family history of other cancers.

4. Discussion

Given that its exact mechanism is not yet clear, research on risk factors for early-stage esophageal cancer and precancerous lesions is still widespread. Our study is a large population-based epidemiological study of esophageal precancerous lesions in which multiple risk factors were assessed simultaneously. In our previous cross-sectional study, we focused more on the exploration of life habits and living conditions, whereas in this study, we conducted a more detailed subgroup analysis of factors such as smoking, alcohol consumption, and family history of cancer. Smoking is one of the most important public health issues recognized in the world and can increase the incidence and mortality of multiple malignant tumors, such as lung cancer, stomach cancer, and liver cancer. Our results suggest that heavy cigarette smoking (≥20 pack-years) is a significant risk factor for early-stage esophageal cancer and precancerous lesions, which is consistent with previous cross-sectional and cohort studies both in Western and Eastern countries.

In addition, physiological experiments have also confirmed that nicotine, an important ingredient in tobacco, not only causes oxidative stress to the esophageal mucosa but also induces methylation of the fragile histidine triad gene in esophageal squamous epithelial cells, which in turn leads to esophageal malignant lesions. Consistent with 3 meta-analyses, heavy alcohol consumption was associated with an increased risk of ESCC. It is generally accepted that alcohol increases the risk of certain cancers, and ethanol metabolism through oxidation by alcohol dehydrogenases or through the microsomal oxidative system (cytochrome P450 E1) may generate toxic metabolites, such as acetaldehyde and reactive oxygen species. These metabolites are generally responsible for upper gastrointestinal carcinogenic effects. Additionally, ethanol can stimulate the expression of specific proteins in intestinal epithelial cells to affect intestinal permeability, which can lead to intestinal leakage and eventually endotoxemia. Once these toxins enter the bloodstream, they...
will have a certain impact on the rate of cancer development. In addition, some inferior liquors are brewed from mildewed foods containing a large amount of strong carcinogen-aflatoxin in rural areas of China, which can also induce the occurrence of esophageal cancer.

Our study found that esophagitis has a promoting effect on the development of esophageal squamous cell carcinoma, which is consistent with previous studies. Such a greater risk could be related to the infiltration of inflammatory cells and basal cell hyperplasia. Previous studies have reported that individuals with poor oral health, diabetes, or hypertension have a higher risk of developing ESCC. In this study, we found no significant relationship between these factors and ESCC after controlling for baseline variables, as shown in Table 3. The risks observed in previous studies may be confused with other risk factors, such as smoking or heavy drinking.

As early as 2007, the World Cancer Research Foundation and the American Institute for Cancer Research reported that excess body fat is a robust risk factor for EAC. Although a higher body mass index (BMI) has been widely reported as a risk factor for EAC, an opposite effect of BMI for ESCC was also observed. Two prospective studies in Norway found a negative correlation between obesity (defined as a BMI > 30) and the risk of ESCC. Unlike previous studies, our study used abdominal obesity as a variable to explore the role of obesity in the development of ESCC. After adjusting for baseline factors, we found that people with abdominal obesity have a 25% lower disease risk than nonobese people. This finding was somewhat surprising since obesity induces the production of reactive oxygen species and pro-inflammatory cytokines, which are triggers for carcinogenesis, and intra-abdominal fat cells tend to be more metabolically active and detrimental than other fat in the body. Given the strong correlation between abdominal obesity and drinking (P < 0.05, data not shown), a possible explanation for this inverse association is the negative moderating effect of alcohol consumption on the association between abdominal obesity and cancer. Unfortunately, currently available epidemiological evidence is too sparse to draw reliable conclusions between abdominal obesity and ESCC. We believe that the true correlation between obesity and the risk of ESCC could be verified after obtaining a sufficient number of cases from queues that are followed up for a long time in the future.

A significantly greater risk was demonstrated among individuals reporting a first degree relative with esophageal cancer in China. In our study, we found that participants with a positive family history of esophageal cancer had a 2-fold higher risk (AOR = 1.92) for early-stage esophageal cancer and precancerous lesions than those without a family history of esophageal cancer. Having a father or mother with esophageal cancer was a significant risk factor for the individual’s development of the disease. In addition, given that genomic studies have revealed the important contribution of genetic susceptibility to the occurrence of ESCC as well, we have enough reason to believe that heredity does play an important role in the occurrence of esophageal malignant lesions. On the other hand, we did not find the same risk among individuals whose siblings have esophageal cancer. Due to the deficiency of exposure information in the siblings, we cannot distinguish whether this effect difference is caused by different exposure factors between siblings or genetic specificity (such as dominant or recessive XXY-linked).

In conclusion, the present study made 3 major findings: we confirmed the significance of previously established risk factors for precancerous esophageal lesions, such as drinking, cigarette smoking, and a family history of esophageal cancer we found a negative correlation between abdominal obesity and early-stage esophageal cancer and precancerous lesions we confirmed that there was a synergistic effect of a family history of esophageal cancer and alcohol consumption on the occurrence of early-stage esophageal cancer and precancerous lesions, as well as a synergistic effect of cigarette smoking and a family history of esophageal cancer.

Although our study is one of the largest studies of early-stage esophageal cancer, it has some limitations. Most of the risk factors included in the study were based on self-reported data and may be susceptible to recall bias. In addition, the order of appearance between exposure factors and early-stage esophageal cancer is difficult to determine. Therefore, a large-scale cohort study on early-stage esophageal cancer and precancerous lesions will be the focus of our work in the next phase. We hope our study will help physicians detect early-stage esophageal cancer and precancerous lesions and prompt the study of esophageal cancer prevention strategies among high-risk individuals.

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Author contributions

Jialin Wang is the primary corresponding author. Author Peipei Lu led the development of this manuscript. Jianhua Gu assisted in data analysis and designed all manuscript tables. Authors Nan Zhang completed the data collection. Jialin Wang added important background knowledge and improved the manuscript by repeated readings and rephrasing as well as critical discussions of the intellectual content. All authors contributed to, read, and approved the final version of this manuscript.
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