




## Research Paper

# Risk Factors Associated with Precancerous Lesions of Esophageal Squamous Cell Carcinoma: a Screening Study in a High Risk Chinese Population

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## Abstract

**Background:** Esophageal squamous cell carcinoma (ESCC) has been having a high mortality rate in China. Most patients are diagnosed in advanced stages, leading to the poor prognosis and low 5-year survival rate. Detection of precancerous lesions or early cancers is the key to improving this situation. Although previous studies have identified some risk factors for ESCC, they rarely paid attention to the premalignant esophageal lesions. We thus initiated a population-based screening study aiming to assess risk factors associated with esophageal precancerous lesions (EPLs) in a high risk Chinese population.

**Methods:** From September 2013 to July 2015, we screened residents aged 40–69 years from 53 randomly selected communities in Feicheng, China (n = 5076). Each participant went through questionnaire interview, physical examination, endoscopy and biopsy. Using logistic regression, we compared participants with EPLs to that with normal esophageal mucosa for finding potential risk factors of EPLs.

**Results:** A total of 570 participants were diagnosed with EPLs. We observed no association between EPLs and tobacco smoking or alcohol consumption in unadjusted or adjusted model. In the adjusted model, the OR (95% CI) was 1.84 (1.18-2.89) for people of drinking shallow-well water comparing to people who was drinking tap-water. In a comparison of participants with good oral health, the ESD/ESCC ORs (95% CI) for those with very poor or poor oral health, were 1.78 (1.28-2.49) and 1.58 (1.16-2.15) respectively. However, no statistical significance was observed after adjustment. Moreover, cereal straw heating (OR = 1.74, 95% CI: 0.90-3.36, P = 0.099) may lead to increased risk of EPLs.

**Conclusion:** In Feicheng population, tobacco smoking or alcohol consumption may not be risk factors of EPLs. Low-quality drinking water raised the EPLs risk. Bad house heating materials, such as cereal straw, may lead to high EPLs risk.

Key words: esophageal squamous dysplasia, population-based, esophageal precancerous lesions, drinking water, house heating method, oral health

## Introduction

The incidence rate of esophageal cancer (EC) is ranked eighth in the most common cancer-related diseases worldwide (1). There were 455,800 new EC

cases and 400,200 deaths caused by EC around the world in 2012 (2). Although some cancers, such as breast cancer and prostate cancer, have higher

incidence rates than EC, they have lower mortality rates, which reflects lower fatality rates compared to EC.

There is also a remarkable difference in EC incidence rates among different geographical regions. The highest incidence rates were found in China, Iran, South America, and South Africa, which is often referred to as the “esophageal cancer belt” (2). As one of the countries in this belt, China bears a heavy disease burden with respect to EC (3), with Feicheng having one of the highest rates of incidence. Whereas the incidence of esophageal adenocarcinoma has been rising slowly and steadily over the past four decades, squamous cell carcinoma (ESCC) is still the most prevalent subtype in China (4, 5). It is among the five leading causes of cancer death in both men and women (6).

For ESCC patients, the cancer stage at first diagnosis is a decisive factor for prognosis (7). Because the early symptoms of ESCC are not obvious enough to attract the patient’s attention, individuals are often in the advanced stages of cancer when they go to hospital for examination. Thus the age-specific 5-year survival rate for adults with EC is 10.9% in Europe (8) and ~10-15% in China (9-11). Moreover, without active and appropriate treatments, patients who have been diagnosed as having EPLs may continue to develop into an advanced stage (12). Currently, the factors causing high rates of ESCC in Feicheng remain obscure. Here we used a population-based design study, a powerful and critical method, to identify the possible risk factors for EPLs/ESCC.

## Materials and Methods

### Setting

This study was launched by the Shandong Cancer Hospital, Shandong Cancer Control and Prevention office, and Department of Biostatistics of Shandong University. From September 2013 to July 2015, we recruited residents aged 40–69 years from 53 randomly selected communities in Feicheng, China. Ethical approval from the medical ethics committee of the Shandong Cancer Hospital was obtained. The reference coding is SDTHEC.

### Study design

Feicheng is located in the central part of Shandong Province, with a total of 605 communities. We randomly selected 53 communities in Feicheng. The work of recruitment was assisted by Feicheng Disease Control Center and Community Health Centers. The purpose and process of this research were thoroughly explained to each eligible

participant. A signed informed consent was mandatory before recruitment.

Inclusion criteria: 1) Being a permanent resident in Feicheng. 2) Aged 40-69 years.

Exclusion criteria: 1) Refusing to participate in the study. 2) Working outside Feicheng more than six months a year. 3) Having endoscopy contraindications. 4) Having an iodine allergy or hyperthyroidism. 5) Having EC history (13).

There are 5076 participants in the final analysis. Figure 1 summarizes the inclusion and exclusion process of this study.

Questionnaire interview was conducted at Community Health Centers by trained investigators using a structured questionnaire. Detailed demographic characteristics, habits, lifestyle information as well as health and disease information was collected. Participants went through a simple physical examination and then endoscopic test at the Cancer Screening Center of Feicheng Hospital. During the endoscopy, physicians used Lugol’s iodine staining method to find suspicious tissues, which were biopsied and analyzed.

In order of severity, esophageal mucosa status mainly includes normal esophageal mucosa, minor mucosa changes, esophagitis, esophageal squamous simple hyperplasia (ESSH), and esophageal squamous dysplasia (ESD) (14). ESD is classified as mild, moderate, or severe. Mild and moderate ESD together falls under low-grade ESD. Severe ESD, including squamous cell carcinoma in situ, is considered as the high-grade ESD (15). Mild ESD is the earliest form of EPLs. The progression, from chronic esophagitis, by way of ESSH, to ESD, is known as a common route to the ESCC (12, 14, 16). In our study, we grouped the participants into 3 groups: ‘normal’, ‘minor changes/esophagitis/ESSH’, and ‘ESD/ESCC’. For the participants with multiple diagnosis records in one biopsy, we only care about the most severe one.

### Statistical analysis

All the variables in this study are categorical. So we calculated frequencies and percentages for each variable. We described the difference in demographic characteristics, habits, lifestyle, and health information between 3 groups by  $\chi^2$ -test (Table 2). To assess the association between ESD/ESCC and the factors of interest, we used multinomial logistic regression model to estimate the unadjusted odds ratios (ORs) with 95% confidence intervals (CIs). Further adjusting for sex and age, adjusted ORs (95% CIs) were also showed in Table 3. The group of ‘normal’ was defined as the reference throughout the whole analysis.

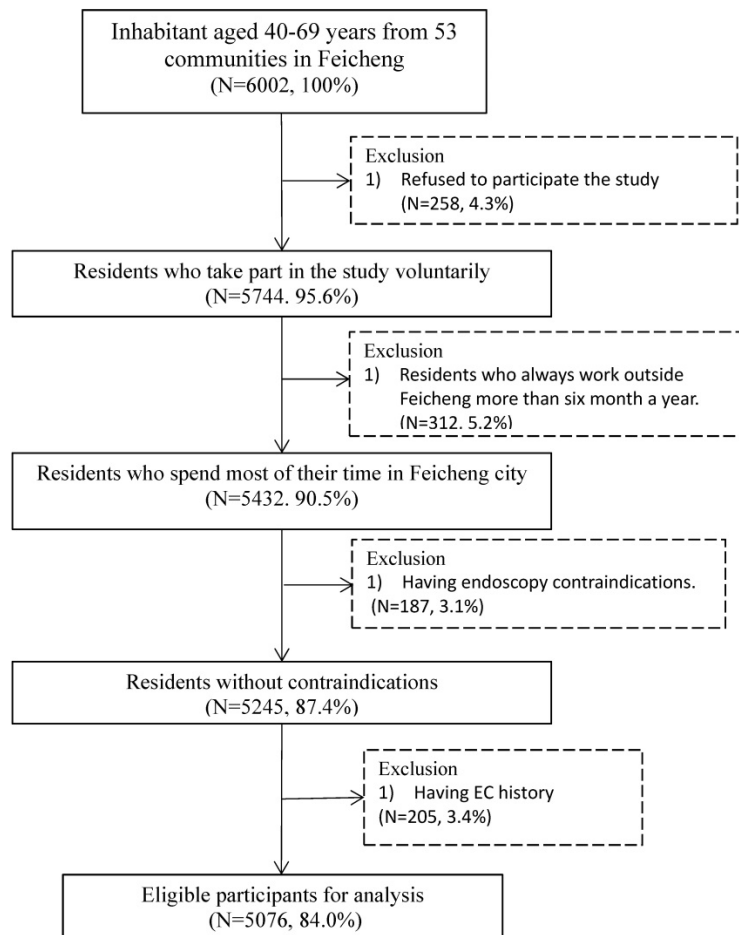


Figure 1. Flow chart of inclusion and exclusion for the screening study in Feicheng

## Results

As shown in Table 1, a total of 570 EPLs cases and 56 ESCC cases were diagnosed. EPLs cases included 406 cases of mild ESD, 105 cases of moderate ESD, and 59 cases of severe ESD (or squamous cell carcinoma in situ). Cases of ESCC were dominated by early-stage cancer, containing 30 cases of intramucosal carcinoma and 26 cases of invasive carcinoma.

Table 1. Diagnosis results among the participants

Type	Number (%)
Normal esophagus	3554 (70.02)
Minor changes, esophagitis and ESSH	896 (17.65)
ESD	570 (11.23)
Esophageal squamous cell carcinoma	56 (1.10)

Table 2 presents the demographic characteristics, as well as distribution of habits, lifestyle and health information. Among the participants, 51.64% were men, 90.84% were farmers. Overall, study population had a relatively low education level, most of individuals didn't or just completed the 9-year compulsory education. And participants who were

diagnosed with ESD/ESCC were more likely older people. Tobacco smoking and alcohol consumption were both significantly different between different pathological groups. Participants who mostly drank tap-water in the past 10 years were less in the group of 'ESD/ESCC' compared with another two groups. In terms of heating method in winter, cereal straw and coal heating were more common in the group of 'ESD/ESCC', electric heating was more common in 'norma' group. Meanwhile, 21.25% participants in the group of 'ESD/ESCC' had a very poor oral health, whereas 9.11% in good oral health.

Table 3 further examined associations between variables of interest and EPLs risk. There was no association observed between EPLs risk and tobacco smoking or alcohol consumption in both unadjusted and adjusted model. As compared with tap-water drinking people, the crude ORs (95% CIs) were 2.10 (1.01-4.37) for lake/pond water drinking people, 2.19 (1.40-3.42) for shallow-well water drinking people, and 1.57 (0.95-2.60) for deep-well water drinking people. And the adjusted OR (95% CI) was 1.84 (1.18-2.89) for people of drinking shallow-well water comparing to people who has been drinking

tap-water. In a comparison of participants with good oral health to those with very poor or poor oral health, the ESD/ESCC ORs (95% CIs) were 1.78 (1.28-2.49) and 1.58 (1.16-2.15) respectively. However, the risks were not statistically significant after adjustment. Moreover, electric heating (OR=0.68, 95% CI:

0.34-1.36) was associated with lower EPLs risk. Cereal straw heating (OR= 1.87, 95% CI: 0.98-3.59) and coal heating (OR= 1.62, 95% CI: 0.92-2.84) both led to increased risk of EPLs. In adjusted model, the OR (95% CI) was 1.74 (0.90-3.36) for participants who have been taking cereal straw heating method.

**Table 2.** Characteristics of 5076 participants from a high risk Chinese population

Factor	Normal (n=3554)	Minor changes/esophagitis/ESSH (n=896)	ESD/ ESCC (n=626)	$\chi^2$	P
Gender					
Male	1879(52.87)	399(44.53)	343(54.79)	22.775	0.000
Female	1675(47.13)	497(55.47)	283(45.21)		
Age					
40-49	656(18.46)	116(12.95)	41(6.55)	121.905	0.000
50-59	1336(37.59)	323(36.05)	185(29.55)		
60-69	1385(38.97)	406(45.31)	333(53.19)		
≥70	177(4.98)	51(5.69)	67(10.70)		
Occupation					
Farmer	3197(89.95)	825(92.08)	589(94.09)	12.933	0.002
Non-farmer	357(10.05)	71(7.92)	37(5.91)		
Education					
No schooling	439(12.35)	145(16.18)	124(19.81)	36.012	0.000
Primary school (1-6 years)	1071(30.14)	268(29.91)	202(32.27)		
Junior high school (7-9 years)	1582(44.51)	381(42.52)	230(36.74)		
≥High school (≥10 years)	462(13.00)	102(11.38)	70(11.18)		
Tobacco smoking					
Non-smoker	2223(62.55)	620(69.20)	391(62.46)	17.221	0.002
Current smoker	917(25.8)	195(21.76)	150(23.96)		
Former smoker	414(11.65)	81(9.04)	85(13.58)		
Alcohol consumption					
Non-drinker	2188(61.56)	577(64.41)	380(60.70)	11.280	0.024
Current drinker	1077(30.30)	263(29.35)	179(28.59)		
Former drinker	287(8.08)	55(6.14)	67(10.71)		
Tea consumption					
Never	696(19.58)	184(20.54)	110(17.57)	3.247	0.517
Occasionally	266(7.48)	68(7.59)	41(6.55)		
Regularly	2592(72.93)	644(71.88)	475(75.88)		
Source of drinking water					
Lake/pond water	71(1.99)	11(1.23)	13(2.08)	25.010	0.000
Shallow-well water	2736(76.98)	705(78.68)	523(83.55)		
Deep-well water	495(13.93)	104(11.61)	68(10.86)		
Tap water	252(7.10)	76(8.48)	22(3.51)		
Meal temperature					
Burning hot	53(1.49)	16(1.79)	11(1.76)	2.200	0.900
Hot	1261(35.48)	320(35.71)	238(38.02)		
Warm	1954(54.98)	489(54.58)	330(52.72)		
Cold	286(8.05)	71(7.92)	47(7.51)		
Exercise					
No exercise	1739(48.93)	420(46.88)	308(49.20)	3.930	0.686
Seldom of exercise	1629(45.84)	438(48.88)	288(46.01)		
Moderate of exercise	154(4.33)	31(3.46)	26(4.15)		
Frequent of exercise	32(0.90)	7(0.78)	4(0.64)		
House heating method					
Cereal straw heating	186(5.23)	48(5.36)	40(6.39)	23.172	0.001
Electric heating	307(8.64)	63(7.03)	24(3.83)		
Coal heating	2705(76.11)	699(78.01)	503(80.35)		
Natural gas heating	122(3.43)	37(4.13)	14(2.24)		
Oral health					
Very poor	589(16.57)	137(15.29)	133(21.25)	28.643	0.000
Poor	1241(34.92)	361(40.29)	249(39.78)		
Moderate	1274(35.85)	297(33.15)	187(29.87)		
Good	450(12.66)	101(11.27)	57(9.11)		
Gastroesophageal reflux disease					
No	2383(67.05)	616(68.75)	444(70.93)	4.086	0.130
Yes	1171(32.95)	280(31.25)	182(29.07)		
Diabetes					
No	3397(95.58)	847(94.53)	608(97.12)	5.876	0.053
Yes	157(4.42)	49(5.47)	18(2.88)		
Family history of cancer					
No	2856(80.36)	696(77.68)	480(76.68)	6.468	0.039
Yes	698(19.64)	200(22.32)	146(23.32)		

**Table 3.** Odds ratios and 95% confidence intervals for the association between investigated variables and high EPLs/ESCC risk

Normal & ESD/ESCC		Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Gender	Male	1.08(0.91-1.28)	0.374	1.32(0.99-1.76)	0.063
	Female	Reference			
Age	40-49	0.17(0.11-0.25)	0.000	0.17(0.11-0.28)	0.000
	50-59	0.37(0.27-0.50)	0.000	0.41(0.29-0.58)	0.000
	60-69	0.64(0.47-0.86)	0.004	0.62(0.45-0.86)	0.004
	≥70	Reference			
Occupation	Farmer	1.78(1.25-2.52)	0.001	1.57(1.10-2.25)	0.013
	Non-farmer	Reference			
Education	No schooling	1.86(1.35-2.57)	0.000	1.57(1.09-2.24)	0.013
	Primary school	1.24(0.93-1.67)	0.143	1.12(0.82-1.52)	0.485
	Junior high school	0.96(0.72-1.28)	0.778	1.06(0.79-1.41)	0.716
	≥High school	Reference			
Tobacco smoking	Former smoker	1.17(0.90-1.51)	0.238	0.88(0.64-1.19)	0.398
	Current smoker	0.93(0.76-1.14)	0.484	0.84(0.65-1.09)	0.200
	Non-smoker	Reference			
Alcohol Consumption	Former drinker	1.04(0.61-1.79)	0.744	1.05(0.75-1.45)	0.790
	Current drinker	0.96(0.79-1.16)	0.654	0.94(0.74-1.19)	0.599
	Non-drinker	Reference			
Source of drinking water	Lake/pond water	2.10(1.01-4.37)	0.048	1.71(0.81-3.58)	0.157
	Shallow-well water	2.19(1.40-3.42)	0.001	1.84(1.18-2.89)	0.008
	Deep-well water	1.57(0.95-2.60)	0.078	1.38(0.82-2.29)	0.217
	Tap water	Reference			
Meal temperature	Burning hot	1.26(0.62-2.59)	0.524	1.40(0.68-2.91)	0.363
	Hot	1.15(0.82-1.61)	0.422	1.18(0.84-1.67)	0.331
	Warm	1.03(0.74-1.43)	0.871	1.07(0.77-1.49)	0.690
	Cold	Reference			
House heating method	Cereal straw heating	1.87(0.98-3.59)	0.058	1.74(0.90-3.36)	0.099
	Electric heating	0.68(0.34-1.36)	0.277	0.79(0.39-1.59)	0.514
	Coal heating	1.62(0.92-2.84)	0.092	1.53(0.87-2.96)	0.144
	Natural gas heating	Reference			
Oral heath	Very poor	1.78(1.28-2.49)	0.001	1.20(0.85-1.70)	0.295
	Poor	1.58(1.16-2.15)	0.003	1.20(0.88-1.65)	0.253
	Moderate	1.16(0.85-1.59)	0.360	1.03(0.75-1.42)	0.865
	Good	Reference			
Family history of cancer	Yes	1.24(1.02-1.52)	0.035	1.30(1.05-1.59)	0.014
	No	Reference			

## Discussion

We conducted a population-based screening study in Feicheng, China, aiming to figure out the risk factors associated with EPLs. We found that drinking low-quality water might lead to an increased risk of having EPLs. Previous studies indicated that ESCC is the result of a combination of multiple risk factors, containing environmental and biological factors (17, 18). Drinking water is one of the basic necessities of life, as well as a potential way of exposure to risk factors. Different from pond water or well water, tap water had been purified and disinfected before delivering to users. Purification and disinfection can significantly reduce the concentrations of most carcinogens. Several studies suggested that high level of nitrate in drinking water would increase the risk of ESCC, possibly through the formation of N-nitroso compounds (19-21). So we should conduct a further study to find out the specific carcinogens in drinking water, which have been increasing the incidence of EPLs/ESCC in Feicheng.

Another main finding of our study was that house heating method may influence the odds of having EPLs/ESCC. Cereal straw heating is associated with the raised risks of having EPLs.

Meanwhile, electric heating might be associated with reduced risk of having EPLs/ESCC. Some studies found that indoor air pollution caused by using stoves or fireplaces is associated with the higher risk of having lung cancer and breast cancer (22-24). Only one study suggested that using heating stoves without ventilator installed in their home may lead to increased risk of ESD (25). Our research examined in details the use of different materials for house heating in this area, and showed that cereal straw heating is a risk factor for EPLs. Our primary hypothesis is that bad heating materials can cause loads of pollutants, such as polycyclic aromatic hydrocarbons and sulfur dioxide, which may contaminate air, water and food. Biomass fuel is widely used in daily heating in Feicheng population, thus significantly increasing the chance of people contacting carcinogens or mutagens.

The third interesting finding was that we observed no significant association between tobacco smoking and the risk of EPLs/ESCC. Tobacco smoking was identified as a strong determinant of ESCC in many western countries (5, 26, 27). And a previous national-wide case-control study (28) that was conducted in China also indicated the same association. However, this is not the case in Feicheng.

Our study even suggested a mild inverse association between tobacco consumption and EPLs/ESCC in the adjusted model. This inverse association occurred both in current smoker and former smoker, but without statistically significant. With respect to alcohol consumption, unlike many studies (27, 29), we didn't observe any statistically significant increased/decreased EPLs/ESCC risks among participants who were current drinkers or former drinkers. This is possibly due to the smokers/drinkers in this area consuming relatively small daily amounts of tobacco/alcohol, and indicates the fact that there must be the other risk factors dominating the incidence of EPLs/ESCC in this population.

Furthermore, several studies reported poor oral health as a risk factor for ESCC (30, 31). People that lacked regular oral hygiene or had too much tooth loss/decay are more susceptible to ESCC (32-34). Only two studies reported the association between poor oral health and the increased risk of ESD but with small cases (25, 35). In unadjusted model, our finding is consistent with these studies. However, after adjusting for sex and age, the increased EPLs/ESCC risk was not statistically significant. Elder people (>60 years old) in poor oral health group accounted for 53.70%. Meanwhile this proportion in moderate oral health group and good oral health group were 38.45% and 27.80% respectively, which may be the main cause of above mentioned results.

To the best of our knowledge, this is the largest population-based screening study to date to investigate the EPLs - both for sample size and number of cases found. The study has several strengths. First of all, due to the population-based research design and the high participation rate (84%), subjects in our study would be more likely representative of the general population in Feicheng. Secondly, by conducting the interview prior to endoscopic test for each participant, we are able to reduce the possible changes in their habits, lifestyle, and behavior after being diagnosed with the disease. Third, we collected comprehensive questionnaire data. And all subjects received the gold standard test (endoscopy with Lugol's iodine staining and biopsy) for EPLs, which allowed us to examine the numerous risk factors accurately.

Meanwhile, we should be cautious about the results interpretation due to limitations of the study. The first concern is recall bias, which is caused by the inaccuracy or incompleteness of the remembering information by study participants, and which is a common issue in cross-sectional study. Our well-trained investigators had tried their best to help every participant to fill out questionnaire forms. During data collection, study objectives and

hypothesis were blinded to all the investigators and participants. Another potential problem must to be considered is sampling error. Generally, physicians would pick out one through three skeptical blocks of tissue for biopsy in one time endoscopy, the risk of false negative results might exist. What's more, our study lacked detailed information on environmental exposure. Although our findings indicated that low quality drinking water and bad house heating methods are risk factors for having EPLs, we are not able to explain the mechanisms underlying these associations. Future plans of our research include a follow-up study and an environmental investigation to confirm the observed associations in this study.

In conclusion, EPLs is brought on by a confluence of risk factors, which vary between different populations though. We should not perform identical strategy to prevent this disease, especially in an area with extremely high incidence rate. In Feicheng population, people who consume tobacco or alcohol may not be more vulnerable to EPLs/ESCC. Low-quality drinking water might raise the risk of having EPLs. Bad house heating methods associated with increased EPLs risk which should be held in high regard.

## Abbreviations

ESCC: esophageal squamous cell carcinoma; ESD: esophageal squamous dysplasia; EPLs: esophageal precancerous lesions; EC: esophageal cancer; ESSH: esophageal squamous simple hyperplasia.

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## Competing Interests

The authors have declared that no competing interest exists.

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