

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 а 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 χ^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

Туре	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

Circle District (1975) District (1975) <thdistrict (1975)<="" th=""> District (1975)</thdistrict>	Factor	Normal (n=3554)	Minor changes/esophagitis/ESSH (n=896)	ESD/ESCC (n=626)	v ²	Р
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Current snoker19(25,b)195(1.76)196(9A)150(23.96)Alcohal consumption11.8508(13.87)12.800.02Non-drinker2186(15.50)57(4.41)8(00,70)11.2800.02Current drinker2186(15.60)56(1.4)77(28.59)11.2800.02Former drinker287(80)56(1.4)67(0.7)3.2470.517Caccosinarily267(3.60)8(60.53)41(65.7)1.520.517Caccosinarily267(7.50)10(17.57)3.2470.517Caccosinarily267(7.50)47(7.58)47(7.58)1.52Source of drinking water11(12.3)10.1(1.51)5.0100.000Shallow-well water278(7.69,80)10(11.61)68(10.86)2.50100.000Shallow-well water278(7.69,80)10(11.61)68(10.86)1.521.52Deep-well water278(7.69,80)10(11.61)28(8.02)1.521.52Maining hot121(54.81)20(5.71)2.0103.0321.521.52Maring hot121(54.81)20(5.71)28(8.02)1.521.52No evercise129(4.98)49(54.58)3.03(2.22)1.521.52Cold corecise159(4.53)20(5.71)28(4.01)1.521.52No evercise159(4.58)20(5.71)28(8.02)1.521.52Cold corecise159(4.58)20(5.71)28(5.02)1.521.52Cold corecise159(4.59)20(5.71)28(5.02) <td< td=""><td>Non-smoker</td><td>2223(62.55)</td><td>620(69.20)</td><td>391(62.46)</td><td>17.221</td><td>0.002</td></td<>	Non-smoker	2223(62.55)	620(69.20)	391(62.46)	17.221	0.002
<table-container>Forme snoker\$(19(4))\$(19(4))\$(13,3)$U$Nocholcossynthm28(81,5)\$7(64,4)80(60,7)1.2800.24Current drinker107(03)26(3,9)67(0.7)U</table-container>	Current smoker	917(25.8)	195(21.76)	150(23.96)		
Alcoharcine Non-drinker188(8)57%(4.1)380(0.70)10.200.024Current drinker107(70.30)26(20.3)170(20.5)10.2Current drinker26(8.0)56.14)170(20.5)1Teaconsumption100.210.21.21.2Never06(9.5)16(0.5)14(6.5)1Cacsionality26(7.0)64(7.18)14(6.5)1Source drinking water112.08)44(7.8)10.00Stallow-wall water236(7.0)10.03(7.6)1.025.00Dang-wall water26(3.0)10.01(1.6)64(1.8)1.020.00Stallow-wall water26(3.0)10.01(1.6)64(1.8)1.020.00Dang-wall water26(3.0)10.01(1.6)2.008.001.021.02Tap water26(3.0)10.01(1.6)2.001.022.001.021.02Tap water26(3.0)10.01(1.6)2.002.002.001.021.021.02Houring bat216(3.6)10.01(2.0)2.002.002.002.001.02 </td <td>Former smoker</td> <td>414(11.65)</td> <td>81(9.04)</td> <td>85(13.58)</td> <td></td> <td></td>	Former smoker	414(11.65)	81(9.04)	85(13.58)		
Non-drinker138(61.5)37(% 4.1)38(06.02)38(06.02)1.2800.20Former drinker27(8.08)56(1.4)67(10.7)1.2800.21Fac consumption18(20.5)10(17.57)3.2470.317Recards286(7.8)68(7.9)41(6.50)7.575.017Qecalization282(7.29)0.47(7.8)32(7.58)0.000Shallow-well water11(1.23)112(2.08)25.0100.000Shallow-well water252(7.10)10(1.63)25.0100.000Shallow-well water252(7.10)10(1.63)25.0100.000Shallow-well water252(7.10)10(1.63)25.0100.000Shallow-well water252(7.10)10(1.63)25.0100.000Shallow-well water250(7.0)10(1.63)25.0100.000Shallow-well water250(7.0)10(1.63)25.0100.000Shallow-well water250(7.0)10(1.63)25.0100.000Shallow-well water250(7.0)10(1.63)25.01010.000Tay water250(7.0)10(1.7)2.00020.00020.000Peop-well water25.01010(1.63)20.00020.00020.000Shallow well water25.01010(1.63)20.00020.00020.000Shallow well water106(4.93)10(4.94)20.00020.00020.000Shallow well water106(4.93)20.00020.00020.00020.000Shallow well water106(4.93) <t< td=""><td>Alcohol consumption</td><td></td><td></td><td></td><td></td><td></td></t<>	Alcohol consumption					
Current drinker107(0.30)263(2.9.5)179(2.9.5)Former drinking25(6.14)67(10.71)3.2470.317Never69(19.58)84(20.54)110(17.57)3.2470.517Occasionally269(27.23)64(7.18)41(6.55)110(17.57,84)5.010Source of drinking water132(0.8)52(83.55)0.000Shallow-well water0576,86)0576,86)02(80.8)1.000Shallow-well water252(71.10)0576,86)02(3.61)0.001Shallow-well water252(71.10)0576,86)02(3.61)0.002Shallow-well water252(71.10)0576,86)02(3.61)02(3.61)0.002Shallow-well water252(71.10)0576,86)02(3.61)02(3.61)0.002Age water252(71.10)0576,86)02(3.61)02(3.61)0.0020.002Shallow-well water252(71.10)0576,86)02(3.61)02(3.7)0.002Hay water195(54.94)480(4.53)30(2.7)0.0100.012Gold actics16(5.44)12(9.45)30(2.7)0.0120.012Karman195(54.94)480(4.58)08(49.01)3.9303.9300.902Soldom of exercise156(3.54)10(4.53)0.0161.0121.012Foregueri of exercise156(3.54)10(4.63)0.0121.0120.012Soldom of exercise156(3.54)43(3.64)0.06(3.03)1.0121.012Coal heating method12(1.41)10(2.9) </td <td>Non-drinker</td> <td>2188(61.56)</td> <td>577(64.41)</td> <td>380(60.70)</td> <td>11.280</td> <td>0.024</td>	Non-drinker	2188(61.56)	577(64.41)	380(60.70)	11.280	0.024
Forme drinker25(8.0)5(6.1)6(907,0)3.2.478.5.17Nex can comprise96(9.5)14(0.5)110(7.57, 3.2.470.5.17Occasionally66(7.5)64(7.18)416.551Regularly6202.3.0644(7.18)475(7.5.8)521(8.5.)1Source of drinking water253(6.5.)253(8.5.)11Lake/ pord water925(7.6.9.)05(7.6.8.)63(0.8.6.)521(8.5.)1Deep-well water025(7.6.9.)04(1.1.6.1.)63(0.8.6.)11Radi memperator101(1.6.1.)0.5.10.0.5.10.11Martin good of the distance102(0.5.7.)0.5.10.0.5.10.10.5.10.1Martin good of the distance102(0.5.1.)0.5.10.0.5.10.110.5.10.1Martin good of the distance102(0.5.1.)102(0.5.1.)0.5.10.110.5.10.111110.5.10.11	Current drinker	1077(30.30)	263(29.35)	179(28.59)		
TacassenginionJest20.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5.5	Former drinker	287(8.08)	55(6.14)	67(10.71)		
Never%ef(9.5%)%4(0.5%)%1/10(7.5%)%.2.4%%.5.7%Occasionally2592(7.9.3)644(71.88)41(6.5%)**Source of drinking water*****Sucer of drinking water11(1.2%)13(2.0%)250(70.0%)0.000Shallow-well water2736(76.98)705(76.86)22(363.55)**Deep-well water450(3.3)104(11.61)66(10.6%)***Tay water252(7.10)76(8.48)22(3.51)***Meal temperature***	Tea consumption					
Occasionally266(7.48)64(7.59)41(6.57)Regularly2592(7.29)64(71.80)475(75.80)Source of drinking water11(1.23)13(2.08)25.010Lake/ pond water73(67.68)73(57.68)52.01052.010Deep-well water252(7.09)76(78.68)64(0.08.6)52.01052.010Tap water252(7.10)76(8.48)20.05.1052.01052.010Meal temperature52.0123.0152.01052.01052.010Hot15(1.64.90)30.03.57.1023.03.02.1052.01050.010Godd1954(5.48)30.03.57.1023.03.02.7050.01050.010Godd1954(5.48)30.03.57.1030.05.27.2050.01050.010Cold1954(5.48)30.03.57.1030.05.27.2050.01050.010Section179.0271.0224.01050.01050.01050.010Section179.0230.05.27.1030.05.27.1050.01050.01050.010Section154.43.0030.03.7030.02.7.1050.01050.01050.01050.010Frequent of exercise154.43.1031.04.6428.04.0150.01050	Never	696(19.58)	184(20.54)	110(17.57)	3.247	0.517
RegularlySeq2(72.93)64(71.89)475(75.89)755Source of inking water71(1.99)1(1.23)13(2.08)25.0100.000Shallow-well water2736(75.98)705(76.85)523(83.55)7Deep-well water232(7.10)705(76.85)22(3.51)7Tap water232(7.10)76(8.45)22(3.51)7Beag-well water232(7.10)76(8.45)22(3.51)7Beag-well water521(7.10)104(1.76)2.009.00Hoat emperator320(3.57)28(8.02)7.51)7Warm126(1.54)320(3.57)32(3.57)77Cold28(8.02)105(7.9)778Varma162(4.54)320(3.57)32(3.67)8.66.98.66.9Seldom of exercise152(4.33)31(3.468.61.9)8.66.98.66.9Seldom of exercise152(4.33)31(3.468.61.9)8.66.98.66.9Seldom of exercise154(4.33)31(3.46)26.15.177Frequent of exercise154(4.33)31(3.40)26.15.177Frequent of exercise30(8.64)30(7.03)24.03.910.61.110.62.11Ideas heating method126(3.43)30(1.31.13.61.23.61.2111Ideas heating307(6.51)69(7.01.030(2.1.111111Ideas heating307(6.51)3.61.23.61.23.61.23.61.21	Occasionally	266(7.48)	68(7.59)	41(6.55)		
SourceSoure	Regularly	2592(72.93)	644(71.88)	475(75.88)		
Lake/pond water71(1.99)11(1.23)13(2.08)25.000.000Shallow-well water278(67.68)705(78.68)523(83.55)523Deep-vell water232(7.10)104(1.61)60(1.08.6)523(83.57)Tap water232(7.10)706.84)23(3.51)523(83.57)Meal temperature23(1.49)16(1.79)11(1.76)2.009.00Hof1261(53.48)20(57.1)238(08.02)523523Cold266(05)489(34.58)30(302.72)57523Cold on descrise159(45.83)480(48.85)30(302.72)57523No exercise159(45.93)430(48.85)284(60.1)53524Seldom of exercise1629(53.44)31(3.64)284(60.1)5353Seldom of exercise169(43.3)314,04284(60.1)535353Seldom of exercise169(53.1)81(5.30)70,7840(6.39)23.1720.01Hoder beatring method535	Source of drinking water					
Shallow-well water273(75.98)70(78.68)52(78.13)62(78.13)62(13.23)62(1	Lake/pond water	71(1.99)	11(1.23)	13(2.08)	25.010	0.000
Deep-will water495(13.93)104(1.16)68(0.86)Tap water22(3.51)21Fap water22(3.51)22.000.900Meal temperature11(1.76)2.2000.900Burning hot261(53.48)260(5.71)28(38.02)11Varam1954(54.98)489(54.58)303(22.72)11Cold26(8.05)71(7.92)207(51)111Exercise129(45.89)304(6.88)304(9.20)3.9300.666Seldom of exercise154(4.33)31(3.46)26(4.15)11Moderate of exercise154(4.33)31(3.46)26(4.15)11House heating method111111Coal heating Nethodit169(7.8)3(7.83)111Coal heating12(3.43)3(7.43)13(1.20)24(3.83)111Coal heating12(3.43)3(1.40)24(3.83)11	Shallow-well water	2736(76.98)	705(78.68)	523(83.55)		
Tap water252(7.10)76(8.48)22(3.51)Meal temperature53(1.49)16(1.79)11(1.76)2.300.900Hot126(13.64)320(35.71)238(8.02)11Warm1954(34.98)330(52.72)330(52.72)11Cold268(6.05)7(7.20)330(52.72)11Exercise17.92477.51)111Exercise153(4.93)420(4.88)308(49.20)3.9300.686Seldon of exercise152(4.54)438(48.88)288(46.01)11Frequent of exercise152(4.54)43(3.64)26(4.15)11Frequent of exercise32(0.90)70.78)4(0.64)24(3.83)0.01Ideatria freedom111111Casel atraw heating method163(7.03)44(3.83)2.1720.01Electric heating370(5.64)63(7.03)24(3.83)2.1720.01Electric heating12(2.43)37(1.31)13(1.22)2.1641Coal heating122(3.43)37(1.31)13(2.23)2.1640.00For Jack Stating13(1.62)13(1.02)13(3.12)2.64.310.00For Jack Stating13(1.22)13(1.22)13(1.23)1.51.5Gadi casting122(3.43)3.01(1.27)13(3.12)2.64.310.00For Jack Stating13(1.22)13(1.22)1.51.51.5Good121(2.45)13(1.23) <td>Deep-well water</td> <td>495(13.93)</td> <td>104(11.61)</td> <td>68(10.86)</td> <td></td> <td></td>	Deep-well water	495(13.93)	104(11.61)	68(10.86)		
Meter	Tap water	252(7.10)	76(8.48)	22(3.51)		
Burning hot53(1.49)16(1.79)16(1.79)11(1.76)2.2000.900Hot126(135.48)320(35.71)238(38.02)11Warm1954(45.89)489(54.58)330(62.27)11Cold268(8.05)71(7.92)47(7.51)11Exercise1739(48.93)420(46.88)308(49.20)3.9300.686Seldon of exercise154(4.33)31(3.46)264(1.5)11Moderate of exercise26(1.5)26(1.5)111Frequent of exercise20(9.09)7(7.92)4(0.64)111House heating method21(9.09)7(7.92)4(0.63)2(3.72)0.01Electric heating307(8.64)69(7.03)4(3.63)1111Coal heating2705(76.11)699(78.01)63(80.35)11	Meal temperature					
Hot126(364)320(35.7)238(30.2)238(30.2)Warm1954(54.98)489(54.58)330(52.72)Cold268(50.7)7(7.92)47(7.51)Exercise826(30.1)826(30.1)Sedora of exercise152(45.84)420(46.88)308(40.10)10.66)Seldon of exercise154(43.0)31(3.60)26(4.15)5.77House hating method154(3.30)70.78)26(4.15)5.77Cereal straw heating186(5.23)48(5.36)40(6.39)23.1720.01Electric heating307(5.64)63(7.03)24(3.83)5.710.01Statural gas heating212(3.43)37(1.3)142(2.4)5.761.72Oral heating122(3.43)37(1.1)132(2.12)2.8.6430.01Poro1241(4.42)31(1.2)24(3.93)5.761.721.72Oral heating124(3.43)30(10.2)132(1.2)2.8.6430.01Oral heating124(3.43)30(1.02)132(1.2)2.8.6430.01Oral heating124(3.42)124(3.42)142(3.43)1.721.72Oral heating124(3.43)13(1.12)132(1.2)2.8.6430.01Oral heating124(3.42)124(3.42)144(3.93)1.741.74Oral heating124(3.42)124(3.42)1.741.741.74Oral heating124(3.42)124(3.42)1.741.741.74Oral heating124(3.42)124(3.42)1.74 <td>Burning hot</td> <td>53(1.49)</td> <td>16(1.79)</td> <td>11(1.76)</td> <td>2.200</td> <td>0.900</td>	Burning hot	53(1.49)	16(1.79)	11(1.76)	2.200	0.900
Warm1954(9.48)489(54.58)330(52.7)Cold286(0.50)71(7.92)47(7.51)Cold286(0.50)71(7.92)47(7.51)Exercise739(84.93)420(4.68)308(49.20)3.9300.686Seldom of exercise162(4.53)31(3.46)288(46.01)1Moderate of exercise154(4.33)31(3.46)26(4.15)1Frequent of exercise32(0.90)70.78)40.64)11House heating method0.01Eceral straw heating186(5.23)48(5.36)203(80.23)3.1720.01Eceral straw heating130(5.27)30(8.02.63)3.1720.01Eceral straw heating120(5.61)69078.01)24(3.83)Coal heating205(76.11)69078.01)630(80.25)Natural gas heating212(3.43)37(15.29)133(12.52)2.8.630.00Por1241(34.92)31(40.29)133(12.52)2.8.640.00Por1241(34.92)301(40.29)137(12.98)2.8.640.00Godo450(2.66)101(1.27)1587615876158Godo450(2.66)101(1.27)15876158158Godo1241(34.92)280(3.15)144(7.93)4.0861.58Godo127(3.55)280(3.15)158(2.9.07)158761.58Godo127(3.29)280(3.12)1581.591.58Godo39	Hot	1261(35.48)	320(35.71)	238(38.02)		
Cold 286(8.05) 71(7.92) 47(7.51) Exercise Exercise 308(49.20) 3,930 0.686 Seldom of exercise 162(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) 70.78 House heating method Coal heating method Coal heating method	Warm	1954(54.98)	489(54.58)	330(52.72)		
Exercise Vertice <	Cold	286(8.05)	71(7.92)	47(7.51)		
No exercise 173(48.93) 420(4.88) 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) 70.78) 40(6.39) 23.172 0.01 House heating method - <td>Exercise</td> <td></td> <td></td> <td></td> <td></td> <td></td>	Exercise					
Seldon of exercise 1629(45.84) 438(48.88) 288(46.01)	No exercise	1739(48.93)	420(46.88)	308(49.20)	3.930	0.686
Moderate of exercise 154(4.3) 31(3.46) 26(4.15) Frequent of exercise 32(0.90) 70.78) 40(6.49) - House heating method - - - - Cereal staw 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 205(76.11) 690(78.01) 503(80.35) - - - Natural gas heating 122(3.43) 37(1.30) 14(2.24) -	Seldom of exercise	1629(45.84)	438(48.88)	288(46.01)		
Frequent of exercise 32(0.90) 7(0.78) 4(0.64) House heating method 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01	Moderate of exercise	154(4.33)	31(3.46)	26(4.15)		
House heating method 186(5.23) 48(3.36) 40(6.39) 23.172 0.01 Electric heating 307(8.64) 63(7.03) 24(3.83) 503(80.35) Natural gas heating 122(3.43) 399(78.01) 503(80.35) 14(2.24) Oral health 14(2.24) 14(2.24) 1400 Poor 589(16.57) 137(15.29) 133(21.25) 28.643 0.000 Poor 1241(34.92) 361(40.29) 24(39.78) 24(39.78) 0.001 Good 1241(34.92) 361(40.29) 24(39.78) 150 0.001 Good 1241(34.92) 361(40.29) 24(39.78) 160 1000 Good 1241(34.92) 361(40.29) 24(39.78) 160 1000 Good 124(34.92) 301(1.27) 57(9.11) 1100 1100 1100 Good 283(67.05) 616(68.75) 444(70.93) 4.086 0.130 Yes 117(32.95) 280(31.25) 182(29.07) 1100 1100 Yes 397(95.81) 847(94.53) 608(97.12) 5.876 0.053 <t< td=""><td>Frequent of exercise</td><td>32(0.90)</td><td>7(0.78)</td><td>4(0.64)</td><td></td><td></td></t<>	Frequent of exercise	32(0.90)	7(0.78)	4(0.64)		
Cereal straw heating 186(5.2) 48(5.36) 40(6.39) 23.172 0.001 Electric heating 307(8.64) 63(7.03) 24(3.83) 203(80.35) Coal heating 2705(76.11) 699(78.01) 503(80.35) Natural gas heating 122(3.43) 37(13.0) 14(2.24) Oral health Yery 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(2.6) 101(11.27) 57(11) Kes 1171(32.95) 280(31.25) 182(29.07) Diabetes Yes 3397(95.58) 847(94.53) <	House heating method					
Electric heating 307(8.64) 63(7.03) 24(3.83) Coal heating 2705(76.11) 699(78.01) 503(80.35)	Cereal straw heating	186(5.23)	48(5.36)	40(6.39)	23.172	0.001
Coal heating2705(76.11)699(78.01)503(80.35)Natural gas heating122(3.43)37(4.13) $14(2.24)$ Oral health $133(21.25)$ 28.643 0.000 Yery poor589(16.57)137(15.29) $133(21.25)$ 28.643 0.000 Poor1241(34.92) $361(40.29)$ $249(39.78)$ $249(39.78)$ Moderate1274(35.85)297(33.15) $87(29.87)$ $57(9.11)$ Good402(2.66)101(1.27) $57(9.11)$ $$	Electric heating	307(8.64)	63(7.03)	24(3.83)		
Natural gas heating 122(3.43) 37(4.13) 14(2.24) Oral health	Coal heating	2705(76.11)	699(78.01)	503(80.35)		
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) 249(39.78) Very poor Moderate 1274(35.85) 297(33.15) 187(29.87) Very poor 57(9.11) Very poor Good 420(2.66) 101(1.27) 57(9.11) Very poor 57(9.11) Very poor Very poor 583(67.05) 616(68.75) 444(70.93) 4.086 0.130 Gastroesophageal reflux disease Very poor 2383(67.05) 616(68.75) 444(70.93) 4.086 0.130 Yes 117(132.95) 280(31.25) 182(29.07) Very poor Very po	Natural gas heating	122(3.43)	37(4.13)	14(2.24)		
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) 249(39.78)	Oral health					
Poor 1241(34.92) 361(40.29) 249(39.78) Moderate 1274(35.85) 297(33.15) 187(29.87) Good 400(12.66) 101(1.27) 57(9.11) Gastroesophageal reflux disease 7 3383(67.05) 616(68.75) 444(70.93) 4.086 0.130 Yes 1171(32.95) 280(31.25) 142(29.07) 1 1 Diabetes 7 3397(95.58) 847(94.53) 608(97.12) 5.876 0.053 Yes 157(4.42) 49(5.47) 18(2.88) 1 1 1 Family history of cancer 7 5.876 0.053 1	Very poor	589(16.57)	137(15.29)	133(21.25)	28.643	0.000
Moderate 1274(35.85) 297(33.15) 187(29.87) Good 450(12.66) 101(11.27) 57(9.11) Gastroesophageal reflux disease 4.086 0.130 Yes 117(32.95) 616(68.75) 444(70.93) 4.086 0.130 Yes 1171(32.95) 280(31.25) 182(29.7) Diabetes 4.086 0.130 Yes 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)	Poor	1241(34.92)	361(40.29)	249(39.78)		
Good 450(12.66) 101(11.27) 57(9.11) Gastroesophageal reflux disease -	Moderate	1274(35.85)	297(33.15)	187(29.87)		
Gastroesophageal reflux disease Ves 2383(67.05) 616(68.75) 444(70.93) 4.086 0.130 Yes 208(31.25) 280(31.25) 18(29.07) 17 Diabets 3397(95.58) 847(94.53) 608(97.12) 5.876 0.053 Yes 157(4.42) 49(5.47) 18(2.88) 17 Family history of cancer Ves 480(76.68) 6.468 0.039 Yes 698(19.64) 200(22.32) 146(23.32) 146(23.32)	Good	450(12.66)	101(11.27)	57(9.11)		
No 2383(67.05) 616(68.75) 444(70.93) 4.086 0.130 Yes 1171(32.95) 280(31.25) 182(29.07) 182(29.07) 182 Diabetes	Gastroesophageal reflux disease					
Yes 1171(32.95) 280(31.25) 182(29.07) Diabetes	No	2383(67.05)	616(68.75)	444(70.93)	4.086	0.130
Diabetes Starter <	Yes	1171(32.95)	280(31.25)	182(29.07)		
No 3397(95.58) 847(94.53) 608(97.12) 5.876 0.053 Yes 157(4.42) 49(5.47) 18(2.88)	Diabetes					
Yes 157(4.2) 49(5.47) 18(2.88) Family history of cancer Family history of cancer 480(76.68) 6.468 0.039 Yes 698(19.64) 200(22.32) 146(23.32) 146(23.32)	No	3397(95.58)	847(94.53)	608(97.12)	5.876	0.053
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) 146(23.32)	Yes	157(4.42)	49(5.47)	18(2.88)		
No 2856(80.36) 696(77.68) 480(76.68) 6.468 0.039 Yes 698(19.64) 200(22.32) 146(23.32)	Family history of cancer					
Yes 698(19.64) 200(22.32) 146(23.32)	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)	Р	Adjusted OR (95% CI)	Р
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
0	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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