Population-based Case-control Study on Risk Factors for Esophageal Cancer in Five High-risk Areas in China

Xibin Sun¹#, Wanqing Chen²#, Zhifeng Chen¹, Denggui Wen¹, Deli Zhao³, Yutong He¹*

Abstract

Objective: To study major etiological factors for esophageal cancer in upper gastrointestinal cancer high risk areas in China. Methods: Five areas with high incidences of esophageal and gastric cancer with good quality cancer registration data were selected for the study: Cixian, Shexian from Hebei Province, Linxian from Henan Province, Feicheng from Shandong Province and Zhuanghe from Liaoning Province. A total of 250 cases were randomly recruited from the cancer registration database diagnosed as arising in the lower esophageal segment since January 1, 2009. Three controls were identified and matched with each case as having similar characteristics, such as gender, sex and residency. Questionnaires were applied by face to face interview with trained staff, and data entry was conducted using EPIDATA software. Conditional logistic models were employed for univariate and multivariate analyses to evaluate odd ratios and 95% confident intervals, with SPSS 13.0 statistic software. Results: In single variable analysis, gastrointestinal history, GERD, smoking, passive smoking, alcohol drinking, hot food, pickled food, overnight vegetable, dried food, no breakfast, false dining posture were found to be risk factors of esophageal cancer. Eating more fresh vegetables and high BMI were protective factors. Gastrointestinal history (OR=12.658), not taking regular meals (3.465), overnight vegetables (OR=3.296), GERD (OR=3.044), hot food (OR=2.510), passive smoking (OR=2.423), pickled food (OR=2.273), alcohol drinking (OR=2.074), seldom eating breakfast (OR=1.987), and false dining posture (OR=1.977) increased the risk of esophageal cancer on multivariate logistic analysis, and fresh vegetables (OR=0.279) and BMI≥25 (OR=0.528) continued to be protective. Conclusions: Esophageal cancer could be caused by genetics acting in synergy with environmental factors. Health education for the general population in high risk areas should be strengthened, with intervention programs of nutrition and lifestyle focusing on effective prevention and control for upper gastrointestinal cancer. Keywords: Esophageal cancer - high risk regions of China - case-control study - risk factor

Introduction

Esophageal cancer occurs in esophageal epithelium, is a common digestive system malignant tumor with a high incidence in developing country. It ranked the eighth in incidence in the world, and had 460,000 new cases per year (Kamangar et al., 2006). With a poor prognosis, about 400,000 persons per year died because of esophageal cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007), which threatened seriously the health of human beings. China is one of the countries with highest incidence rate and mortality rate of esophageal cancer. The incidence cases and deaths reached to 52.8% and 49.3% in total worldwide, respectively (Parkin et al., 2005). In China, the incidence rate and mortality rate of esophageal cancer were 195.5 per million and 152.1 per million according to the cancer registration data, and ranked the sixth and the fourth, respectively (Chen et al., 2008; Zhao and Chen, 2008). The incidence of esophageal cancer in our country shows distinct regional difference. The first national death cause investigation preliminarily surveyed the epidemiological status of esophageal cancer in our country, also found some areas with high incidence of esophageal cancer, but the exact reason was not clear. In our study, main risk factors for esophageal cancer in upper gastrointestinal cancer high risk areas in China were studied, in order to offer a theoretical basis for cancer prevention.

Materials and Methods

Study population

Five areas with high incidence of esophageal cancer and gastric cancer with good quality of cancer registration data were selected for the study, including Cixian, Shexian from Hebei Province, Linxian from Henan Province,
Feicheng from Shandong Province and Zhuanghe from Liaoning Province. Totally 50 cases were randomly recruited from each cancer registry database diagnosed as cancers in lower segment of esophagus since January 1st, 2009. Case information and pathology diagnosis should be clear. Efforts were made to 1:3 individual-matching the cases and controls by several factors, including same gender, age with 2-year intervals and same village. Also, controls should have no history of malignancy and no family history of upper gastrointestinal cancer. At last, a total of 250 cases and 750 controls comprised the subjects in this analysis ultimately.

Data collection

Considering of influencing factors of esophageal cancer, a structured questionnaire was designed by experts’ repeated argument. It was interviewed face-to-face by trained professionals, and it included general information, drinking water sources, smoking, alcohol drinking, tea drinking, regular meals, dining posture, taste, breakfast eating, refrigerator using; overnight vegetable eating, fresh vegetable, fresh fruits, meat and eggs, milk, beans, garlic, rice and flour, dried foods, pickled food, fried foods, hot foods, moldy foods, history of digestive diseases, body mass index (BMI), gastroesophageal reflux disease, and so on.

Quality control

①All cases were diagnosed by pathological data, and signed by attending physician. ②In order to decrease the memory bias, the interviewee should be patients himself or his closest relative. ③The interviewers should be trained professionally, understand content of the questionnaire and natives living habits, know some of the common idiom, and also should learn to communicate with the local residents. ④After every day investigation, the interviewers should summarize the problem occurred in the investigation and solve promptly. The questionnaire with poor quality must be investigated once again.

Statistical analysis

EPI-DATA was used for data entry and SPSS 13.0 for data analysis. Table 1 showed the items of questionnaire and their values. Conditional logistic model was used for univariate and multivariate analysis to evaluate the association between exposure factors and esophageal cancer risk. At last, the odd ratios (OR) and 95% confident interval (CI) of risk factors were calculated by multivariate logistic analysis.

Results

General information

Totals of 250 esophageal cancer cases and 750 controls were collected in our study. Of 250 cases, the male was 180 cases, while the female was 70 cases. The average age of case group and control group was 61.21±8.946 years and 60.8±8.898 years, respectively. No significant difference existed in age, marriage status, ethnic and job occupation between case group and control group (Table 2).

### Table 1. Variables in the Questionnaire

<table>
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<tr>
<th>Variables</th>
<th>Value</th>
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</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
</tr>
<tr>
<td>Marital status</td>
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</tr>
<tr>
<td>Job occupation</td>
<td>1=peasant 2=worker 3=other</td>
</tr>
<tr>
<td>Ethnic group</td>
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</tr>
<tr>
<td>Drinking water sources</td>
<td></td>
</tr>
<tr>
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<td>1=running water 2=cellar water, pool water, surface well water, river water, lake water 3=deep well water</td>
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<tr>
<td>Alcohol drinking</td>
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<tr>
<td>Tea drinking</td>
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<tr>
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<tr>
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<td>Fresh fruit</td>
<td>1=everyday or often 2=sometimes or never</td>
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<td>Moldy foods</td>
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<td>BMI</td>
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Lifestyles and esophageal cancer risk

Smoking, passive smoking and alcohol drinking increased the risk of esophageal cancer. The ORs were 2.055, 1.957 and 1.941, respectively. There was a dose-response relationship between smoking amount and esophageal cancer risk. The risk increased significantly while the smoking amount was more than 30 cigarettes per day (OR=3.027). No significant association existed between drinking water sources and esophageal cancer risk.

Not regular meal, overnight vegetables, seldom eating breakfast and false dining posture could increase the risk of esophageal cancer (Table 3).

Diet factors and esophageal cancer risk

Often eating pickled food, fried foods and hot foods could increase the risk of esophageal cancer, while eating vegetables and fruits could decrease the risk of esophageal cancer (Table 4).
Table 2. Distribution of Influencing Factors on Case and Control

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<td>%</td>
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*: t value

Table 3. Univariate Analysis of Lifestyles and Esophageal Cancer Risk

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Table 4. Univariate Analysis of Diet Factors and Esophageal Cancer Risk

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<td>83</td>
<td>33.2</td>
<td>247</td>
<td>32.90</td>
</tr>
<tr>
<td>Garlic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>29</td>
<td>11.6</td>
<td>129</td>
<td>17.20</td>
</tr>
<tr>
<td>Sometimes</td>
<td>142</td>
<td>56.8</td>
<td>388</td>
<td>51.70</td>
</tr>
<tr>
<td>Often</td>
<td>79</td>
<td>31.6</td>
<td>233</td>
<td>31.10</td>
</tr>
<tr>
<td>Rice and flour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td>24</td>
<td>9.6</td>
<td>90</td>
<td>12.00</td>
</tr>
<tr>
<td>Everyday</td>
<td>226</td>
<td>90.4</td>
<td>660</td>
<td>88.00</td>
</tr>
<tr>
<td>Dried foods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>49</td>
<td>19.6</td>
<td>181</td>
<td>24.10</td>
</tr>
<tr>
<td>Sometimes</td>
<td>171</td>
<td>68.4</td>
<td>493</td>
<td>65.70</td>
</tr>
<tr>
<td>Often</td>
<td>30</td>
<td>12.0</td>
<td>76</td>
<td>10.10</td>
</tr>
<tr>
<td>Pickled food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>168</td>
<td>67.2</td>
<td>595</td>
<td>79.30</td>
</tr>
<tr>
<td>Often</td>
<td>82</td>
<td>32.8</td>
<td>155</td>
<td>20.70</td>
</tr>
<tr>
<td>Fried foods</td>
<td></td>
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</tr>
<tr>
<td>Never</td>
<td>19</td>
<td>7.6</td>
<td>136</td>
<td>18.10</td>
</tr>
<tr>
<td>Sometimes</td>
<td>208</td>
<td>83.2</td>
<td>545</td>
<td>72.70</td>
</tr>
<tr>
<td>Often</td>
<td>23</td>
<td>9.2</td>
<td>69</td>
<td>9.20</td>
</tr>
<tr>
<td>Hot foods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>141</td>
<td>56.4</td>
<td>577</td>
<td>76.90</td>
</tr>
<tr>
<td>Often</td>
<td>109</td>
<td>43.6</td>
<td>173</td>
<td>23.10</td>
</tr>
<tr>
<td>Moldy foods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>236</td>
<td>94.4</td>
<td>703</td>
<td>93.70</td>
</tr>
<tr>
<td>Sometimes</td>
<td>14</td>
<td>5.6</td>
<td>47</td>
<td>5.83</td>
</tr>
</tbody>
</table>

Table 5. Univariate Analysis of Healthy Status and Esophageal Cancer Risk

<table>
<thead>
<tr>
<th>Factors</th>
<th>Case</th>
<th>Control</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>History of digestive diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>164</td>
<td>65.60</td>
<td>706</td>
</tr>
<tr>
<td>Yes</td>
<td>86</td>
<td>34.40</td>
<td>44</td>
</tr>
<tr>
<td>GERD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>148</td>
<td>59.20</td>
<td>596</td>
</tr>
<tr>
<td>&gt;=8</td>
<td>102</td>
<td>40.80</td>
<td>154</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>213</td>
<td>85.20</td>
<td>555</td>
</tr>
<tr>
<td>&gt;=25</td>
<td>37</td>
<td>14.80</td>
<td>195</td>
</tr>
</tbody>
</table>

Table 5 showed that history of digestive diseases and gastroesophageal reflux disease were risk factors of esophageal cancer, the ORs were 8.01 and 3.43, respectively. BMI>=25 was protective factor, and the OR was 0.42.

Multivariate analysis
Variables with statistical significance entered into the multivariate logistic regression model. The results showed that gastrointestinal history (OR=12.658), not regular meal (OR=3.465), overnight vegetables (OR=3.296), gastroesophageal reflux disease (OR=3.044), hot food (OR=2.510), passive smoking (OR=2.423), pickled food
Table 6. Multivariate Analysis of Influencing Factors and Esophageal Cancer Risk

<table>
<thead>
<tr>
<th>Factors</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive smoking</td>
<td>0.885</td>
<td>0.295</td>
<td>9.015</td>
<td>0.003</td>
<td>2.423</td>
<td>1.360~4.317</td>
</tr>
<tr>
<td>Drinking</td>
<td>0.730</td>
<td>0.283</td>
<td>6.624</td>
<td>0.010</td>
<td>2.074</td>
<td>1.190~3.616</td>
</tr>
<tr>
<td>Regular of meal</td>
<td></td>
<td></td>
<td>7.875</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular of meal (1)</td>
<td>0.318</td>
<td>0.262</td>
<td>1.475</td>
<td>0.225</td>
<td>1.375</td>
<td>0.823~2.298</td>
</tr>
<tr>
<td>Regular of meal (2)</td>
<td>1.243</td>
<td>0.443</td>
<td>7.875</td>
<td>0.005</td>
<td>3.465</td>
<td>1.455~8.253</td>
</tr>
<tr>
<td>Dining posture</td>
<td>0.682</td>
<td>0.267</td>
<td>6.505</td>
<td>0.011</td>
<td>1.977</td>
<td>1.171~3.338</td>
</tr>
<tr>
<td>Breakfast</td>
<td>0.686</td>
<td>0.307</td>
<td>4.995</td>
<td>0.025</td>
<td>1.987</td>
<td>1.088~3.627</td>
</tr>
<tr>
<td>Overnight vegetable</td>
<td>1.193</td>
<td>0.268</td>
<td>19.771</td>
<td>0.000</td>
<td>3.296</td>
<td>1.948~5.576</td>
</tr>
<tr>
<td>Vegetables</td>
<td>-1.276</td>
<td>0.304</td>
<td>17.565</td>
<td>0.000</td>
<td>0.279</td>
<td>0.154~0.507</td>
</tr>
<tr>
<td>Pickled food</td>
<td>0.821</td>
<td>0.266</td>
<td>9.532</td>
<td>0.002</td>
<td>2.273</td>
<td>1.350~3.828</td>
</tr>
<tr>
<td>Hot foods</td>
<td>0.920</td>
<td>0.260</td>
<td>12.562</td>
<td>0.000</td>
<td>2.510</td>
<td>1.509~4.176</td>
</tr>
<tr>
<td>History of digestive diseases</td>
<td>2.538</td>
<td>0.290</td>
<td>76.760</td>
<td>0.000</td>
<td>12.658</td>
<td>7.174~22.335</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.639</td>
<td>0.270</td>
<td>5.598</td>
<td>0.018</td>
<td>0.528</td>
<td>0.311~0.896</td>
</tr>
<tr>
<td>GERD</td>
<td>1.113</td>
<td>0.246</td>
<td>20.481</td>
<td>0.000</td>
<td>3.044</td>
<td>1.880~4.930</td>
</tr>
</tbody>
</table>

(OR=2.273), alcohol drinking (OR=2.074), seldom eating breakfast (OR=1.987), false dining posture (OR=1.977) could increase the risk of esophageal cancer, and fresh vegetables (OR=0.279), BMI>=25 (OR=0.528) were protective factors (Table 6).

Discussion

Esophageal cancer is the result of both effect of environmental factors and genetic susceptibility, and the way of living and behaving is one of the most important influencing factors. However, the exact mechanism is still not clear. Thus, association study of influencing factors and esophageal cancer risk is still a topic to be concerned. The risk factors of esophageal cancer are discrepant in different countries and regions. For example, in developed country smoking, alcohol drinking and Barrett esophagitis are main risk factors, and in developing country nitrosamine, mold pollution, lack of vitamin, unhealthy lifestyles and smoking are main risk factors. There are many case control studies on influencing factors and esophageal cancer risk, but the results are inconsistent. Thus, we conducted a population-based, multi-centers case control study in five areas with high incidence of esophageal cancer, and the attributable risk proportion (ARP) was 13.4%~21.1% in rural areas, and 27.6%~31.3% in urban areas. Liao and Tian, 2009 carried out a meta analysis on esophageal cancer, and the attributable risk proportion (ARP) was 13.4%~21.1% in rural areas, and 27.6%~31.3% in urban areas. Xie et al. (2005). In our study, no association was found between smoking and esophageal cancer risk, although passive smoking could increase the risk of esophageal cancer significantly. The real reason is not clear, which needs to be studied further. In addition, we also found that alcohol drinking increased the esophageal cancer risk. Alcohol, a solvent for carcinogens, can promote carcinogen access to the esophageal mucosa, which can enhance the effect of damage effects, especially for the individuals who are both smoking and drinking. Seldom eating breakfast and long-term irregular diet will lead to esophageal campaign and coordinate obstacles, and will result in the damage of esophagus. A Meta analysis indicated that irregular diet could increase the risk of esophageal cancer, the OR was 2.76 (95%CI: 2.42~3.14) (Wang et al., 2007). Residents in high incidence area are accustomed to having a meal crouching, which greatly increases the burden of the digestive system and the chance of occurring chronic esophagus injuries. It is consistent with the Chen et al. (2004) report. Great quantity of researches confirm that excess intake of pickled food can increase the esophageal cancer risk. Residents in high incidence area are fond of sour cabbage, in which trace benzopyrene, nitrosamine and Roussin ’s methyl ester can be detected. Roussin ’s methyl ester can supply secondary amine with NO to form nitrosamine, which is a recognized strong carcinogen. According to the studies on nitrosamine and its precursor in vivo and in vitro of residents in high incidence area of esophageal cancer, nitrosamine is strongly associated with the risk of esophageal cancer. Thus, Chinese sour cabbage has been defined as human carcinogenic substances (2B) by IARC (International Agency for Research on Cancer, 1993). The salt in overnight vegetable can translate to nitrates and trace nitrite, which is also one of the carcinogens. It is consistent with our result that eating overnight vegetable is a risk factor of esophageal cancer. Moreover, it is said that hot foods can increase esophageal cancer risk, maybe because high temperature can injury esophageal mucosa or increase the sensitivity of risk factors. Hot food more than 70℃ can effect the growth cycle of esophageal mucosa epithelial cells, and create conditions to cancerous change (De Jong et al., 1972). Recently there were plenty of studies on the association between hot foods and esophageal cancer risk, including 50 case control studies and 2 cohort studies, much of which showed that eating hot foods could increase the risk of esophageal cancer.
References


Yutong He et al (Farin et al., 2009).

Regardless of univariate or multivariate analysis, vegetables still is a protective factor of esophageal cancer. Scientific research has shown that the fresh vegetables contain abundant anticancer substance and various minor elements. Fresh vegetables are rich in vitamin C, which can avoid cell mutation, reduce cell genetic damage caused by poisonous substance, and also can decrease the formation of nitrosamine, so it has good ability of preventing cancer. Besides, fresh vegetables are rich in cellulose that supposed to prevent cancer. Vegetables also contain carotenoid and tocopherol, which can boost human immunity. Chlorophyll in vegetables helps to prevent cancer and reduce chance of cancer for the individual smoking or drinking. Green broccoli is rich in sulfurophane, while mushroom is rich in purine bases, vitamin B and so on. In a word, intake of fruits or vegetables (>50g/day) can reduce 20% risk of esophageal cancer (World Cancer Research Fund/ American Institute for Cancer Research, 2007).

It is reported that individuals with history of the digestive system diseases (including gastroduodenal ulcer, esophagitis, atrophic gastritis, hepatitis, cirrhosis, and so on) increased the risk of esophageal cancer, and the OR value was high. Stomach content thing caused inflammation, erosion, and even ulcer, bleeding. If not control, it will result in esophageal stricture and the change of cell types in diseased area (squamous epithelial cell to columnar epithelial cell), and eventually lead to Barrett esophagitis that generally considered the precancerous lesion of esophageal cancer. In our study, we also found high BMI (≥25) was a protective factor of esophageal cancer, which was conflicting with results of western country, maybe because of the different pathologic types. One population-based cohort study in China followed 22 000 healthy individuals (40-79 years old) 10 years, and found BMI was correlated negatively with mortality of esophageal cancer if BMI>18.5. The mortality decreased 25% when BMI increased 5kg/m². High BMI was a protective factor of esophageal cancer (Smith et al., 2008), which was consistent with our study.

This being said, esophageal cancer is the result of both effect of environmental factors and genetic susceptibility. If the genetic background can’t be changed, change the had dietary habits and behavior patterns are the most effective prevention of esophageal cancer. Consequently, we should carry out health education in population in the long run, and appeal keeping away from the risk factors of esophageal cancer, and actively take part in endoscopic examination of the people in high risk area in order to find, diagnosis and treatment as early as possible, eventually to reduce the incidence and mortality of esophageal cancer in high risk areas.