Endoscopic survey of esophageal cancer in a high-risk area of China

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INTRODUCTION

Esophageal cancer (EC) is one of the most common malignant tumors with a high incidence in such regions as China, Iran, South Africa, Uruguay, France and Italy[1], of which China has almost half of the total cases with also the highest mortality rate, the fourth leading cause of cancer-related deaths in China. According to the data derived from 1/10 sample death investigation in the whole population of China in 1990-1992, the mortality rate of esophageal cancer was 27.73/100 000 for men and 13.63/100 000 for women, which were 3.1 and 3.6 times, respectively[2]. Some southern regions of the Taihang Mountains on the borders of Henan, Shanxi and Hebei provinces have significantly higher mortality rates of esophageal cancer. Cixian County in Hebei Province is also one of the areas with the highest mortality rate in China, where an endoscopic survey was conducted by Hebei Cancer Institute during the period between December 2001 and May 2002, and in this paper the results are reported.

MATERIALS AND METHODS

Cixian County is located at 36.30° northern latitude, 114.40° eastern longitude, on the east side of the Taihang Mountains along the Zhanghe River. It occupies an area about 1 014 square kilometers with a population of 634 470. This region contains greatly diverse geographic conditions, ranging from mountainous, hilly regions to long-stretched plains, each constituting about one-third of its total area. The climate is mainly under the influence of the warm seasonal wind from the mainland, with an annual average temperature of 18-25 °C and a rainfall between 600-700 mm. The dominant brown and light-colored soil yields mainly such farm products as wheat, corn, millet, rice, sweet potato and beans. Iron and coal are the main mineral resources, and the residents use coal mainly for daily cooking and heating[3].

As a key science research project sponsored by the National Tenth Five-Year Plan of China, the survey was conducted among the residents of 9 villages aged between 40 and 69 years in the hilly region of Cixian County, which is known for a higher incidence of esophageal cancer than the plain regions. The total population of the 9 villages was 12 048, and the annual incidence of esophageal cancer in the whole population of the area was acknowledged of the benefits of such a massive investigation in the whole population of China in 1990-1992.

RESULTS

Histologically, the detection rates of squamous epithelial acanthosis, squamous epithelial atrophy, and basal cell hyperplasia in the esophagus were 1.9% (38/2 013), 0.1% (3/2 013) and 0.9% (18/2 013) respectively, and those of mild, moderate, and severe esophagitis were 34.9% (703/2 013), 1.6% (33/2 013) and 0.2% (2/2 013) respectively. Mild, moderate, and severe esophageal dysplasia were detected in 8.6% (172/2 013), 7.8% (157/2 013) and 2.6% (53/2 013) respectively in the selected population, whereas in situ carcinoma, intramucosal carcinoma, invasive squamous carcinoma of the esophagus in 2.5% (50/2 013), 0.2% (4/2 013) and 0.7% (14/2 013) respectively. The detection rates of non-atrophic gastritis and atrophic gastritis of the cardia were 36.3% (730/2 013) and 11.5% (232/2 013) respectively, with mild and severe dysplasia of the cardia detected in 2.5% (51/2 013) and 0.8% (17/2 013), respectively, in this population; the rates of intramucosal adenocarcinoma and invasive adenocarcinoma of the cardia were 0.1% (3/2 013) and 0.8% (17/2 013) respectively. The detection rate of esophageal cancer at early stage was 79.4% (54/68). The survey rate (ratio of examined population to expected population) was 73.8% (2 013/2 725).

CONCLUSION

Histologic types of the esophageal and cardiac mucosa were characterized by endoscopic survey in a high-risk population of esophageal cancer, which may help the early detection and treatment of esophageal and cardiac cancers and dysplasia, and reduce the mortality of such malignancies.

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beginning of the survey, the subjects were asked to fill an epidemiological questionnaire, followed by physical examination performed by the physicians to exclude persons with serious contraindications to endoscopy. Endoscopic examinations were then performed by specialists following the procedures described by Wang et al. [4]. The detailed results were recorded and the biopsy specimens obtained were fixed in 80% alcohol and stained by hematoxylin-eosin (HE) for subsequent pathological diagnosis by pathologists.

Finally, the data were input into a computer to set up a survey information database and statistical analysis was performed using SPSS 10.0 software with chi-square test.

RESULTS

Survey rate

Of the totally 12 048 residents of the 9 villages, 2 992 were within the age range between 40 and 69 years, and after exclusion of 267 residents with contraindications (including 32 patients with cancer, 29 with heart diseases, 29 with cerebrovascular diseases, 55 with hypertension, 56 with other diseases, 59 already died, and 14 emigrants), the total number of subjects enrolled in this survey was 2 013 (including 973 male and 1 040 female subjects, with the male to female ratio of 0.94:1), and the survey rate was therefore 73.8% (Table 1).

Endoscopic findings of the esophagus

As shown in Table 2, the histologic detection rates of *in situ* carcinoma, intramucosal carcinoma, and invasive squamous carcinoma were 2.5% (50/2013), 0.2% (4/2013), and 0.7% (14/2013), respectively; early cancerous changes were detected in 2.7% (54/2013) of the subjects, which occupied 79.4% (54/68) of total esophageal cancer cases. Male subjects had comparable incidence of esophagitis [35.9% (349/973)] with that in female subjects [37.6% (391/1040), $\chi^2 = 0.645$, $P = 0.422$], but had significantly higher incidence of dysplasia [23.1% (225/973) vs 15.1% (157/1040) in female, $\chi^2 = 21.072$, $P = 0.000$]. The incidence of esophageal cancer did not vary significantly between the male and female subjects [3.3% (32/973) vs 3.5% (36/1040), $\chi^2 = 0.001$, $P = 0.98$].

Table 3 shows that with a 5-year increase in age, the histologic incidence of esophageal cancer and dysplasia all tended to be increased from the relatively low level in the 40-year-old group to the highest in the 65-year-old group (trend $\chi^2 = 135.943$, $P = 0.000$; trend $\chi^2 = 182.782$, $P = 0.000$). The rates of esophagitis in different age groups varied significantly ($\chi^2 = 12.475$, $P = 0.029$), as well as the rates of dysplasia ($\chi^2 = 141.184$, $P = 0.000$), and esophageal cancer ($\chi^2 = 74.855$, $P = 0.000$).

### Table 2 Detection rates of the histologic changes in the esophagus (%)

| Type                  | Male (%) | Female (%) | Total (%) |
|-----------------------|----------|------------|-----------|
| Normal squamous epithelium | 308 (31.7) | 392 (37.7) | 700 (34.8) |
| Squamous epithelial acanthosis     | 19 (2.0)   | 19 (1.8)   | 38 (1.9)  |
| Squamous epithelial atrophy        | 1 (0.1)    | 2 (0.2)    | 3 (0.1)   |
| Esophagitis                       |           |            |           |
| Mild                               | 337 (34.6) | 366 (35.2) | 703 (34.9) |
| Moderate                           | 11 (1.1)   | 22 (2.1)   | 33 (1.6)  |
| Severe                             | 1 (0.1)    | 3 (0.3)    | 4 (0.2)   |
| Dysplasia                          |           |            |           |
| Mild                               | 114 (11.7) | 58 (5.6)   | 172 (8.6) |
| Moderate                           | 82 (8.4)   | 75 (7.2)   | 157 (7.8) |
| Severe                             | 29 (3.0)   | 24 (2.3)   | 53 (2.6)  |
| In situ carcinoma                  | 25 (2.6)   | 25 (2.4)   | 50 (2.5)  |
| Intramucosal carcinoma             | 2 (0.2)    | 2 (0.2)    | 4 (0.2)   |
| Invasive carcinoma                 | 5 (0.5)    | 9 (0.9)    | 14 (0.7)  |
| Others                             | 31 (3.2)   | 33 (3.2)   | 64 (3.2)  |
| Total                              | 973 (100.0)| 1040 (100.0)| 2013 (100.0)|

Endoscopic findings of the gastric cardia

The incidence of cardiac cancer was much lower than that of esophageal cancer ($\chi^2 = 26.767$, $P = 0.000$), and early cardiac cancer only occupied 15% (3/20) of cardiac cancer cases. The rates of gastritis involving the cardia were 44.5% (433/973) in male and 50.8% (529/1040) in female subjects, showing significant difference between them ($\chi^2 = 14.184$, $P = 0.004$). The incidence of cardiac cancer was much lower than that of esophageal cancer ($\chi^2 = 8.159$, $P = 0.004$). The rates of dysplasia also varied significantly between them [4.9% (48/973) in male vs 1.3% (12/1040) in female, $\chi^2 = 7.012$, $P = 0.008$], but not that of cardiac cancer, [1.3% (13/973) in male vs 0.7% (7/1040) in female, $\chi^2 = 0.007$, $P = 0.943$], as shown in Table 4.

A 5-year interval, the incidence of cardiac cancer and dysplasia both increased from the level in the 40-year-old group to the highest in the 65-year-old group (trend $\chi^2 = 8.487$, $P = 0.000$; trend $\chi^2 = 26.09$, $P = 0.000$, Table 5). The rates of gastritis involving the cardia and dysplasia of the cardia also varied significantly ($\chi^2 = 11.223$, $P = 0.047$; $\chi^2 = 18.901$, $P = 0.002$), as well as that of cardiac cancer ($\chi^2 = 43.351$, $P = 0.000$).

### Table 1 Statistics of the residents of the 9 target villages enrolled in this survey

| Village       | Total population | Aged between 40-69 (yr %) | Contrain-dication | Expected population | Examined population | Survey rate (%) |
|---------------|-----------------|--------------------------|------------------|--------------------|-------------------|-----------------|
| Hebei Village | 1 184           | 304 (25.7)               | 29               | 275                | 220               | 80.0            |
| Taichen Village | 1 648          | 412 (25.0)               | 39               | 373                | 287               | 76.9            |
| Xichengji Village | 1 682        | 381 (22.7)               | 53               | 328                | 283               | 86.3            |
| Zhonghao Village | 699            | 183 (26.2)               | 23               | 160                | 130               | 81.3            |
| Donghao Village | 1 860          | 494 (26.6)               | 26               | 468                | 208               | 44.4            |
| Chejiao Village | 1 618          | 383 (23.7)               | 38               | 345                | 276               | 80.0            |
| Bai Village    | 1 679           | 415 (24.7)               | 27               | 388                | 284               | 73.2            |
| Donghelan Village | 1 076        | 271 (25.2)               | 17               | 254                | 208               | 81.9            |
| Xihelan Village | 602            | 149 (24.8)               | 15               | 134                | 117               | 87.3            |
| Total          | 12 048          | 2 992 (24.8)             | 305              | 2 725              | 2 013             | 73.8            |

The percentages in bracket indicate the rates of the population aged 40-69 years.
Table 4 Incidence of pathological changes detected histologically in the cardia (%)

| Type                              | Male (%) | Female (%) | Total (%) |
|-----------------------------------|----------|------------|-----------|
| Normal adenoepithelium            | 301 (31.0) | 329 (31.7) | 630 (31.4) |
| Non-atrophic gastritis            | 323 (33.2) | 407 (39.1) | 730 (36.3) |
| Atrophic gastritis                | 110 (11.3) | 122 (11.7) | 232 (11.5) |
| Dysplasia                         |          |            |           |
| Mild                              | 36 (3.7)  | 15 (1.4)   | 51 (2.5)  |
| Severe                            | 12 (1.2)  | 5 (0.5)    | 17 (0.8)  |
| Intramucosal adenocarcinoma       | 1 (0.1)   | 2 (0.2)    | 3 (0.1)   |
| Invasive adenocarcinoma           | 12 (1.2)  | 5 (0.5)    | 17 (0.8)  |
| Others                            | 178 (18.3) | 155 (14.9) | 333 (16.5) |
| Total                             | 973 (100.0) | 1040 (100.0) | 2013 (100.0) |

DISCUSSION

The prognosis of esophageal and cardiac cancer is the poorest among the patients with digestive carcinomas as more than 90% of them are not clinically identified until at an advanced stage, when surgery is denied due to either local tumor invading the surrounding tissues or distant metastasis, and therefore the 5-year survival rate of esophageal cancer is below 10%[5-7]. Early-stage asymptomatic esophageal cancer is basically curable with, for instance, conventional surgery and endoscopic resection, resulting in a 5-year survival rate of the patients reaching 90% or above[8-10].

For esophageal cancer prevention and treatment, a series of systematic researches including clinical, laboratory and field investigation were carried out in high-risk areas such as Linxian and Cixian counties since 1959[11-16], but at present the etiological factors have not yet been identified, and the incidence and mortality rates of esophageal cancer still remain high in those areas. A variety of detecting methods have been attempted by Chinese scientists to identify early esophageal cancer and precancerous lesions, such as exfoliative balloon cytology (EBC), occult blood bead (OBB), conventional endoscopy with

Table 3 Age-related distribution of the incidence of pathological changes in esophagus

| Type                                | 40-                   | 45-                      | 50-                    | 55-                   | 60-                   | 65-69                  |
|-------------------------------------|-----------------------|--------------------------|------------------------|-----------------------|-----------------------|------------------------|
| Normal squamous epithelium          | 355 (44.8)            | 176 (38.4)               | 92 (28.6)              | 56 (24.9)             | 14 (9.4)              | 7 (10.4)               |
| Squamous epithelial acanthosis      | 11 (1.4)              | 4 (0.9)                  | 10 (3.1)               | 7 (3.1)               | 5 (3.4)               | 1 (1.5)                |
| Squamous epithelial atrophy         | 1 (0.1)               | 1 (0.2)                  | 1 (0.3)                | -                     | -                     | -                      |
| Basal cell hyperplasia              | 6 (0.8)               | 6 (1.3)                  | 3 (0.9)                | 1 (0.4)               | 2 (1.3)               | -                      |
| Esophagitis                         |                       |                          |                        |                      |                      |                        |
| Mild                                | 304 (38.4)            | 167 (36.5)               | 90 (28.0)              | 71 (31.6)             | 53 (35.6)             | 18 (26.9)              |
| Moderate                            | 17 (2.1)              | 2 (0.4)                  | 9 (2.8)                | 4 (1.8)               | 1 (0.7)               | -                      |
| Severe                              | -                     | 1 (0.2)                  | 2 (0.6)                | 1 (0.4)               | -                     | -                      |
| Dysplasia                           |                       |                          |                        |                      |                      |                        |
| Mild                                | 37 (4.7)              | 36 (7.9)                 | 41 (12.7)              | 26 (11.6)             | 21 (14.1)             | 11 (16.4)              |
| Moderate                            | 19 (2.4)              | 30 (6.6)                 | 43 (13.4)              | 26 (11.6)             | 26 (17.4)             | 13 (19.4)              |
| Severe                              | 12 (1.5)              | 12 (2.6)                 | 12 (3.7)               | 6 (2.7)               | 9 (6.0)               | 2 (3.0)                |
| In situ carcinoma                   | 3 (0.4)               | 8 (1.7)                  | 10 (3.1)               | 14 (6.2)              | 8 (5.4)               | 7 (10.4)               |
| Intramucosal carcinoma              | -                     | 2 (0.4)                  | -                      | -                     | 2 (1.3)               | -                      |
| Invasive carcinoma                  | -                     | 2 (0.4)                  | 3 (0.9)                | 4 (1.8)               | 3 (2.0)               | 2 (3.0)                |
| Others                              | 27 (3.4)              | 11 (2.4)                 | 6 (1.8)                | 9 (4.0)               | 5 (3.4)               | 6 (9.0)                |
| Total                               | 792 (100.0)           | 458 (100.0)              | 322 (100.0)            | 225 (100.0)           | 149 (100.0)           | 67 (100.0)             |

Table 5 Age-related distribution of detection rates of pathological changes in gastric cardia

| Type                                | 40-                   | 45-                      | 50-                    | 55-                   | 60-                   | 65-69                  |
|-------------------------------------|-----------------------|--------------------------|------------------------|-----------------------|-----------------------|------------------------|
| Normal adenoepithelium              | 295 (37.2)            | 156 (34.1)               | 81 (25.2)              | 61 (27.1)             | 27 (18.1)             | 10 (14.9)              |
| Non-atrophic gastritis              | 319 (40.3)            | 169 (36.9)               | 116 (36.0)             | 60 (26.7)             | 47 (31.5)             | 19 (28.4)              |
| Atrophic gastritis                  | 90 (11.4)             | 45 (9.8)                 | 38 (11.8)              | 34 (15.1)             | 14 (9.4)              | 11 (16.4)              |
| Dysplasia                           |                       |                          |                        |                      |                      |                        |
| Mild                                | 13 (1.6)              | 8 (1.7)                  | 10 (3.1)               | 8 (3.6)               | 8 (5.4)               | 4 (6.0)                |
| Severe                              | -                     | 8 (1.7)                  | 2 (0.6)                | 3 (1.3)               | 4 (2.7)               | -                      |
| Intramucosal adenocarcinoma         | -                     | -                       | 1 (0.3)                | -                     | 1 (0.7)               | 1 (1.5)                |
| Invasive adenocarcinoma             | -                     | 1 (0.2)                  | 1 (0.3)                | 3 (1.3)               | 5 (3.4)               | 7 (10.4)               |
| Others                              | 75 (9.5)              | 71 (15.5)                | 73 (22.6)              | 56 (24.9)             | 43 (28.9)             | 15 (22.4)              |
| Total                               | 792 (100.0)           | 458 (100.0)              | 322 (100.0)            | 225 (100.0)           | 149 (100.0)           | 67 (100.0)             |
smear or biopsy, sparse hydrochloric acid preliminary screening, serum total salic acid detection (TSA), otolarynlogologic examination and so forth, but all these methods are marred by certain disadvantages besides their respective advantages in the early detection of esophageal cancer and precancerous lesions[17-19].

A massive screening in the population of 126 187 in Cixian was carried out by Hebei Cancer Institute and 16 748 high risk participants aged 40 years and older were screened with exfoliative balloon cytology, the survey rate was 71.4%, resulting in the identification of 179 cases of esophageal cancer, 172 esophageal precancerous lesions, 866 stage II severe esophageal epithelial dysplasia (SEED II), 3 179 stage I severe esophageal epithelial dysplasia (SEED I) and 5 346 mild esophageal epithelium dysplasia (MEED), with the detection rates of MEED, SEED I, SEED II, esophageal precancerous lesions and esophageal cancer being 31.92%, 18.98%, 5.17%, 1.03% and 1.07%, respectively[20]. Most of the researches indicate that exfoliative balloon cytology is an effective, economic and practicable method, having higher detection rate for esophageal cancer than conventional endoscopy, but only cytological diagnosis is obtained and a further endoscopic biopsy and histopathologic confirmation are necessary. This method is now insufficient for esophageal cancer screening because of the severe discomfort and low acceptance by the target subjects.

Esophageal chromoendoscopy with multi-point biopsy and histopathologic examination has developed rapidly since 1974, which greatly increased the detection rate of esophageal cancer and precancerous lesions, and at the same time it is capable of characterizing and defining the scope of the lesions to provide guidance for treatment and follow-up, also suitable for the secondary prevention of esophageal cancer[21-33]. Currently, the secondary prevention with early detection, early diagnosis and early treatment through chromoendoscopy survey has become the major research concern in the prevention and control of esophageal cancer.

The occurrence and development of esophageal cancer is a slow process involving multiple factors and genes and undergoing multiple stages. Prior to carcinization of the squamous esophageal epithelium, the basal cell hyperplasia or simple hyperplasia takes place and evolves into mild, moderate, severe dysplasia cells that develop, in sequence, into in situ carcinoma, early invasive cancer and advanced cancer[34-36]. As a part of the entire research project, a massive esophageal chromoendoscopical survey was initially conducted in the high-risk area without preliminary screening, and the high survey rate reaching 73.8% indicates that the population’s compliance to the survey was high after adequate health education. The distribution of histologic types of the esophageal and cardiac mucosa in high-risk area can be accurately obtained by esophageal chromoendoscopical survey, which possesses the advantage of accurate pathologic diagnosis and differentiation of the histologic types, well defined scope of the lesions and their invasive depth.

This study will, after defining the incidences of the pathologic changes of the esophageal and cardiac mucosa in the population, contribute to the early treatment of esophageal and cardiac cancer and dysplasia, increase their cure rates, and reduce the mortality of such malignancies.

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