

The Relationship between a Cohort Endoscopic Screening of 15,000 Subjects and the Death of Patients with Esophageal and Gastric Cancers in High-Risk Areas

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OBJECTIVE Ci-xian County is located in the north of China and is a high-risk area for esophageal cancer (EC). In 2004, the incidence rate of EC in the county was 127/100,000 and 93/100,000 in the male and female population, respectively, and that of gastric cancer (GC) was 72/100,000 and 36/100,000. Since 2001 a cohort screening, supported by a special national fund, utilizing endoscopic examination with iodine staining for the target population at the age ranging from 40 to 69 years was carried out, so as to reduce the incidence and mortality rates in the high-risk areas of EC.

METHODS In October 2001, 4 townships in the Ci-xian County, Hebei, China were selected, with 22,016 cases in the intervention group (IVG) and 33,410 in the control group (CG). The total population coverage reached 55,000. There were 3257 males and 3339 females in the IVG with the age ranging from 40 to 69 years, and 4299 males and 4430 females in the CG with the same range of the age. Endoscopic screening with iodine staining was used in the IVG, with a screening rate of 53.2%. During the screening by endoscopic examination, 97 cases were found to have esophageal squamous epithelium, carcinoma-in-situ at the cardiac glandular epithelium or intra-mucosal carcinoma. Additionally, 102 cases were identified to have severe atypical hyperplasia in the esophagus and gastric cardia. The natural incidence rate of cancer and the mortality were observed in the CG. The ICD-0 version was used in the tumor incidence and death registration coding. During a period from June to September 2008, based on the information of the tumor registration database of the incidence and mortality in the Ci-xian County, the cohort groups were studied and followed.

RESULTS There were 133 patients with untreatable EC and 48 with GC in the IVG, while there were 259 and 37 patients in the CG who died of esophageal and gastric cancer, respectively. The relative risk (RR) of death was 0.76 in the male patients with EC, 95%CI (0.59-0.98), $P = 0.038$, and in the female patients the RR was 0.51, 95%CI (0.35-0.75), $P = 0.000$. The RR of death in the GC patients was 2.45, (1.40-4.29) in the male, $P = 0.01$, and 0.99, (0.47-1.99), in the female cases, $P = 0.906$.

CONCLUSION Six years after a cohort screening of a large population by endoscopic examination with iodine staining in areas at high risk for EC, the death risk in the male and female patients with EC has decreased compared with that in the control group. The difference between the 2 groups was statistically significant. However, no protective method used to decrease the death risk in GC patients has been found during this period of endoscopic screening.

KEY WORDS: endoscopic screening, esophageal cancer, gastric cancer, mortality.

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Introduction

Ci-xian County, in Hebei Province, located in the north of China is a high-risk area for esophageal cancer (EC), with an incidence rate of 127/100,000 in the male population and of 93/100,000 in the female population. The morbidity rates of gastric cancer (GC) are 72/100,000 and 36/100,000, respectively in the males and females of the county^[1]. Since 2001, with the support of a special state fund^[2], a cohort screening for a target population of ages ranging from 40 to 69 years was conducted, using iodine staining during endoscopic examination, in order to reduce the morbidity and the mortality rates of esophageal and gastric cancers in this high-risk area. The aim of our study is to probe the relationship between the death rates of patients with EC and GC and the outcomes of cohort screening with endoscopic examination in order to detect EC and GC in the public.

Materials and Methods

Establishment of the cohort

During a period from October 2001 to October 2002, a total of 55,426 cases from 4 townships of Ci-xian County, Hebei Province were selected and divided into the intervention group (IVG) with endoscopic screening and the control group (CG). There were a total of 22,016 subjects in the IVG with the ages ranging from 0 to 85 years, among which 3,257 were male with the age ranging from 40-69, and 3,339 were female with same range of the age. In the CG, there were 33,410 cases, among which 4,299 were male with the age ranging from 40-69 and 4,430 were female with the same range of the age.

In our study, the predefined age limit of the population in the IVG ranged from 40 to 69 years. First, based on the data supplied by the local agencies of public security, the database of tumor incidence and registration of total death causes were checked by the section of epidemiology at our institution. All data were recorded in the cohort database after rejecting the cases with tumor onset and death registration and emigrated families. In order to enhance the compliance of the subjects in the IVG in accepting the endoscopic screening, a general publicity event on the early diagnosis and treatment of EC was carried out by the medical staff at the provincial and county levels before the screening. The epidemiological baseline questionnaire and a letter of informed

consent were completed and signed by all subjects participating in the screening, and routine physical examination was conducted by physicians, so as to obviate the contraindications of endoscopic examination.

Of the 22,016 patients in the IVG, 6,596 were at the age ranging from 40-69 years. Excluding individuals with contraindications, including those going to areas outside Ci-xian County for work, and others, the exact number of the subjects receiving endoscopic screening was 3506. The total screening rate was 53.2%.

Screening technique and data analysis

The scope of the endoscopic examination included the esophagus, the gastric cardia, the stomach and the duodenal bulb. Routine 12 g/L iodine staining (20-30 ml) of the total mucous membrane of esophagus was performed. After staining, the mucous membranes showing positive staining or with dubious lesions were taken for biopsy. Routine pathologic sampling at the site of 25 cm from the superior end of the esophagus, and 2 cm from below the border of the cardiac mucosal ridge root was performed in all subjects, and an independent diagnosis was made in each case by 2 pathologists.

ICD-0 was used for the tumor incidence and death registration coding. Esophageal squamous carcinoma (ESC) and gastric adenocarcinoma diagnosed by histologic examination composed 85% of the total deaths.

Indicators of end-point analysis were used to calculate the relative risk (RR) of death in the EC and GC patients, in the IVG and CG, and in the 95% confidence interval (CI). SPSS 11.0 software was used for establishment and analysis of the cohort database.

Results

Pathologic results of endoscopic screening

In the cases receiving the endoscopic screening, 8 cases did not have pathologic examination because of miscellaneous reasons such as failure of endoscopy-guided biopsy. The pathologic results of severe atypical hyperplasia and infiltrating carcinoma in the esophagus and in the cardia are shown in Table 1.

Follow-up

During the period from May to September 2008, follow-up of the subjects in the IVG and CG from the 4 townships was performed and verification of the registered

Table 1. Pathology results of precancerous lesions and cancer from endoscopic screening

Group	Cases	Pathologic diagnoses of esophageal lesions					Pathologic diagnoses of cardiac lesions			
		Severe atypical hyperplasia	Carcinoma in situ	Intramucosal carcinoma	Infiltrating carcinoma	Total	Severe atypical hyperplasia	Intramucosal carcinoma	Infiltrating carcinoma	Total
Male	1642	53	36	13	9	111	15	5	15	35
Female	1690	38	35	6	9	88	6	2	5	13
Total	3332	91	71	19	18	199	21	7	20	48

database of tumor incidence and death rate was conducted. The survival status and death in the cohort group during the time of follow up was verified, with an emphasis on discrimination in the incidence and mortality of the patients with EC and the patients with carcinoma of gastric cardia (CGC). Based on the results of the follow-up, the registered database of tumor incidence and death during the year 2002-2007 maintained in the tumor registry office of Ci-xian County was rechecked. In the 3506 patients completing the endoscopic examination, 174 of them were lost during the follow-up period. The follow-up rate was 95.0% (3,332/3,506). During the 6-year follow-up, 133 EC patients and 48 GC patients in the IVG died, while in the CG, 259 EC and 37 GC patients died (Tables 2-5).

Discussion

In areas at high risk for EC in China, this is the first time that endoscopic screening in a large population has been conducted. The results of 6-year follow-up have shown that there was a decrease of the death risk both in male and in female patients with EC, with a significant difference between the 2 groups. The decrease in death rates in the EC patients of the IVG closely related to the detection of early EC and precancerous changes via the

endoscopic screening. A total of 97 cases in the IVG were diagnosed by iodine staining during endoscopic examination as esophageal squamous epithelium, carcinoma in situ at the cardiac glandular epithelium or intramucosal carcinoma, and 102 were found to have severe esophageal and cardiac atypical hyperplasia (Table 1).

Surgical procedures such as endoscopy-guided excision of the mucous membranes were performed in 90% of these patients. Treatment, which proved effective, interrupted the continuous progression of the lesion, and therefore, cut down on the mortality. It has been reported in China^[3] that in areas at high risk for EC, the postoperative 10-year survival rate of early EC patients diagnosed by endoscopic screening was 72.9%, and the 5-year survival rate of those undergoing endoscopy-guided mucosectomy was 100%. Katada et al.^[4] reported that the 5-year survival rate of patients who underwent an endoscopy-guided simple resection of lesions with infiltration of the muscularis mucosae was 79.5%. It was reported by Pech et al.^[5] that endoscopy-guided mucosectomy used for high-grade esophageal intraepithelial neoplasia and mucosal adenocarcinoma accompanied with Barrett’s esophagus was conducted in 349 patients, with a 5-year survival rate of 84%. Generally, it is believed that over time, the effect of endoscopic screening as increasing the long-term survival rate of ESC patients

Table 2. Analysis of the deaths of male EC patients from the cohort screening population.

Age (years)	IVG			CG			Statistics		
	Population	Death toll in EC cases	Death rate (%)	Population	Death toll in EC cases	Death rate (%)	RR	95% (CI)	P
40-	903	5	0.55	858	10	1.17	0.47	0.16-1.39	0.163
45-	761	12	1.58	1190	25	2.1	0.75	0.37-1.50	0.408
50-	552	15	2.72	894	25	2.8	0.97	0.51-1.86	0.929
55-	407	18	4.42	554	31	5.6	0.78	0.43-1.42	0.414
60-	331	20	6.04	396	35	8.84	0.66	0.38-1.17	0.156
65-69	303	26	8.58	407	40	9.83	0.86	0.51-1.45	0.571
Total	3257	96	2.98	4299	166	3.86	0.76	0.59-0.98	0.038

There was a downtrend in the RR of EC in the male populations from various age groups of the IVG, compared with that in the CG. The overall RR value was 0.76, and there was a statistically significant difference between the two groups.

Table 3. Analysis of female EC deaths from the cohort screening population.

Age (years)	IVG			CG			Total		
	Population	EC death	Death rate (%)	Population	EC death	Death rate (%)	RR	95% (CI)	P
40-	931	1	0.11	823	3	0.36	0.29	0.03-2.83	0.259
45-	801	4	0.5	1222	8	0.65	0.61	0.18-2.03	0.414
50-	575	5	0.87	933	22	2.36	0.36	0.14-0.97	0.034
55-	401	12	2.99	626	25	3.99	0.74	0.37-1.49	0.401
60-	380	8	2.11	451	14	3.1	0.67	0.28-1.62	0.372
65-69	251	6	2.39	375	21	5.6	0.41	0.16-1.04	0.053
Total	3339	36	1.08	4430	93	2.1	0.51	0.35-0.75	0.000

There was also a downtrend in the RR of EC in the female populations from various age groups of the IVG, compared with that in the CG. This is especially pronounced in the population of the 50-year age group, with a 54% decrease in the RR, and a significant difference between the IVG and the CG. There was a 49% decrease in the overall RR value, P = 0.000.

Table 4. Analysis of male GC deaths from the cohort screening population.

Age (years)	IVG	CGC	Distal GC	Uncertain site	Total	Death rate (%)	CG	CGC	Distal GC	Uncertain site	Total	Canceration rate (%)	RR	95% (CI)	P
40-	903	1	1	1	3	0.33	858	1	1	-	2	0.23	1.43	0.24-8.56	0.696
45-	761	2	1	1	4	0.53	1190	1	0	-	1	0.08	6.28	0.76-56.32	0.060
50-	552	2	1	2	5	0.91	894	2	1	-	3	0.34	2.72	0.65-11.41	0.156
55-	407	1	2	-	3	0.74	554	0	3	-	3	0.54	1.36	0.27-6.79	0.704
60-	331	8	1	-	9	2.72	396	1	1	2	4	1.01	2.74	0.84-8.98	0.083
65-69	303	7	4	-	11	3.63	407	3	2	1	6	1.47	2.54	0.93-6.94	0.061
Total	3257	21	10	4	35	1.07	4299	8	8	3	19	0.44	2.45	1.40-4.29	0.010

In the comparison of the death rates of GC in males of various age groups between the IVG and the CG, the RR value ranged from 1.43 to 6.28, without significant differences between the groups. The total RR of death = 2.45, P = 0.010.

Table 5. Analysis of female GC deaths from the cohort screening population.

Age (years)	IVG	CGC	Distal GC	Uncertain site	Total	Death rate (%)	CG	CGC	Distal GC	Uncertain site	Total	Death rate (%)	RR	95% (CI)	P
40-	931	0	0	-	0	0.00	823	1	2	-	3	0.36	-	-	-
45-	801	1	1	-	2	0.25	1222	0	0	-	0	0.00	-	-	-
50-	575	1	1	1	3	0.52	933	2	1	-	3	0.32	1.63	0.33-8.08	0.549
55-	401	0	0	-	0	0.00	626	0	2	-	2	0.32	-	-	-
60-	380	3	0	-	3	0.79	451	1	4	-	5	1.11	0.71	0.17-2.89	0.639
65-69	251	4	1	-	5	1.99	375	2	3	-	5	1.33	1.50	0.43-5.25	0.519
Total	3339	9	3	1	13	0.39	4430	6	12	-	18	0.41	0.99	0.47-1.99	0.906

In the comparison of the death rates of GC in the females of 50 and 65-year age groups between the IVG and the CG, the RR value ranged from 1.50 to 1.63, without significant differences between the groups. The total RR of death = 0.99, P = 0.906.

and decreasing the death rate may become more conspicuous.

However, the most significant concern in our study was that the RR of male GC patients in the IVG was 2.5, 95% CI (1.40-4.29), P = 0.01, compared to that in the CG, while for the female GC patients both at the age of 50 and of 65 years, the RR = 1.5-1.6. This was similar to the tendency of the RR of the male GC patients. Further, the total RR value of female GC patients was 0.99. Nevertheless, the differences were not statistically significant. Analysis of the results of cancer diagnosed via the endoscopic screening demonstrated that ESC and cardiac adenocarcinoma (CAC) detected early in male patients accounted for 84.5% and 25%, respectively, and those in females, accounted for 91.9% and 28.6%, respectively (Table 1). It suggested that the effect of the endoscopic examination on early detection of CAC was far lower than that on early detection of ESC. This phenomenon was also confirmed in our previous studies^[6]. Among the male patients who died of GC in the IVG, 60% were CGC patients (21/35), and in the females, it was 69.2% (9/13) (Tables 4, 5). It should be noted that the long-term survival rate of advanced CGC found by the endoscopic screening failed to increase, however, this could be attributed to the registration of tumor morbidity and the death rate occurring relatively earlier. Taken together, these 2 factors might underlie the finding that the RR of male GC patients was higher in the IVG than that in the CG; however, further in-depth analysis is necessary to differentiate between the females and males in this respect. In the male group, the RR of GC death cases was higher than in the controls while there was no such tendency in the female group.

In Japan, GC ranks first in the death rate for malignant tumors^[7]. In the world, Japan is the only country where an in-depth, large population-based GC screening and study were conducted. Hosokawa et al.^[8] conducted a retrospective cohort analysis of a population of 11,763 people,

with an age ranging from 40 to 75 years. The results showed that in a comparison between the population with endoscopic screening and the control group, there was a decrease in the RR of the GC patients, RR = 0.35, 95% CI (0.14-0.86). In the study population, the RR of males was 0.22, (0.07-0.70). The author pointed out that early GC reached 78% via the endoscopic screening. After a cohort observation of 47,605 people, Miyamoto et al.^[9] found that there was a 46% decrease in the RR of GC patients who had undergone endoscopic examination, RR = 0.54, 95% CI (0.38-0.77). Currently there has been a 50% decrease in the death rate of both male and female Japanese GC patients. There is consensus that early diagnosis of GC decreased the death rate of the patients^[6]. In 2008, Hamashima et al.^[10] conducted an in-depth analysis of the role of the large population-based GC screening in reference to 4 aspects, i.e. X-rays, endoscopy, serum pepsin and HP antibody, based on 1,715 papers regarding the endoscopic screening of GC which were published in Japan during a period from 1985 to 2005. The authors then recommended that X-ray screening be the first choice for a large population if the opportunity to conduct population screening is available. Nevertheless, it was shown in an analysis of the relationship between the endoscopic screening and the early diagnosis of GC in Japan^[6,10,11] that in 2/3 of the Japanese GC patients, the pathogenic site was the gastric body or the pylorus. At present, local lesions have been found in 53% of GC cases diagnosed in Japan, while in the USA the rate is 27%. Of special concern is that if the intra-mucosal and sub-mucous lesions are regarded as the diagnostic criteria of early CGC, the early CGC would only account for 3.5% of the GC cases (204/5,863) in Japan, i.e., the level of early diagnosis of the distal GC would be higher than that of proximal GC in Japan. Likewise in China, it was seen in a study on endoscopic screening conducted in the EC high-risk area of Taihang Mountains^[12] that when intra-mucosal carcinoma was regarded as the defined standard of early ESC and CAC, the former accounted for 77.4% and the latter for 31.4% of the total cases. As it is well-known, based on the coding rules of the International Classification of Diseases, Eight Revision (ICD-8), CGC was classified according to the statistics of GC. In 2000, CGC was termed as adenocarcinoma of the esophagogastric junction by the WHO^[13]. Over the past 10 years, epidemiologic studies have shown that with a drop in the incidence and death rates of EC in the EC high-risk areas of China, there has been an apparent rise in the incidence of CGC^[14]. During a period from 1998 to 2002, the incidence rates of ESC and CGC in males respectively ranged from 82.5 to 123.5/100,000 and from 34.5 to 69.5/100,000 in the Ci-xian, Lin-xian and She-xian counties in Taihang Mountains, while in females, the incidence rates of ESC and CGC respectively ranged from 51.8 to 90.7/100,000 and from 10.3 to 41.4/100,000. The incidence rate of gastric adenocarcinoma could surpass that of ESC in the

She-xian County in Hebei Province and in the Lin-xian County in Henan Province if commingling statistics of CGC and distal GC were conducted^[12]. It is obvious that attention should be directed to the incidence and death rates of CGC in the EC high-risk areas of China. Further, early diagnosis of CGC is the key to decreasing the death rates of upper gastrointestinal tumors in the EC high-risk areas.

Another significant finding from the follow-up data that we discovered is that in males, the death toll of EC in the age groups of 60-64 and 65-69 years accounted for 48% of the total cases (46/96), while in females of the same age groups, the proportion reached 42% (16/38) (Table 1). One specification in the project planning stipulated that the endoscopic screening rate should achieve 70%. However, since there was a long-held belief of an inherently poor prognosis of EC in the population in the high-risk areas, the screening rate failed to reach the design specification. It is believed that in the future, strengthening the understanding of early diagnosis and treatment of EC in the population of the advanced age group will raise the compliance of the public and awareness of the benefits of receiving endoscopic screening, and as a result, significantly cut down on the death rate of ESC in high-risk areas.

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