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## Age scope of high-risk population for esophageal cancer in Ci county

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### Abstract

**AIM:** To define the age scope of high-risk population for esophageal cancer (EC) in Ci county.

**METHODS:** The results of endoscopic examination of 2 013 subjects, cytological screening of 16 763 persons and records of 9 265 patients with EC were analyzed by Ridit methods, the standard age group was 45-49 year group.

**RESULTS:** The average age of patients with moderate esophageal epithelium dysplasia by endoscopic examination was 53.5 years, of severe esophageal epithelium dysplasia, 51.4 years, early EC, 55.6 years. The average age of stage one severe epithelium dysplasia (SEEDI) by cytological screening was 51.2 years, of stage two severe epithelium esophageal dysplasia (SEED II) 51.6 years, of advanced EC 61.7 years. In the group of 40-year olds, the value of Ridit by pathological diagnosis was 0.46, 95% CI, 0.45-0.47, that by cytological diagnosis was 0.45, 95% CI, 0.43-0.47. As the age increased at five-year intervals, the value of Ridit increased significantly.

**CONCLUSION:** In Ci county of a high incidence area of EC, the age definition of high-risk population should be above 45 years.

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**Key words:** Esophageal cancer; High-risk population; Age; Ridit analysis

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### INTRODUCTION

Esophageal cancer (EC) is one of the most common malignant tumors, and occurs at an especially high frequency in some areas of China. In 1990 s, a sample-investigation of malignant tumor mortality conducted in China revealed that EC was the fourth leading cause of cancer death in China<sup>[1]</sup>. In the past 40 years, EC researches have been carried out extensively in China. Ci county in Hebei province is one of the areas with the highest mortality rate in China, the incidence rates of EC was 123.9/100 000-153.8/100 000 for men and 85.3/100 000-108.1/100 000 for women<sup>[2,3]</sup>. Exfoliative balloon cytologic screening has been carried out as a major secondary prevention procedure and high-risk population of EC was defined above 30-year olds from 1970s to the beginning of 1990s endoscopic examination became the major secondary prevention procedure and high-risk population was defined as above 40-year olds after 1990 s<sup>[4,5]</sup>. To increase the economic benefit ratio of mass survey in high-risk EC areas and concentrate on high-risk populations, the results of cytological screening and endoscopic examination, the data of EC incidence registered from 1988 to 1997 were analyzed to explore the high incidence age group of EC.

### MATERIALS AND METHODS

The cytological screening results of 16 763 persons aged above 40 years, endoscopic examination of 2 013 people and records of 9 265 cases with EC were analyzed, including male, 15 145 and female, 12 896. The data of incidence of EC from 1988 to 1997 came from cancer registry station in Ci county Tumor registry adopts the code of ICD-9<sup>[6]</sup>.

The criterion of cytological diagnosis was as follows<sup>[8]</sup>: normal esophageal epithelium cell (normal), mild esophageal epithelium dysplasia (MEED), stage one severe esophageal epithelium dysplasia (SEED I), stage two severe esophageal epithelium dysplasia (SEED II), near EC (NEC) and EC (EC). Pathological diagnostic criterion was mild esophageal epithelium dysplasia (ED), moderate epithelium dysplasia (MD), severe epithelium dysplasia (SD), early EC (carcinoma *in situ* and intramucosal carcinoma) and invasive carcinoma<sup>[9,10]</sup>. According to epidemiological research, NEC, SEED I and II diagnosed by cytology, ED, MD and SD diagnosed by pathology were regarded as precancerous lesions (PL). The age group was divided at five-year intervals.

Statistical analysis according to the consecutive rank of diagnosis criterion in cytology and pathology, non-parameter Ridit analysis was conducted. The accumulation direction

**Table 1** Age distribution of MEED, PL and EC detected by cytological screening of 16 763 persons

Histology grade	Age						Total
	40 yr	45 yr	50 yr	55 yr	60 yr	65 yr	
Normal (case, %)	2 718 (50.6)	1 518 (43.8)	1 094 (39.1)	945 (35.6)	651 (29.5)	95 (30.7)	7 021
MEED	1 574 (29.3)	1 100 (31.7)	928 (33.1)	882 (33.2)	758 (34.9)	104 (33.1)	5 346
PL	1 056 (19.7)	816 (23.6)	745 (26.6)	782 (29.5)	720 (33.2)	98 (31.7)	4 217
EC	20 (0.4)	29 (0.8)	31 (1.1)	46 (1.7)	41 (1.9)	12 (3.9)	179
Total	5 368	3 463	2 798	2 655	2 170	309	16 763

MEED: mild esophageal epithelia dysplasia, PL: precancerous lesion, EC: EC.

**Table 2** Age distribution by endoscopic pathologic screening of 2 013 persons

Pathology grade	Age						Total
	40 yr	45 yr	50 yr	55 yr	60 yr	65 yr	
Normal (case, %)	746 (94.2)	388 (84.7)	239 (74.2)	165 (73.3)	83 (55.7)	33 (49.3)	1 654
PL	43 (5.4)	57 (12.4)	67 (20.8)	39 (17.3)	47 (31.5)	17 (25.4)	270
Early cancer	3 (0.4)	10 (2.2)	11 (3.4)	14 (6.2)	11 (7.4)	8 (11.9)	57
Advanced cancer	0 (0.0)	3 (0.7)	5 (1.6)	7 (3.1)	8 (5.4)	9 (13.4)	32
Total	792	458	322	225	149	67	2 013

PL: precancerous lesion.

**Table 3** Ridit value by histology by age distribution in comparison with standard group

Age (yr)	Cases	Ridit value	95%CI
45 <sup>1</sup>	3 463	0.5	
40	5 368	0.46	(0.45-0.47)
50	2 798	0.53	(0.51-0.54)
55	2 655	0.55	(0.54-0.56)
60	2 170	0.58	(0.57-0.59)
65	309	0.59	(0.55-0.62)
Total	16 763		

<sup>1</sup>Standard group.

**Table 4** Ridit value for endoscopic pathology by age distribution in comparison with standard group

Age (yr)	Cases	Ridit value	95%CI
45 <sup>1</sup>	458	0.5	
40	792	0.45	(0.43-0.47)
50	322	0.55	(0.52-0.58)
55	225	0.56	(0.52-0.60)
60	149	0.65	(0.60-0.70)
65	67	0.69	(0.62-0.76)
Total	2 013		

<sup>1</sup>Standard group.

**Table 5** Average age of each histology grade by cytology screening

Histology grade	Cases	mean±SD	t value	P
MEED	5 346	50.3±7.56	7.162	<0.001
SEEDI	3 179	51.2±7.70	3.554	<0.001
SEED II	866	51.6±7.54	4.537	<0.001
NEC	172	52.4±7.14	5.527	<0.001
EC	179	54.4±7.23		

of frequency was from normal to cancer, the standard group was 45-year-olds group (no invasive carcinoma in 40-year-olds group). The formula of mean Ridit value was:  $R = \sum f R/n$ , 95% CI:  $R \pm 1/\sqrt{3n}$ . We used SPSS (10.0) software in statistical processing.

## RESULTS

According to the results of exfoliative balloon cytological screening, the detecting rates of precancerous lesions in the 40-year-olds group and 45-year-olds group were 19.7% (1 056/5 368) and 23.6% (816/3463), respectively, the detecting rates of cancer were 0.4% (20/5 368) and 0.8% (29/3 463) (Table 1). As the age increased at five-year intervals in these two groups, the detecting rates of precancerous lesion and cancer increased significantly with age by 19.8% and 100%, respectively.

According to the pathological results of endoscopic examination, the detecting rates of precancerous lesion was 5.4% (43/792) for 40-year-olds group and 12.4% (57/458) for 45-year-olds group, respectively, the detecting rates of cancer were 0.4% (3/792) and 2.2% (10/458), respectively (Table 2), the detecting rates of precancerous lesion and cancer increased by 129.6% and 450.0% in the old-age group, respectively.

The 45-year-olds group being the standard group, the Ridit value of 40-year-olds group was significantly lower than that of the standard group. With the age increasing at five-year intervals, the Ridit value increased in all from the 45-year-olds group to the highest for the 65-year-olds group, which had statistical difference between them (Tables 3 and 4).

As shown in Table 5, the mean ages of SEED I and II by cytological diagnosis were 51.2 and 51.6 years, standard deviation was 7.54 and 7.70. Cancer group being the control group, there was statistical significance between control group and other groups.

The mean ages of patients with precancerous lesion of esophagus diagnosed by pathology were 51.4 and 53.5 years, standard deviation was 7.3 and 7.9. The invasive cancer diagnosed by endoscopic examination being the control group, there was statistical significance between control group and other groups (Table 6).

**Table 6** Average age of each pathology grade by endoscopic screening and tumor registration

Pathology grade	Cases	mean±SD	t value	P
Mild dysplasia	172	51.6±7.90	5.250	<0.001
Moderate dysplasia	157	53.5±7.42	4.220	<0.001
Severe dysplasia	53	51.4±7.26	4.764	<0.001
Early cancer	50	55.6±7.31	2.248	<0.05
Advanced cancer <sup>1</sup>	9 265	61.7±11.23	1.086	>0.05
Advanced cancer	31	56.7±6.76		

<sup>1</sup>From tumor registration.

## DISCUSSION

The occurrence and development of EC is a slow process involving multi-factors, multi-steps and multi-genes, the carcinogenesis of esophageal squamous epithelium can be illustrated in the order of basal cell hyperplasia or simple hyperplasia→mild dysplasia→moderate dysplasia→severe dysplasia→carcinoma *in situ*→early invasive cancer→advanced cancer, which is a continuous process<sup>[10-12]</sup>. From the viewpoint of cytology, the evolution process of EC is sequenced as mild dysplasia→severe dysplasia→near to carcinoma→carcinoma<sup>[7,8]</sup>.

Compared with that of the 40-year-olds group (19.7%, 0.4%) by cytological criterion, the detecting rate of precancerous lesion and cancer of the 45-year-olds group (23.6%, 0.8%) increased by 19.8%, 100%, respectively (Table 1). Similarly, by pathological criterion, the detecting rate of precancerous lesion and cancer of 45-year-olds group (12.4%, 2.8%) increased by 129.6%, 450.0%, respectively (Table 2) compared with that of the 40-year-old group (5.4%, 0.4%). If the age of the candidate population for screening increased by five years, the detecting rate of cancer would rise markedly, especially by pathological criterion.

In Japan<sup>[13]</sup>, the population older than 50 years and with a smoking or drinking history over 20 years was considered as a high-risk population, the detecting rate of SD was 2.6% (417/1 799). In this research on Ci county, the detecting rate of SEED in the 40-year-olds group was 1.5% and in the 45-year-olds group 3.3%. The crude incidence rates of EC in 35-, 40- and 45-year-olds groups of Japanese men in the mid-1990s were 0.2/100 000, 1.8/100 000 and 7.6/100 000, respectively<sup>[14]</sup>. The crude incidence rates of EC in 35-, 40-, and 45-year-olds groups of Iran which is one of the high-incidence areas in Asia in 1995 were 21.4/100 000, 48.3/100 000, and 66.8/100 000 for males respectively<sup>[14]</sup>. The incidence rates of 45-year-olds group in Japan and Iran were higher than that of 40-year-olds group, which increased by 322.2% and 38.3%, respectively.

According to exfoliative balloon cytological screening and endoscopic pathological results, the Rdit values of 40-year-olds group were all lower than 0.5, and there was a statistical significance in 95% CI, showing that the detecting rates of precancerous lesions and cancer in 40-year-olds group were all lower than that of 45-year-olds group. The Rdit value increased with age at five-year intervals, with statistically significant differences (Tables 3 and 4).

The research of the incidence age and natural history of EC is for defining high-risk population. Screening survey is suitable for cancers that progress slowly. The mean age of precancerous lesion was 50-53 years, standard deviation was 7.5 years by analysis of the mean ages of different precancerous lesions and cancer diagnosed by cytology and pathology. The mean age of patients, diagnosed by pathology, with early carcinoma was 55.6 years. That is to say, the mean age of patients with precancerous lesions was younger than those with early carcinoma by 4-5 years. Cytological diagnosis failed to suggest the clinical stage of EC, since exfoliative balloon cytological screening could only obtain a few of middle-layer cells of squamous epithelium, vice-fundus cell and fundus cell were almost nil<sup>[10]</sup>. The high-incidence age of esophageal carcinoma in Black Americans was between 55 and 69 years, while for White Americans it was above 70 years. Occident scholars regarded Barrett's esophagus and gastro-esophageal reflux disease as precancerous disease and suggested the age scope of EC screening to be above 50 years by the cost-utility analysis<sup>[15-19]</sup>. The mean incidence age of esophageal carcinoma of 9 265 cases registered in Ci county cancer station from 1988 to 1997 was 61.7 years. Most of those cases were middle or advanced stage, the mean at diagnosis was 10 years older than that of precancerous lesions by pathology and five years older than that of early carcinoma or invasive carcinoma. For an early carcinoma to progress into middle or advanced stage, the ladder phenomenon of incidence age of precancerous lesions and cancer also reflected the natural history of esophageal carcinoma. In the process of developing into esophageal carcinoma, the incidence age of different grades of esophageal lesions diagnosed by cytology or pathology had statistical significance (Table 5) except 9 265 cases registered in Ci county cancer station from 1988 to 1997 (Table 6). It is reasonable to define an age scope for EC screening in a high-risk area of Ci county of patients above 45 years according to the analysis of incidence age and detection rate of different lesions in the esophagus.

In addition, biological features of tumor are the basis of screening, the carcinomatous conversion rate of precancerous lesion in esophagus was correlated with age. In the report of Ding<sup>[19]</sup>, only 1.2% (1/83) of the population younger than 40 years diagnosed with severe dysplasia of epithelial cells by cytology developed into carcinoma after nine years, so did the treated group. But the natural carcinomatous conversion rate of 40-49-year olds rose to 13.1% (27/206). Hou *et al*<sup>[20]</sup>, reported that the natural carcinomatous conversion rate of 40-49-year group was 8.0% and rose to 12.3% in the 50-59-year group. The incidence rate of 40-year group in Lin county, another high-risk area of EC in Henan Province, was 198.73/100 000

for men and 191.53/100 000 for women in 1970s, and decreased to 79.91/100 000 for men and 52.24/100 000 for women in 1990s<sup>[21]</sup>.

According to the detecting rate of precancerous lesions and cancer by cytology or pathology, the mean incidence age of middle or advanced EC in high-risk areas, the natural history and developing trend of EC by epidemiological survey and analysis, it is appropriate to define the age scope of high-risk population of EC as above 45 years, which is of more benefit to EC screening. For instance, based on the age structure of Ci county population in 1988-1992<sup>[22]</sup>, the population of 40-year-olds group accounted for 24.9% of the total of 40-74-year olds. It will benefit the secondary prevention of EC and condense high-risk population of EC if the age scope of high-risk population is defined as above 45 years.

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