RESEARCH ARTICLE

Prevalence and Age, Gender and Geographical Area Distribution of Esophageal Squamous Cell Carcinomas in North China from 1985 to 2006

Xiao-Shan Feng[1,2]*, Yan-Tong Yang[2,3], She-Gan Gao[1,2], Yi Ru[1,2], Gong-Ping Wang[2,3], Bo Zhou[2,3], Yu-Feng Wang[1,2], Peng-Fei Zhang[1,2], Pu-Yu Li[1,2], Yong-Xuan Liu[1,2]

Abstract

Objective: To establish the prevalence and distribution profile of esophageal squamous cell carcinomas (ESCCs) over a 22-yr period in North China. Methods: Using endoscopy for primary diagnosis and histological analysis for the further confirmation, a total of 74,854 ESCC patients aged 20-89 between January 1985 and December 2006 were investigated to analyze the epidemiological profile including prevalence rates, distribution of age-of-onset, gender and geographical area of ESCC in Luoyang, the highest incidence area of North China. Results: A total of 4092 cases of ESCC were finally diagnosed among 74,854 patients who had their first endoscopies. The prevalence among males was higher than that among females (p<0.01), resulting in an overall male:female OR of 1.2 (95%CI, 1.2–1.3). The prevalence in rural areas was higher than in urban areas (p<0.01), resulting in an overall rural:urban OR of 2.6 (95%CI, 2.4–2.9). The rural:urban ORs and the 95% CI increased continuously from 2.6, 2.3-3.0 to 2.7, 2.2-3.3, respectively, for 4 consecutive periods during the 22-yr study period. Moreover, the median age of onset among females was higher than that among males (p<0.01). For both sexes and in both areas, the prevalence rates declined and the median age of onset rose for 4 consecutive periods in the 22-yrs time frame (p<0.01). Conculsions: These data reveal the epidemiological profile of ESCC in the area of North China, and suggest that urban areas and rural people account for a growing proportion of the ESCC patients although the prevalence of ESCC significantly declined and the median age-of-onset postponed over the 22-yrs period. Moreover, the prevalence status of ESCC in rural areas also underlines the need for public health initiatives aimed at reducing risk factors of this fatal disease.

Keywords: Epidemiology - carcinoma - esophagus - squamous cell carcinoma - endoscopy urban/rural China

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Introduction

Esophageal cancer (EC) is the 8th most common cancer worldwide and the 6th leading cause of cancer deaths (Parkin et al., 2001; Jemal et al., 2011). In the western countries, the most prevalent malignant tumor in esophagus is adenocarcinoma that has been shown mainly comes from the progression of Barrett's esophagus (Devesa et al., 1998; Rubenstein et al., 2011; Alexandropoulou et al., 2013), but in most area of China, especially North China, squamous cell carcinoma is the primary EC type (Das, 2010; Wang et al., 2013; Liu et al., 2013). Whereas the clinical statistical data of esophageal adenocarcinoma was well documented in most western countries, the epidemiological profile including prevalence and the distribution of age, gender, and area of Esophageal Squamous Cell Carcinoma (ESCC) in North China, the area with highest incidence, is very limited (Das, 2010).

Endoscopy with biopsy is currently known as the primary method for the diagnosis of ESCC (Dawsey et al., 1998; Das, 2010; Roshandel et al., 2012). This approach directly provides images of esophagus for clinical evaluation and biopsy specimens for pathological analysis that has been considered as the final diagnosis with the best sensitivity and specificity. However, endoscopy has not been accepted to apply in large-scale population surveys because of the intolerable invasive suffering and the higher cost for the patients in developing countries. In this regard, van Blankenstein (van Blankenstein et al., 2005) was the first to employ a large amount of the primary endoscopy patients at the endoscopy unit, replacing the large-scale population survey, to describe the prevalence and distribution of Barrett's Esophagus (BE). In his study, A total of 492 cases of BE were identified in 21, 899 first endoscopies, then the prevalence and age, gender distribution of BE was successfully described, and

*[1]Department of Oncology, [3]Department of Gastrointestinal Oncology Surgery, The First Affiliated Hospital of Henan University of Science and Technology, [2]Cancer Institute, Henan University of Science and Technology, Luoyang, China *For correspondence: samfeng138@126.com*

the very similar demographics of intestinal metaplasia and intestinal metaplasia plus BE was found, which suggested they may be two consecutive stages in the same metaplastic process (van Blankenstein et al., 2005). Success of van Blankenstein and several other studies (Guardino et al., 2006; Jung et al., 2011) demonstrated the effectiveness and efficiency of primary endoscopy patients but not the large-scale population in assessing the prevalence and distribution of esophagus diseases.

To assess the epidemiological profile of ESCC in North China, we use the same approach as described above to investigate 74, 854 endoscopy patients from the primary endoscopy unit in the first affiliated hospital of Henan University of Science and Technology, a nationwide hospital in North China, during the past 22 years, and evaluate the epidemiological status of ESCC.

Materials and Methods

Patients

This study was approved by The First Affiliated Hospital of Henan University of Science and Technology Institutional Review Boards in 2007.

The First Affiliated Hospital of Henan University of Science and Technology, located in North China, is nationwide hospital and also the largest primary medical center in Luoyang City. Almost all inhabitants receive their medical care or received their first diagnosis in this medical center. In addition, there is only one endoscopy unit in this medical center, thus avoiding selection bias. When a decision to perform an endoscopic examination was made, information about the patient, including name, sex, date of birth, address, ethnicity and citizen ID number was collected and entered in his/her endoscopic medical record. After the endoscopic examination, endoscopy reports and histology reports, if they were needed during the examination, were attached to the endoscopic medical record. The endoscopic medical records dating back to 1985 are kept in the hospital archives.

Two designated oncologists independently entered all the endoscopic medical records from January 1985 to December 2006 into two computer databases. Next, the two databases on the same population were compared, and any differences were re-checked and re-entered.

All the cases of ESCC that were diagnosed by endoscopy and histologically confirmed in the 22-yrs period from January 1985 to December 2006 were included in the study. The patients with only adenocarcinoma of the esophagogastric junction were excluded.

Because the number of cases of ESCC diagnosed in 1985-1986 was far smaller than in the subsequent 2-yr periods, we divided all the cases of ESCC into 4 study periods for statistical comparison: 1985-1991 (7 -yrs), 1992-1996 (5 -yrs), 1997-2001 (5 -yrs) and 2002-2006 (5 -yrs). There were no cases of ESCC in the 0–19 age group and only six cases of ESCC in the 90+ age group, so the results for these two groups were discarded. In accordance with the criteria used in other studies, only the first endoscopies should be included in the number of endoscopies for calculating prevalence (van Blankenstein et al., 2005). The prevalence of ESCC per 100 first endoscopies was then calculated from the number of cases of ESCC for each sex, each 10-yrs age group, each area (rural and urban) and each of the 4 study periods (van Blankenstein et al., 2005). In addition, the age of onset of ESCC by sex was also calculated.

Endoscopy and Biopsy

An endoscope (Olympus GIF Series, Tokyo, Japan) and biopsy forceps (MTN-BF, Nanjing, China) were used for the endoscopic examination and the histological biopsy. All the biopsy specimens were immediately placed in a 95% buffered ethanol solution and embedded in paraffin. Next, the gastrointestinal pathologist made the pathological diagnosis after staining the specimens with hematoxylin and eosin. All the ESCC diagnoses in this study were reviewed by a designated pathologist.

Statistical Analysis

The Shapiro-Wilk test was applied to determine whether the sample was normally distributed. The results for the non-normally distributed data were reported as medians and interquartile ranges. The Wilcoxon's Mann-Whitney rank sum test and the Kruskal-Wallis rank sum test were applied to identify statistically significant differences by sex in the age of onset of ESCC in the 4 periods and over the total 22-yr period.

The univariate binary Logistic regression analysis of the prevalence results was applied in three steps. The first step was to identify statistically significant differences by sex (dependent variable is diagnosis, covariate variable is sex) and by area (dependent variable is diagnosis, covariate variable is area) in the ESCC prevalence in the 4 study periods and over the total 22-yrs period. The second step was to identify the changing trends in the ESCC prevalence by both sex (dependent variable is diagnosis, covariate variable is period), and by area (dependent variable is diagnosis, covariate variable is period) over 4 continuous study periods. The third step was to calculate all ORs and 95%CIs. Moreover, multivariate binary Logistic regression is applied to identify risk factors for ESCC (dependent variable is diagnosis, covariate variable is sex, age of onset and period).

The level of statistical significance was set at $\alpha = 0.05$, andα' is corrected to 0.0083 in the multiple comparisons.

Results

To assess the prevalence of ESCC, we first tabulate the patients with clear diagnosis by age and gender, and then calculate the prevalence rates of different groups. We found for the overall patients during last 22-year periods, 2, 487 males and 1605 females were confirmed with ESCC from the 42, 146 male and 32, 709 female first endoscopy examination receivers, respectively. The overall prevalence rates of male patients with 5.90% and female patients with 4.91% exhibit the significance difference with p value < 0.001. Moreover, further analysis was performed to evaluate the incidence trends of ESCC in different genders. In males, the ESCC prevalence for 1985-2006 increased rapidly between the ages of 20 and 59, after which the rate of increase fell sharply. The male

Table 1. The Prevalence Rates of ESCC among Males by 10-yr Age Bands for the 4 Study Periods and for the Total 22-yr Period

Periods	Male								
	Age bands	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Totals
1985-1991	Endoscopies n	817	1680	2083	3496	2663	558	32	11329
	ESCC n	5	46	123	254	230	57	2	717
	prevalence	0.61	2.74	5.90	7.27	8.64	10.22	6.25	6.33
1992-1996	Endoscopies n	517	950	1317	1851	1918	573	58	7184
	ESCC n	1	17	79	134	172	48	4	455
	prevalence	0.19	1.79	6.00	7.24	8.97	8.38	6.90	6.33
1997-2001	Endoscopies n	286	899	1565	2703	3378	1512	87	10430
	ESCC n	1	14	104	210	215	108	6	658
	prevalence	0.35	1.56	6.65	7.77	6.36	7.14	6.90	6.31
2002-2006	Endoscopies n	408	1379	2070	3301	3517	2192	336	13203
	ESCC n	1	11	74	207	228	116	20	657
	prevalence	0.25	0.80	3.57	6.27	6.48	5.29	5.95	4.98
1985-2006	Endoscopies n	2028	4908	7035	11351	11476	4835	513	42146
	ESCC n	8	88	380	805	845	329	32	2487
	prevalence	0.39	1.79	5.40	7.09	7.36	6.80	6.24	5.90

*There was no significant difference in the male prevalence of ESCC prevalence among the period 1985-1991, 1992-1996, and 1997-2001 (*p*>0.05), but a significant decrease was observed in the period 2002-2006 (*p*<0.001 with any other period)

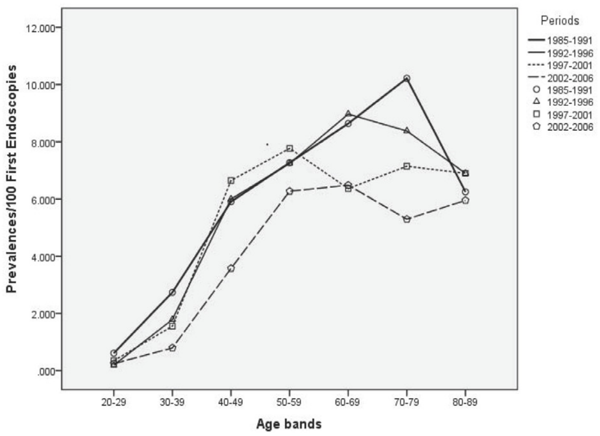

Figure 1. The Prevalence Rates of ESCC among Males for the 4 Study Periods. The logistic regression revealed a significant difference in the prevalence rates of ESCC for males by age among the 4 study periods (*p*<0.001)

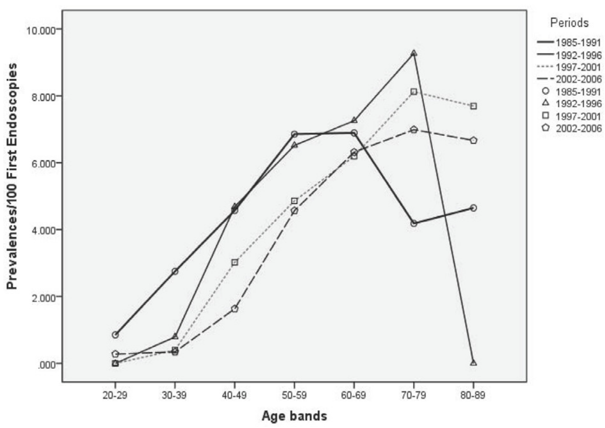

Figure 2. The Prevalence Rates of ESCC among Females for the 4 Study Periods. The logistic regression revealed a significant difference in the prevalence rates of ESCC for females by age among the 4 study periods (*p*<0.001)

prevalence eventually reached a maximum of 7.36 per 100 first endoscopies in the 60-69 age group. In females, the ESCC prevalence increased with age and reached a maximum of 6.95 per 100 first endoscopies in the 70-79 age group. The maximum ESCC prevalence for both sexes combined in the 60-69 age group was 7.02/100 first endoscopies. These data characterized the prevalence rates and the distribution of ESCC in different genders for the patients in the high incidence area of North China.

We next calculate the age-specific prevalence rates in different period and analyze their distribution in different genders. As showed in Tables 1 and 2 and Figures 1, 2 and 3, the prevalence of male patients in the overall 22-yrs period was initially far higher than female patients between the ages of 20 and 69, after which those decreased a lower level between the ages of 70 and 89 (*p*<0.001). Logistic regression demonstrated the overall male:female OR and 95%CI in the prevalence of ESCC was 1.23 and 1.77–2.58. As the male prevalence became lower after 70 years old, the overall male:female OR and 95%CI in the prevalence of ESCC can be influenced by the overall male:female ratio in ESCC patients between the ages of 70 and 89. In this study, the overall male:female ratio in ESCC patients (1.55:1) was higher than that in 70-89 age group (1.34:1), the lower male:female ratio in this age group can bring the lower overall male:female OR and 95%CI in the prevalence of ESCC. These age-specific data suggested that 40-79 age band (82.3% for males, 84.4% for females) and male (*p*<0.001) is susceptible for ESCC.

As the area of the patients has been demonstrated critical for the epidemiological profile, we next analyze the area-specific ESCC prevalence for both the four study periods and the overall 22-yr periods. As showed in Tables 3 and graphically presented in Figures 4, we found that there were higher ESCC prevalence in rural areas during any period (*p*<0.001), and the rural:urban OR and 95%CI

Table 2. The Prevalence Rates of ESCC among Females by 10-yr Age Bands for the 4 Study Periods and for the Total 22-yr Period

Periods		Female							
	Age bands	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Totals
1985-1991	Endoscopies n	351	944	1749	2655	2437	717	43	8896
	ESCC n	3	26	80	182	168	30	2	491
	prevalence	0.85	2.75	4.57	6.85	6.89	4.18	4.65	5.52
1992-1996	Endoscopies n	312	631	1046	1427	1240	356	12	5024
	ESCC n	0	5	49	93	90	33	0	270
	prevalence	0.00	0.79	4.68	6.52	7.26	9.27	0.00	5.37
1997-2001	Endoscopies n	286	748	1521	2304	2470	923	65	8318
	ESCC n	0	3	46	112	153	75	5	394
	prevalence	0.00	0.40	3.02	4.86	6.19	8.13	7.69	4.74
2002-2006	Endoscopies n	355	1159	1776	2803	2580	1588	210	10471
	ESCC n	1	4	29	128	163	111	14	450
	prevalence	0.28	0.35	1.63	4.57	6.32	6.99	6.67	4.30
1985-2006	Endoscopies n	1304	3482	6092	9189	8727	3584	330	32709
	ESCC n	4	38	204	515	574	249	21	1605
	prevalence	0.31	1.09	3.35	5.60	6.58	6.95	6.36	4.91

*There was no significant difference in the female prevalence of ESCC prevalence among the period 1985-1991, 1992-1996, and 1997-2001 (p>0.0083), but a significant decrease was observed in the period 2002-2006 (p=0.003 with period 1985-1991, p<0.001with period 1992-1996)

Table 3. The Prevalence Rates of ESCC by area for the 4 Study Periods and for the Total 22-yrs Period

		Periods				
		1985-1991	1992-1996	1997-2001	2002-2006	Totals
Urban	Endoscopies n	7717	4642	3909	5848	22117
	ESCC n	241	143	99	124	607
	prevalence	3.12	3.08	2.53	2.12	2.74
Rural	Endoscopies n	12507	7565	14837	17825	52736
	ESCC n	967	582	954	983	3486
	prevalence	7.73	7.69	6.43	5.51	6.61
Total	Endoscopies n	20225	12208	18747	23674	74854
	ESCC n	1208	725	1053	1107	4093
	prevalence	5.97	5.94	5.62	4.68	5.47
P Value (Rur:Urb)		<0.001	<0.001	<0.001	<0.001	<0.001
OR (Rur:Urb)		2.6	2.62	2.64	2.69	2.63
95%CI of OR (Rur:Urb)		2.25-3.00	2.18-3.16	2.14-3.26	2.23-3.26	2.41-2.88

Rur, Rural; Urb, Urban; *There was no significant difference in the urban prevalence of ESCC prevalence for among the period 1985-1991, 1992-1996, and 1997-2001 (p>0.05), but a significant decrease was observed in the period 2002-2006 (p<0.001 with period 1985-1991, p=0.002 with period 1992-1996). There was no significant difference in the rural prevalence of ESCC prevalence between the period 1985-1991 and 1992-1996 (p=0.921), but a significant decrease was observed in the period 1997-2001 (p<0.001 with any other period) and 2002-2006 (p<0.001with any other period)

Table 4. The Median Age of Onset of ESCC by Sex for the 4 Study Periods and for the Total 22-yrs Period

Sex	Median Age (Quartile Range)										*P* Value
	1985-1991		1992-1996		1997-2001		2002-2006		Totals		
Male	57	50-63	59	50-65	59.5	51-67	60	54-68	59	51-66.00	0.000†
Female	57	50-62	58	50-63	62.0	55-68	63	56-70	60	53-66.25	0.000†
P Value	0.004*		0.544*		0.000*		0.001*		0.001*		

*Wilcoxon's Mann-Whitney rank sum test; †Kruskal-Wallis rank sum test

in the prevalence of ESCC continually rose from 2.60 and 2.25-3.00 in 1985-1991 to 2.69 and 2.23-3.26 in 2002-2006. These results suggested that the rural patients account for larger proportion in the total ESCC patients (p<0.001), and the proportion is growing. As the ESCC prevalence in both areas decreased during the 22 years (p<0.001), the greater reduction of ESCC prevalence in urban area maybe the key reason for the proportion of rural patients growing.

In addition, the ages of onset of ESCC for both sex were also calculated (Tables 4 and Figures 5). In both sexes, the onset of ages of ESCC rose over the 22-yrs

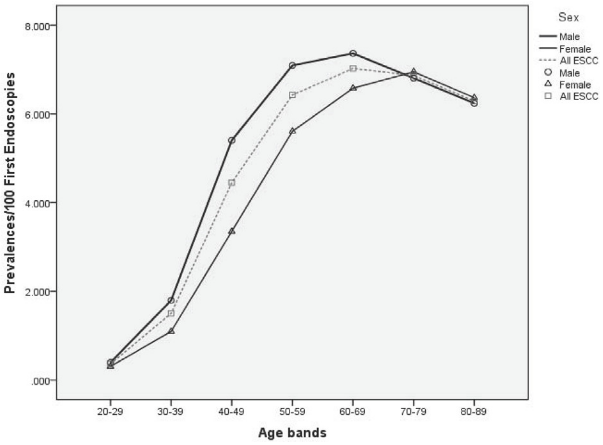

Figure 3. The Prevalence Rates of ESCC over the Total 22-yrs Period. The prevalence of ESCC is higher among males than among females (p<0.001). The overall male:female OR was 1.23 (95% CI 1.77–2.58)

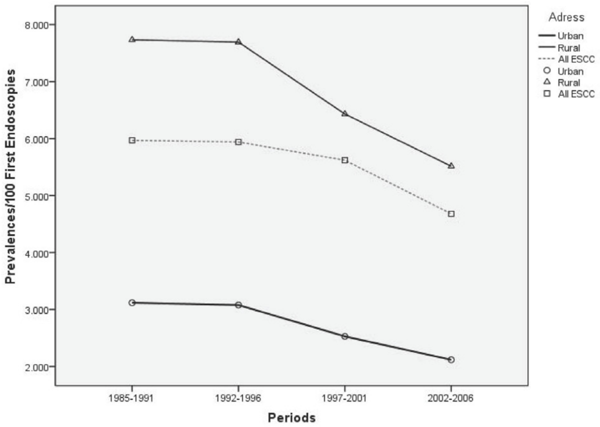

Figure 4. The Rural and Urban Prevalence Rates of ESCC for the 4 Study Periods. The prevalence of ESCC is higher in rural areas than in urban areas (p<0.001). The overall rural:urban OR was 2.63 (95% CI 2.41–2.88)

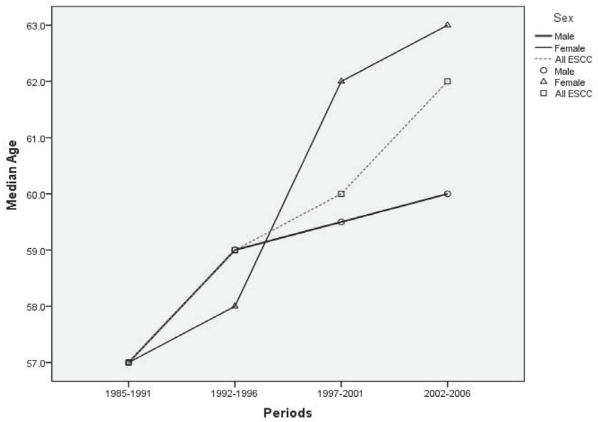

Figure 5. The Age of Onset of ESCC for Both Males and Females for the 4 Study Periods. The Kruskal-Wallis rank sum test revealed a significant difference in the age of onset of ESCC for both sexes among the 4 study periods (males: p<0.001, females: p<0.001)

period (p<0.001) , which indicated the development of earlier diagnosis and therapy benefit the cancer patients and postpone the onset age of ESCC. Moreover, the male onset age of ESCC rose from 57 in 1985-1991 to 59 in 2002-2006. However, the female onset age of ESCC was higher than the male (p<0.001), it postpone from 57 in 1985-1991 to 60 in 2002-2006.

At last, multivariate binary Logistic regression suggested that all the age of onset (p<0.001), demographic area (p<0.001) and study period (p<0.001) were independent risk factors for ESCC in our study.

Discussion

In this study, we utilized a novel epidemiological approach set up by Dr. Blankenstein to assess the prevalence and distribution of ESCC in North China. To our knowledge, this is the first time to use the primary endoscopy patients, but not large-scale population, to analyze the epidemiological profile of ESCC. Our results suggested that male patients is more susceptible than female to the ESCC and the area play a critical role in the prevalence of ESCC. Of most important is we found the onset age of male is later than female, and the onset age for both sex have continuing rose during the 22 years.

It has been showed that samples size and measurement errors are critical for the quality of epidemiological survey, and thus affect the study conclusion. In our study, our sample size is adequate: fit includes 74, 854 (5.87%) of the 1, 274, 254 inhabitants over the age of 20 yrs in Luoyang City who underwent a first endoscopy , and our samples were performed by the same group of experienced endoscopists and pathologists. therefore, we believe that this study could provide an estimate of the epidemiological characteristics of ESCC in Luoyang City.

Although the novel diagnosis and therapeutics approach of ESCC was increasingly developed and applied in the hospital, the effects of these new modern scientific techniques on the epidemiological profile remain unclear, especially for the ESCC in North China. In this study, we found that the prevalence of ESCC for both sex and both area of ESCC declined in 22 years period, and moreover, the prevalence was higher in males compared with females, resulting the overall male:female OR was 1.23 (95% CI 1.77–2.58) . The decline of the prevalence rates might be attributed to the development of novel diagnosis and therapeutic approaches. On the other hand, lifestyle might be the other factor contributing to the prevalence rate of ESCC. In this regard, Liu et al (Liu et al., 2013) reported that the incidence of ESCC increased in Linzhou City, the other city in the same area of North China, from 2003 to 2009. This study pointed out that the new risk factors, including smoking and high alcohol consumption, play a more important role (Lagergren et al., 2010; Amani et al., 2013). Thus, downward trends of ESCC in Luoyang might be attributed to the decreasing risks with socioeconomic level elevation and lifestyle modification, like intake of pickled or salted vegetables, preference for a high salt diet and prevalence of Helicobacter pylori infection (Xibin et al., 2002; Xibib et al., 2003; Kamangar et al., 2009; Lin et al., 2011; Song et al., 2013).

The previous studies (Wang et al., 2007; Zhang et al., 2012; Dar et al., 2013; Hakami et al., 2013) have suggested that living in rural area is a risk factor for ESCC, as there are worse socioeconomic level, and more unhealthy eating habits. However, the exact statistical difference in prevalence of ESCC between urban and rural areas are not mentioned in these studies. Our current study described and compared rural-specific and urban-specific prevalence of ESCC in a long period. The higher ESCC prevalence in rural areas for any study period (p<0.001) indicated the prevalence of ESCC might be related with the financial status of patients. The decline of ESCC prevalence in both areas and the greater reduction of ESCC prevalence in urban area consolidates our conclusion, and also indicates the public health initiatives aimed at reducing unhealthy lifestyles, especially unhealthy eating habits, is urgent to reduce the incidence of ESCC.

Chen et al. (2013) have demonstrated the onset age of ESCC significantly differ between male and female patients in Taiwan. The mean age at onset of all female patients was significantly greater than that of the male. Our results also support this conclusion, and moreover, for the first time, reveal the onset age of ESCC in North China. The male median onset of age of our study is similar with that of Chen's study (60 vs 59). However, the female median onset of age is apparently different (71 vs 60) that might be attributed to the different socioeconomic levels and gender factor in view of the higher development of Taiwan in study period and women generally pay more attention to their lifestyle. The other evidence supporting our conclusion is Liu's study (Liu et al., 2013) that showed a similar overall median onset age of ESCC (60) in Linzhou city , located in North China and nearby the Luoyang city.

It have been demonstrated life expectancy was involved in the epidemiological profile of cancers (Cheng et al., 2012; Chen et al., 2013). In our current study, apparent rise of the male median onset age of ESCC from 57 to 59, and the female from 57 to 60, respectively, might be attributed to the increase of average life expectancy for Chinese. With the development of the Chinese economy and improvements in medical condition, the incidence rate of early-onset ESCC was reduced and Chinese average life expectancy has risen during the past decades (United Nations, 2009). An increasing number of older people could be diagnosed with ESCC, whereas they might not have lived to the age of onset in previous periods. Similarly, the higher age of onset of ESCC in females compared with males may be the result of the greater average life expectancy in females compared with males (United Nations, 2009).

In summary, our current study is the first to describe the prevalence and distribution status of ESCC in North China with a novel epidemiological approach. We found the prevalence of ESCC is higher in male and rural area patients though the overall rates decline and the median age of onset increases, which suggested that rural areas and male patients are more urgent need for the public health initiatives aimed at reducing risk factors such as unhealthy lifestyles.

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