Diseases of the Esophagus (2017) **30**, 1–7
DOI: 10.1111/dote.12468

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Updated incidence rates and risk factors of esophageal cancer in Nan'ao Island, a coastal high-risk area in southern China

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SUMMARY. **Esophageal cancer (EC) is one of the most common cancers in China. The purpose of this study was to investigate the updated incidence rates and risk factors of EC in Nan'ao Island, where the EC incidence rate was chronically the highest in southern China. To calculate the annual incidence rate, data on 338 EC cases from Nan'ao Cancer Registry system diagnosed during 2005–2011 were collected. A case-control study was conducted to explore the EC risk factors. One hundred twenty-five alive EC patients diagnosed during 2005–2011 and 250 controls were enrolled into the case-control study. A pre-test questionnaire on demography, dietary factors, drinking water treatment, and behavioral factors was applied to collect information of all participants. The average EC incidence rates during 2005–2011 were $66.09/10^5$, $94.62/10^5$, $36.83/10^5$ for both genders, males and females, respectively, in Nan'ao Island. The EC incidence rate in males was 2.40- to 4.55-fold higher than that in females in the period from 2006 to 2011 ($P < 0.05$). Considering the onset age, males tend to be much younger than females and reached peak incidence rate at a younger age ($P < 0.05$). Drinking water treatment by filter (odds ratio [OR] = 0.28, 95% confidence interval [95% CI] = 0.13–0.58) and fruit consumption (OR = 0.55, 95% CI = 0.32–0.94) reduced the risk for EC. On the contrary, the pickled vegetables consumption (OR = 2.64, 95% CI = 1.46–4.76) and liquor drinking (OR = 2.32, 95% CI = 1.21–4.44) increased the risk for EC. These results may be of importance for future research on EC etiology and prevention strategies.**

KEY WORDS: **esophageal cancer, high-risk area, incidence rates, Nan'ao Island, risk factors.**

INTRODUCTION

Esophageal cancer (EC) is one of the most common cancers, ranking the 10th leading cancer cause worldwide, its incidence rates are the highest in Southern Africa and Eastern Asia and the lowest in Western and Middle Africa.[1] In 2012, China had 223 306 new EC cases, accounting for 69.13% of all EC cases in the world.[1] Chinese National Annual Cancer Registration Reports in 2010 showed that the incidence rate

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of EC was 21.88/10^5, ranking the fifth most common malignant tumor of the country.[2] In China, there are six high-risk EC areas, such as Cixian County and Shexian County in Hebei Province, Linzhou City in Henan Province, Yangcheng County in Shanxi Province, Nan'ao County (Island) in Guangdong Province and Yanting County in Sichuan Province. The EC incidence rates in these 'hot spots' were obviously higher than other parts of China, forming a unique geographic distribution profile of EC.[3] Nan'ao Island located in South China Sea with four towns, approximately 70 000 inhabitants and an area of 130.90 km^2. It is in the southeast of Shantou City with 11.8 miles apart to the land. It was reported that EC incidence rate has reached to an average of 74.47/10^5, being the most prevalent cancer and making up 35.45% of the total malignant tumor cases in Nan'ao Island during 1995–2005.[4] EC has become one of the leading medical burdens for local population.

Literature review indicated that the EC incidence rate has sharply increased in America and Europe where esophageal adenocarcinoma comprises the majority of EC cases, whereas decreased or remained stable in Asia and Africa where esophageal squamous cell carcinoma is predominant.[5–9] In China, a similar declining trend has been observed.[5] However, in some areas, such as Linzhou City and Nan'ao Island, the EC incidence rate kept increased in recent years.[4,10] In Nan'ao Island, the EC incidence rate increased from 60.15/10^5 to 88.15/10^5 during 1995–2004.[4] With 10 years development since 2004, the living standard has been improved markedly in the island, will the EC incidence rate in the region be changed accordingly? But no updated EC incidence in Nan'ao Island was available thereafter.

In terms of the EC etiology, although they are not very clear, some lifestyles and dietary factors such as cigarette smoking, alcohol consumption, low intake of fresh fruits and vegetables have been found associated with EC, especially in Nan'ao Island.[11–13] The fact that EC incidence rate in Nan'ao Island has been staying at high level for years indicated that local residents exposed to EC related risk factors such as certain risk factors related to drinking water. For unavailability of tap water in Nan'ao Island, the rain water gathered in pond or reservoir, or shallow well water is the only water supply source for local residents. Only until the end of 2012, less than one-tenth people in Houzhai Town of the island can use tap water supplied by an undersea water pipeline from Shantou City. The quality of drinking water was identified to be relevant to EC, and some pre-treatments can improve the quality of drinking water.[14–16] Treating water by water filter and natural sinking method were popular way to improve water quality in Nan'ao Island. Little information was reported in previous studies about the effects of drinking water treatment on the EC in this island.

This study aims to identify the EC incidence rate during 2005–2011 and EC related risk factors in Nan'ao Island.

MATERIALS AND METHODS

Calculation of incidence rate of EC

The Nan'ao Cancer Registry is based at Nan'ao County People's Hospital in collaboration with Shantou University Medical College. The framework of this registry consists of three parts: village clinics and town hospitals provided primary impression; county hospital offered X-ray, pathological diagnosis, and treating data; Shantou University Medical College provided professional guidance.

The EC cases newly diagnosed during Jan 1, 2005–Dec 31, 2011 in cancer registry were ascertained by their demographics, cancer site, morphology, X-ray, pathological diagnosis, and stage of cancer. All EC cases were identified and classified by using the 10th version of the International Classification of Diseases (ICD-10) (ICD code for EC is C15). Totally, 338 EC cases (245 males, 93 females) newly diagnosed during 2005–2011 were used to compute the incidence rate. The demographic data of local population in the period from 2005 to 2011 were collected from the Nan'ao Statistical Bureau. The incidence rate is the quotient of annual new EC cases over the total population in a given year, denoting 10^5 as the cardinal number.

Case-control study

One hundred twenty-five alive EC cases diagnosed during 2005–2011 were asked to enroll in the case-control study conducted from June, 2012 to August, 2013 in Nan'ao Island. Two controls per case were randomly selected from Household Registry to match the EC based on age (±5 years), gender, and place of residence (case and controls live in the same village or community). Finally, 250 controls without cancer and digestive system disease participated in the study.

A pretested questionnaire was used to collect individual data on four aspects: demographic characteristics (age, gender, education, occupation, and place of residence), dietary factors (fruit, vegetables, pickled vegetables, and salted meat), drinking water treatment (status, method, and duration), and behavioral factors (smoking and liquor drinking). All of participants in case-control study were investigated by trained students of Shantou University Medical College with assistance from local students and villagers by

Table 1 EC incidence rate (per 10^5) in Nan'ao Island during 2005–2011

	Total				Male				Female				Comparison of M and F		
Year	Case	Crude	AIR1	AIR2	Case	Crude	AIR1	AIR2	Case	Crude	AIR1	AIR2	χ^2	P	Ratio (M/F)
2005	46	63.36	39.44	41.92	29	79.02	50.26	54.20	17	47.36	28.98	30.08	2.87	>0.05	1.67
2006	45	61.76	38.07	42.27	32	86.77	55.16	61.64	13	36.13	21.47	23.58	7.56	0.006	2.40
2007	59	81.54	48.67	53.61	44	120.15	75.62	85.55	15	41.97	22.72	24.68	13.57	<0.001	2.86
2008	49	67.44	43.03	46.87	36	95.82	64.61	71.75	13	37.05	22.01	23.75	9.30	0.002	2.59
2009	53	72.56	42.16	47.90	38	103.26	62.66	76.15	15	41.38	23.23	26.19	9.64	0.002	2.50
2010	45	61.06	38.87	41.91	37	99.64	64.90	72.40	8	21.88	13.93	15.21	18.26	<0.001	4.55
2011	41	55.24	35.67	40.48	29	77.93	52.86	62.00	12	32.42	18.74	20.12	6.96	0.008	2.40
Total	338				245				93						
Mean		66.09	40.82	44.92		94.62	60.84	69.08		36.83	21.56	23.27	9.56	0.002	2.57
APC (95%CI)*	−1.94 (−8.45, 5.03)				0.11 (−8.32, 9.31)				−6.53 (−14.44, 2.10)						

*APC was estimated for EC crude incidence rate. AIR1, the age-standardized incidence rate adjusted for the Chinese population in 2000; AIR2, the age-standardized incidence rate adjusted for the world population in 2000; APC, annual percentage change; EC, esophageal cancer; Crude, the crude incidence rate; F, female; M, male.

face-to-face interviews. Informed consent was obtained from all individual participants included in the study.

This study was approved by the Ethics Committee of Shantou University Medical College.

Statistical analysis

To estimate EC incidence rate, crude incidence rate, age-standardized incidence rate adjusted for the China population in the year 2000 (AIR1) and world population in the year 2000 (AIR2) based on 5-year age groups were calculated, respectively. Also, age distribution of EC incidence rate was analyzed. The chi-square test was used to determine whether the differences between the incidence rates were statistically significant. The annual percentage change (APC) of incidence rate was computed to assess the annual changes of the EC incidence by Joinpoint software (version 4.0.1, the Surveillance Research Program of the US National Cancer Institute).

In case-control study, chi-square test and t-test were used to compare the distributions of demographic data between control and case groups. The association between dietary factors, drinking water treatment, behavioral factors, and EC were explored by non-conditional logistic regression. All of the analyses were adjusted for age (as a continuous variable), gender, education, occupation, and place of residence. Since only 6 of 245 (2.45%) smokers were tobacco smokers, they were combined with cigarette smokers in the analysis (1 g of tobacco was considered equivalent to one cigarette). The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to estimate the risks for EC. All analyses were performed with SPSS software, version 16.0 (SPSS Inc., Chicago, IL). All presented P values were 2-sided, with less than 0.05 as statistical significance.

RESULTS

Updated EC incidence rates and its changes during 2005–2011 in Nan'ao Island

Table 1 presents the EC incidence rates during 2005–2011 in Nan'ao Island. The average crude EC incidence rate for both genders, males and females were $66.09/10^5$, $94.62/10^5$, and $36.83/10^5$, respectively. The EC incidence rate in males was 2.40- to 4.55-fold higher than that in females in the period from 2006 to 2011 ($P < 0.05$). The crude incidence rates increased slightly in males (APC = 0.11, 95% CI = −8.32–9.31) while declined in females (APC = −6.53, 95% CI = −14.44–2.10) and in total (APC = −1.94, 95% CI = −8.45–5.03), but all of these changes were not statistically significant ($P > 0.05$) implying no change in EC incidence rate by year during 2005–2011.

Age distribution of EC incidence rates in Nan'ao Island

Figure 1 shows age distribution of crude incidence rates of EC according to gender. It can be seen that there were substantial differences in age distribution of EC incidences according to gender. Males tend to have EC at younger age than females. Female did not have EC until reached at 45–49 age group, while male started to have EC at 35–39 age group, which was 10 years younger than females. Moreover, when computing by 5-year age groups, the incidence rate in males exceeded that in females in most of age group. Although incidence rate for both sexes were gathered at age of 75–84 approximately, gender disparity existed at peak of incidence rate. EC incidence rate in males reached a maximum of $490.04/10^5$ at the 70–74 age group, whereas that in females reached a maximum of $215.55/10^5$ at the 80–84 age group.

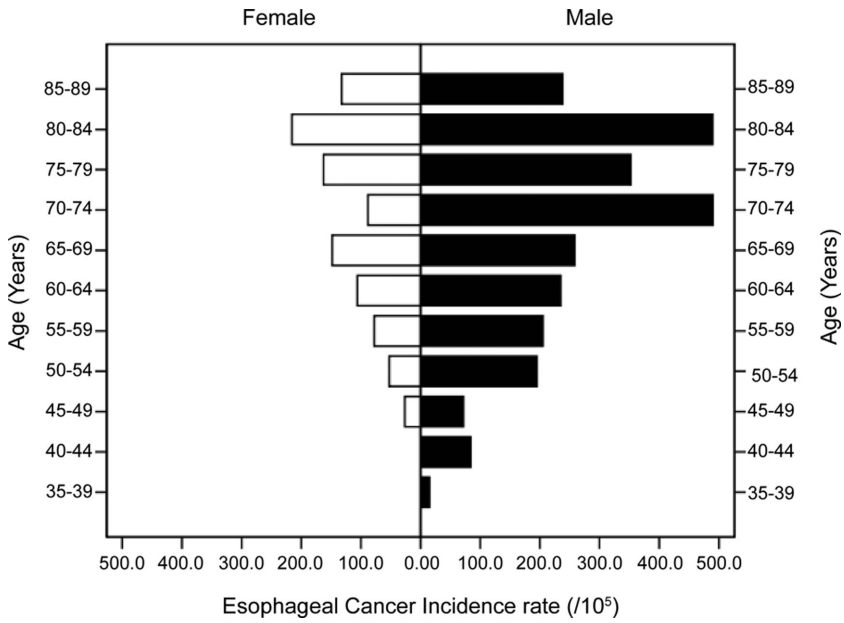

Fig. 1 Average incidence rates of esophageal cancer (/10^5) for males and females during 2005–2011, Nan'ao Island, China. The white bar shows incidence rates of each 5-year age group for females, while the black bar is shown for males. The crude incidence rates of esophageal cancer (/10^5) by age groups of 35–39 years, 40–44years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years, and 85–89 years were 0.00, 0.00, 26.39, 52.62, 82.36, 105.78, 148.10, 88.27, 162.73, 215.55, and 88.32 for females, respectively; 15.01, 84.04, 71.89, 195.14, 205.06, 234.72, 258.46, 490.04, 352.62, 489.43, and 238.20 for males, respectively.

Table 2 Characteristics of EC cases and control participants in case-control study conducted in Nan'ao Island.

Characteristics	Cases ($n=125$) No.	%	Controls ($n=250$) No.	%	P*
Age (Mean [SD])	59.04 (11.06)		59.77 (10.81)		>0.05
Gender					
Male	96	77.00	192	77.00	>0.05
Female	29	23.00	58	23.00	
Education level					
Under primary school	33	26.00	76	30.00	<0.001
Primary school graduate	74	59.00	87	35.00	
Junior high school graduate	15	12.00	55	22.00	
High school graduate or above	3	2.00	32	13.00	
Occupation					
Farmer	41	33.00	78	31.00	0.002
Fishman	56	45.00	75	30.00	
Other	28	22.00	97	39.00	
Place of residence					
Houzhai town	72	58.00	144	58.00	>0.05
Yun'ao town	27	22.00	54	22.00	
Shen'ao town	19	15.00	38	15.00	
Qing'ao town	7	6.00	14	6.00	

*Calculated with the chi-square test for categorical variables and t-tests for continuous variables. EC, esophageal cancer; SD, standard deviation.

Potential risk factors for EC in Nan'ao Island

The characteristics of 125 cases and 250 controls participated in the study were given in Table 2. We found no significant differences between the two groups in terms of gender, age, and place of residence ($P > 0.05$). However, differences presented between groups in education level and occupation ($P < 0.05$).

Table 3 presents associations between dietary factors, drinking water treatment, behavior factors, and EC. The OR for treating drinking water with filter 0.28 (95% CI = 0.13–0.58). Moreover, a protective effects was found between the longer duration of water treatment and EC (OR = 0.52, 95% CI = 0.27–1.00 for >6 years treatment compared with non-treatment), although the result were borderline significant. Consumption of pickled vegetables was positively related to the genesis of EC in a dose-response manner ($P_{trend} = 0.006$), indicating a risk factor for EC. Higher consumption of fruit was a protective factor for EC (OR = 0.55, 95% CI = 0.32–0.94). Liquor drinking was another significant EC risk factor (OR = 2.32, 95% CI = 1.21–4.44). No significant associations between consumption of salted meat (OR = 1.31, 95% CI = 0.58–2.95), vegetables (OR = 0.71, 95% CI = 0.34–1.48), cigarette smoking (OR = 1.84, 95% CI = 0.81–4.18), and EC were detected.

DISCUSSION

This study provides the updated incidence rates and risk factors for EC in Nan'ao Island. The results indicate a relatively higher risk of EC (69.08/10^5) in the period of 2005–2011 in Nan'ao Island comparing with the averaged EC incidence rate of 21.88/10^5 in China. Pickled vegetables and liquor drinking were found to increase the risk for EC. We also identified that treating drinking water by water filter and consumption of fruit reduce the risk for EC.

Table 3 Associations between drinking water treatment, dietary factors, behavioral factors, and risk of EC in Nan'ao Island.

Factor	Cases ($n=125$)		Controls ($n=250$)			95% CI	
	No.	(%)	No.	(%)	OR*	Lower	Upper
Status of drinking water treatment							
No	28	22.00	34	14.00	1.00	Reference	
Yes	97	78.00	216	86.00	0.55	0.30	1.04
Method of drinking water							
No treatment	28	22.00	34	14.00	1.00	Reference	
Water filter method	29	23.00	122	49.00	0.28	0.13	0.58
Natural sinking method	68	54.00	94	38.00	1.08	0.54	2.17
Duration of water treatment (years)							
No treatment	28	22.00	34	14.00	1.00	Reference	
≤6	41	33.00	84	34.00	0.62	0.31	1.28
>6	56	45.00	132	53.00	0.52	0.27	1.00
Salted meat (times/week)							
<1	81	65.00	170	68.00	1.00	Reference	
1–2	29	23.00	60	24.00	1.17	0.67	2.04
≥3	15	12.00	20	8.00	1.31	0.58	2.95
P trend						>0.05	
Pickled vegetables (times/week)							
<1	44	35.00	122	49.00	1.00	Reference	
1–2	35	28.00	69	28.00	1.43	0.78	2.60
≥3	46	37.00	59	24.00	2.64	1.46	4.76
P trend						0.006	
Fruit (times/week)							
<3	97	78.00	153	61.00	1.00	Reference	
≥3	28	22.00	97	39.00	0.55	0.32	0.94
Vegetables (times/week)							
<5	16	13.00	26	10.00	1.00	Reference	
≥5	109	87.00	224	90.00	0.71	0.34	1.48
Smoking status†							
No	38	30.00	92	37.00	1.00	Reference	
Yes	87	70.00	158	63.00	1.84	0.81	4.18
Liquor drinking status†							
No	53	42.00	136	54.00	1.00	Reference	
Yes	72	58.00	114	46.00	2.32	1.21	4.44

*Adjusted for age (as a continuous variable), occupation, and education. †Cigarette smoking was defined as having smoked at least one cigarette per day for more than 1 year. Liquor consumption was defined as drinking liquor at least 12 times per year for more than 1 year. CI, confidence interval; EC, esophageal cancer; OR, odds ratio.

It is well established that EC incidence rate decreased over years in sub-Saharan Africa, Iran, and China.[5–7] EC incidence rates in Nan'ao Island also decreased from $74.47/10^5$ in period 1995–2004 to $66.09/10^5$ in period 2005–2011, although the decline was not statistically significant (Supporting Information Table S1).[4] Nationwide nutritional surveys conducted in China reported quality of diet had been improved and consumptions of animal products, fruit, and oil had been increased.[17] It is believed that improvement of dietary habits may play an important role in the decreasing EC incidence rate in Nan'ao Island.

Our study indicates that EC incidence rate in Nan'ao Island is still higher than that in other areas in south of China such as Guangzhou ($7.61/10^5$), Wuhan ($9.00/10^5$), and Xiamen ($27.76/10^5$).[18] Also, the AIR2 for EC in Nan'ao Island ($44.92/10^5$) is much higher than that in China ($14.81/10^5$).[18] According to previous epidemiological studies, family cancer history, fermented fish sauce, pickled products, alcohol consumption, and tobacco smoking increased the risk of EC in Nan'ao Island.[11,12] Besides, history, chorography, and genealogy records indicated that ancestors of Nan'ao residents migrated from central plains of China hundreds even thousand years ago, where the high-risk regions for EC locate. The population in Nan'ao Island may carry some genetic risk factors for EC. Recently, inherited susceptibility to EC has been found in some large families in China.[19] Certainly, further research is needed to figure out the cause of high incidence of EC in Nan'ao Island.

Nan'ao males had on average 2.57-fold higher EC incidence rates compared with that of females, which was coincided with previous studies.[1,2,4–9] When considering the age of onset, males tend to be much younger than females and reached a peak of incidence rate at a younger age. This can be partly attributed to two aspects: internal factors and external factors. Internally, females secrete estrogen while males merely do. Research suggests estrogen inhibits the growth of EC cells and protects against EC, although no firm conclusions can yet be drawn of the role of estrogen in human EC etiology.[20] Externally, according to previous studies, both smoking and alcohol drinking have been recognized to increase the risk for EC.[21–23] Epidemiologic Surveys reported that men have had an earlier, longer, and more intense exposure to cigarettes

than women.[24,25] Compared with males, females are more motivated to pursue healthy behavior, being less likely to be smokers or drinkers. Thus, males, as the absolute dominate group of smokers and drinkers, are more likely to contract EC at a young age. According to our result, for gender disparity at EC onset age, the targeted screening age should be 50 years and above and 55 years and above for males and females, respectively, in this area.

We found that treating drinking water by water filter or natural sinking method did reduce the risk for EC, especially the former method. Furthermore, the longer period the water filter used the higher reduction in risk for EC. The only source of drinking water is shallow well water and rain water on this isolate island. In some high EC areas of China, well water has been reported to be polluted often by nitrogenous compounds.[14,15,26] Nitrogenous compounds are strong animal carcinogens and related to many kinds of cancers in the nasal cavity, esophageal, and stomach in several animal models.[27,28] Moreover, population-based studies also show well water polluted with nitrogenous compounds is significantly related to the high incidence of EC.[14,26] Previous study indicated that the use of water filter has been identified to reduce the contaminants in drinking water.[16] These may suggested that there are some unknowing contaminants in the local drinking water and increase the risk for EC in Nan'ao Island. And this may be one of important risk factors for the high incidence of EC in Nan'ao Island. Certainly, further research is needed to figure out what the exact risk factors is in drinking water.

Additionally, we found consumption of pickled vegetables and liquor elevated the risk for EC in Nan'ao Island, which was consistent with previous studies.[21–23,29] Our study confirmed that consumption of fruit was well-established protective factor for EC in Nan'ao Island. However, the protective effects between vegetables consumption and EC did not show a statistical significance in our study. Considering cigarette smoking, two studies indicated that compared with non-smokers, the pooled OR for current smokers ranged from 2.32 to 3.73.[30,31] However, in our study, the positive association between cigarette smoking and EC was not statistically significant. This may be attributed to the small sample size, and a possible confounding factor, the environmental polycyclic aromatic hydrocarbons (PAH). As we know, cigarette smoke contains a large number of carcinogens, such as PAH which is risk factor for EC.[13] However, PAH exposure is not considered in this study. We are interesting to explore the association between PAH exposure and EC incidence in Nan'ao Island in further study.

Three main limitations present in our study. First, the sample size of case-control study is relatively small, although all the EC patients alive to date have been enrolled. Second, we did not quantitatively measure the diet intake for each participant. However, it is reasonable to estimate the potential dietary risk factors for EC by using food frequency items in pretest questionnaire. Third, the effects of drinking water treatment on EC could not illustrate the relationship between water quality and EC directly, because the measurements of water quality indices were not tested at this stage. This may need further studies to confirm the causality between water quality and EC.

In summary, our study provides the updated data on the epidemic of EC in Nan'ao Island; shows for the first time an association between drinking water treatment and EC onset in Nan'ao, narrowing further research to the quality of drinking water and EC onset on this high-risk island; provides reference for future cancer control strategies of EC in this high-risk area of China.

ACKNOWLEDGMENTS

This study was supported by the National High Technology Research and Development Program of China (grants 2012AA02A503 and 2012AA02A209); the National Basic Research Program of China (grant 2012CB526600); the Natural Science Foundation of China-Guangdong Joint Fund (grants U0932001 and U1301227); the National Science Foundation of China (grant 81172264) and Key Laboratory Project for College and University of Guangdong Province (grant KLB11009). The authors thank the staff of Jiangsu HengRui Medicine Sales Company Limited. Also, we thanks the esophageal cancer patients and control participants who agreed to be interviewed.

AUTHOR CONTRIBUTIONS

Tan HZ contributed to study design, data collection, data analysis, interpretation, and drafting for 4% of the study work; Lin WJ, Huang JQ, Dai M, Fu JH contributed to study design, data collection, interpretation, and guide the filed investigation for 4%; Zhang JJ contributed to study design, data analysis, interpretation data, guide the filed investigation, and revise the manuscript for 4%; Li EM and Xu LY JJ contributed to study design, data analysis, interpretation data, and revise the manuscript for 4%, respectively; Huang QH, Chen WM, Xu YL, Ye TT, Lin ZY, Lin XS, Cai JX, Dong YH, Luo HY, Chen SH, Huang YL, Yang J, Lin AX, Yuan XQ, Chen SY, Wang KS, Zhuang CY, Wang SC, Lin LL, Zou XF, Song ZH, Fang XH, Chen T, Zhang JH, Li KQ, Chen LH, Lin XP, Lin JM, Lin JN, Lin PL, Chen JT, Lin KM, Hong XC contributed to conduct filed investigation, data collection, data analysis, and interpretation for 2%, separately; Wang LD contributed to guide the filed investigation and revise the manuscript for 2% in the study work.

References

1 Ferlay J S I, Ervik M, Dikshit R *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer. 2013. [Accessed 7 May 2015.] Available from URL: http://globocaniarcfr.
2 Chen W, Zheng R, Zhang S *et al.* Annual report on status of cancer in China, 2010. Chin J Cancer Res 2014; 26 (1): 48–58.
3 Wang X, Fan J C, Wang A R *et al.* Epidemiology of esophageal cancer in Yanting—regional report of a national screening programme in China. Asian Pac J Cancer Prev 2013; 14 (4): 2429–32.
4 Su M, Liu M, Tian D P *et al.* Temporal trends of esophageal cancer during 1995–2004 in Nanao Island, an extremely high-risk area in China. Eur J Epidemiol 2007; 22 (1): 43–8.
5 Zhao J, He Y T, Zheng R S, Zhang S W, Chen W Q. Analysis of esophageal cancer time trends in China, 1989–2008. Asian Pac J Cancer Prev 2012; 13 (9): 4613–7.
6 Tettey M, Edwin F, Aniteye E *et al.* The changing epidemiology of esophageal cancer in sub-Saharan Africa—the case of Ghana. Pan Afr Med J 2012; 13: 6.
7 Roshandel G, Sadjadi A, Aarabi M *et al.* Cancer incidence in Golestan Province: report of an ongoing population-based cancer registry in Iran between 2004 and 2008. Arch Iran Med 2012; 15 (4): 196–200.
8 Hur C, Miller M, Kong C Y *et al.* Trends in esophageal adenocarcinoma incidence and mortality. Cancer 2013; 119 (6): 1149–58.
9 Bosetti C, Levi F, Ferlay J *et al.* Trends in oesophageal cancer incidence and mortality in Europe. Int J Cancer 2008; 122 (5): 1118–29.
10 Liu S Z, Wang B, Zhang F *et al.* Incidence, survival and prevalence of esophageal and gastric cancer in Linzhou city from 2003 to 2009. Asian Pac J Cancer Prev 2013; 14 (10): 6031–4.
11 Liu M, Su M, Tian D P, Zhang G H, Yang H L, Gao Y X. Heredity, diet and lifestyle as determining risk factors for the esophageal cancer on Nanao Island in Southern China. Fam Cancer 2010; 9 (2): 229–38.
12 Li K, Yu P. Food groups and risk of esophageal cancer in Chaoshan region of China: a high-risk area of esophageal cancer. Cancer Invest 2003; 21 (2): 237–40.
13 Kamangar F, Chow W H, Abnet C C, Dawsey S M. Environmental causes of esophageal cancer. Gastroenterol Clin North Am 2009; 38 (1): 27–57.
14 Zhang X L, Bing Z, Xing Z *et al.* Research and control of well water pollution in high esophageal cancer areas. World J Gastroenterol 2003; 9 (6): 1187–90.
15 Keshavarzi B, Moore F, Najmeddin A, Rahmani F, Malekzadeh A. Quality of drinking water and high incidence rate of esophageal cancer in Golestan province of Iran: a probable link. Environ Geochem Health 2012; 34 (1): 15–26.
16 Yamamoto K, Kakutani N, Yamamoto A, Tsuruho K, Mori Y. Use of a home water filter in the reduction of trihalomethanes and total organic halogen in tap water: forty-one samples from Osaka City and surrounding cities of Japan in 1999, 2000, and 2004. Bull Environ Contam Toxicol 2006; 77 (3): 323–30.
17 Zhang B, Wang H J, Du W W *et al.* Food consumption trend of Chinese adults in nine provinces (autonomous region) from 1989 to 2006. Zhonghua Yu Fang Yi Xue Za Zhi 2011; 45 (4): 330–4.
18 Chen W, He Y, Zheng R *et al.* Esophageal cancer incidence and mortality in China, 2009. J Thorac Dis 2013; 5 (1): 19–26.
19 Guohong Z, Min S, Duenmei W *et al.* Genetic heterogeneity of oesophageal cancer in high-incidence areas of southern and northern China. PLoS One 2010; 5 (3): e9668.
20 Chandanos E, Lagergren J. The mystery of male dominance in oesophageal cancer and the potential protective role of oestrogen. Eur J Cancer 2009; 45 (18): 3149–55.
21 Pandeya N, Williams G M, Sadhegi S, Green A C, Webb P M, Whiteman D C. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. Am J Epidemiol 2008; 168 (1): 105–14.
22 Tramacere I, Pelucchi C, Bagnardi V *et al.* A meta-analysis on alcohol drinking and esophageal and gastric cardia adenocarcinoma risk. Ann Oncol 2012; 23 (2): 287–97.
23 Islami F, Fedirko V, Tramacere I *et al.* Alcohol drinking and esophageal squamous cell carcinoma with focus on light-drinkers and never-smokers: a systematic review and meta-analysis. Int J Cancer 2011; 129 (10): 2473–84.
24 Lund I, Lund K E. Lifetime smoking habits among Norwegian men and women born between 1890 and 1994: a cohort analysis using cross-sectional data. BMJ Open 2014; 4 (10): e005539.
25 Yazbek J C, Haddad R, Bou Khalil R *et al.* Prevalence and correlates of alcohol abuse and dependence in Lebanon: results from the Lebanese Epidemiologic Survey on Alcohol (LESA). J Addict Dis 2014; 33 (3): 221–33.
26 Yokokawa Y, Ohta S, Hou J *et al.* Ecological study on the risks of esophageal cancer in Ci-Xian, China: the importance of nutritional status and the use of well water. Int J Cancer 1999; 83 (5): 620–4.
27 Ivankovic S, Seibel J, Komitowski D, Spiegelhalder B, Preussmann R, Siddiqi M. Caffeine-derived N-nitroso compounds. V. Carcinogenicity of mononitrosocaffeidine and dinitrosocaffeidine in bd-ix rats. Carcinogenesis 1998; 19 (5): 933–7.
28 Fong L Y, Lau K M, Huebner K, Magee P N. Induction of esophageal tumors in zinc-deficient rats by single low doses of N-nitrosomethylbenzylamine (NMBA): analysis of cell proliferation, and mutations in H-ras and p53 genes. Carcinogenesis 1997; 18 (8): 1477–84.
29 Islami F, Ren J S, Taylor P R, Kamangar F. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. Br J Cancer 2009; 101 (9): 1641–7.
30 Tramacere I, La Vecchia C, Negri E. Tobacco smoking and esophageal and gastric cardia adenocarcinoma: a meta-analysis. Epidemiology 2011; 22 (3): 344–9.
31 Oze I, Matsuo K, Ito H *et al.* Cigarette smoking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2012; 42 (1): 63–73.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Comparison of the EC incidence rate (per 10^5) between the period.