RESEARCH COMMUNICATION

Clustering and Geographic Variation of Upper Gastrointestinal Cancers in a High-risk Region of Esophageal Cancer in Northern China

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Abstract

Aim: Geographic variation of upper gastrointestinal carcinomas (UGIC) was assessed in a high-risk region in northern China. Methods: Shexian, Linzhou, Yangcheng and Cixian are four counties with world age-standardized incidence rates (ASR) of esophageal cancer as high as 124.9, 99.5, 160.1, and 164.9 per 100,000 respectively for males, and 70.8, 68.8, 92.1, and 104.6 for females for 1998 to 2002. Geographically, Shexian is entirely mountainous, Linzhou and Yangcheng are mostly mountainous, and Cixian is one-third mountains, one-third hills, and the other third plains. The corresponding populations is 382,000, 982,000, 395,000 and 625,000 as in 2000. In the present analyses, the world ASRs of esophageal squamous cell carcinoma (ESCC), adenocarcinoma of the esophagogastric junction (AEG), gastric non-cardia carcinoma (GNCC), and the percentages of these in overall tumor ASRs for 1998 to 2002 were compared across the four counties to show geographic variation and clustering. Additionally, site-specific detection rates of precursors and cancers in our population-based endoscope surveys with local 40- to 69-year-old residents were also compared between a Cixian commune (2,013 surveyed) and a Shexian commune (1,514). Results: ASRs for ESCC, AEG, and GNCC combined amount to 210.5 to 325.8 per 100,000 in men and 117.5 to 185.7 in women, accounting for respectively 70.6 to 82.1% and 53.4 to 77.0 % of the all ASRs. In geographic distribution, the percentages of AEG and GNCC in UGICs increased from Cixian (males 32.8%, females 22.1%) to Yangcheng (50.7%, 38.6%) and Linzhou (52.7%, 41.4%), and further to Shexian (61.7% , 61.9); while that of ESCC decreased in the same direction from Cixian, to Yangcheng and Linzhou, and further to Shexian (67.2% , 77.9% ; 49.3% , 61.4% and 47.3%, 58.6% ; to 38.3% , 38.1%). Similarly, the detection rates of low- and high-grade intraepithelia neoplasia as well as cancers of the esophagus were significantly higher in the Cixian commune than the Shexian commune (8.7, 4.4, 0.7% vs 7.0, 3.2, 0.4% P=0.004); but the rates for the esophagogastric junction were systematically and significantly lower in the Cixian than in the Shexian commune (2.2, 0.5, 0.8 % Vs 3.3, 0.9, 1.7 %, P=0.001). Conclusions: Clustering of upper gastrointestinal carcinomas may suggest the existence of common risk factors, while geographic variation in topography/histology may be related to regional differences in carcinogen exposure. These observations identify a need for environment improvement, such as programs to improve drinking water conditions. To study high susceptibility in a historically low mobile population, international collaborative research in this region may prove to be very fruitful.

Keywords: High-risk region - upper gastrointestinal carcinomas - clustering - geographic variation - China

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Introduction

One distinct feature about the epidemiology of esophageal cancer is the marked geographic variation. In global statistics for 2002, Parkin estimated that 52.8 percent of esophageal cancer cases of the world occurred in China (243,854/462,000) (Parkin et al., 2005), of which most cases are diagnosed in eight high-risk regions (highlighted in red in Figure 1) (Yang, 1980). The worldwide age-standardized incidence rates (ASR) of esophageal cancer in 2002 were estimated as 11.5 for males and 4.7 for females (Parkin et al., 2005), while in high-risk areas in China, ASR were as high as 164.9 and 104.6 in Cixian County, 124.9 and 70.8 in Shexian County, 99.5 and 68.8 in Linzhou city (formerly known as Linxian County), and 160.1 and 92.1 in Yangcheng County respectively (Zhang et al., 2006).

The geographic variation is even more striking when smaller units are studied, as is found within the southern Taihang Mountain range areas where the three northern

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Chinese provinces of Henan, Hebei and Shanxi border each other. In a large survey encompassing 181 counties with an approximately 50 million population carried out in 1976 in the three provinces, great variation shows in county-specific crude mortality rates of esophageal cancer. The two counties with the highest mortality rates are Yangcheng (135.2/100,000) and Hebi (139.8/100,000). The two counties with the lowest rates are Hunyuan (1.4/100,000) and Tatong (2.8/100,000).The relatively high mortality rates are all from counties where the borders of the 3 provinces meet on the south side of the Taihang Mountain. From these high-incidence counties, extending outwards on all sides, the figures gradually decreases, giving an impression of irregular concentric belts. The ratio between the highest mortality rates in the innermost belt and the lowest rates in the outermost belt is approximately 100:1 (Yang, 1980).

In the high-risk region, not only humans, marked geographic variations are also observed in the prevalence rate of gullet cancers in domestic fowls. In the late 1970s, a big survey was performed to investigate the prevalence rate of pharyngeal and esophageal cancers in chickens in three counties with high-, middle-, and low-mortality-rates of esophageal cancer (namely Linzhou, Fanxian, and Hunyuan County, the mortality rate being 131.8, 23.7, and 1.3 per 100,000 respectively in humen for 1973 to 1975). Among 18,774 chickens in Linxian, 33 cases of histologically proven gullet cancers were found, whereas only 2 cases each were found in 11,399 chickens in Fanxian and in 9,420 chickens in Hunyuan County. Thus, the prevalence rates were 175.8, 17.6, and 21.2 per 100,000, correlating well with the above mortality rates.

From these, it seems that, unlike the sporadically occurring esophageal cancers in the western world where tobacco, alcohol, and Barret's esophagus are key risk factors, the excessive level of esophageal cancer in the high-risk region in northern China may be related to local environmental or nutritional risk factors, and these factors should have considerable geographic variations as well.

Since the early 1990s, owing to the wide spreading use of endoscope and biopsy in the diagnosis of upper gastrointestinal cancer to give topography/morphology information, similar geographic variation has been observed for adenocarcinoma of the esophagogastric junction (AEG) and gastric noncardia carcinoma (GNCC) as that for esophageal cancer, of which 90.6% is esophageal squamous cell carcinoma (ESCC) (Yang, 1980). This article aims to introduce these recent observations and discuss the possible meanings.

Materials and Methods

As shown in Figure 1, Shexian and Cixian (both of Hebei province), Linzhou (formerly known as Linxian, of Henan province), and Yangcheng (of Shanxi province) are four counties located in the Southern Taihang Mountain range region in northern China where the mortality rate of esophageal cancer is among the highest in the world. The three northern-central Chinese provinces border each other at the four counties. Taken together, the four counties are on the northern latitude from 35°12' to 36°55' and

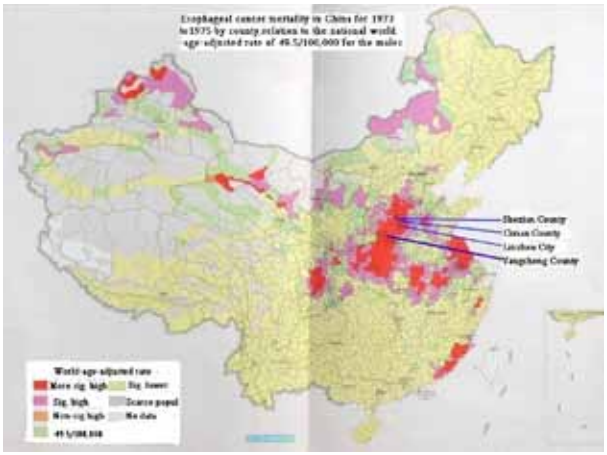

Figure 1. Location of Shexian, Cixian, Linzhou (Formerly Linxian), and Yangcheng in the Southern Taihang Mountain High-risk Region and Geographic Variation in World-age-adjusted Mortality Rates for Esophageal Cancer in China

eastern longitude from 112° to 114°40. Geographically, Shexian is entirely mountainous, Linzhou and Yangcheng are mostly mountainous, and Cixian is one-third covered by mountains, one-third by hills, and the other third by level land. The population of Cixian, Shexian, Yangcheng , and Linzhou are 625,000, 382,000, 395,000, and 982,000 respectively by the 5th national census for the year of 2000.

As mentioned earlier, the four counties are shown to have the highest mortality rate of esophageal cancer (>80 /100,000) for 1973 to 1975 by the 181-county and 50-million-people mass mortality survey (Yang, 1980). After the survey, a population-based cancer registry and a cancer research center were established by the order of the central Chinese government in each of the four counties, and registration on incident tumors and all-cause deaths has been kept going ever since.

Tumor Registration

Each of the four tumor registries runs a three-level-case-reporting-network. The three-levels refer to the administration-unit of village, commune, and the county. In a counties, disregarding the population number, there are usually 20 communes and over 300 villages.

Every month from the village to the commune level, village clinicians report by government order newly diagnosed tumor cases to the physician at the public commune hospital who is in charge of local tumor registration. The physician then checks the accuracy and dates of the diagnoses and reports the list to the county registry. The county registry is established in the county cancer center. The registrars are usually members of the epidemiology and/or pathology section of the cancer center.

After receiving the list of new cancer cases from the commune physician, the county-registrars will go to the concerned clinic, hospital, or the patient's home to check the diagnosis, and on the way also to collect under-reported cancer cases.

To ensure reporting completeness, emphasis is placed on collection of cancer cases from medical and insurance records from various sources such as local

and nearby hospitals, Upper gastrointestinal cancer screening centers (one in each county), government health insurances, and the demographic department. To obtain clinicopathological information for tumor-coding, registrars regularly visit by government order local hospitals to abstract medical record room, surgery, pathology, and endoscope department data.

The SPSS 10.0 to 13.0 (Statistical Package for Social Science, SPSS Incorporation, Chicago) (SPSS Incorporation, 2006) has been routinely used at every registry to register cases,to delete repetitions as well as update datasets. The data quality for upper gastrointestinal carcinomas in the four counties is reliable in terms of completeness and accuracy, but may not be so for other carcinomas such as childhood leukemia.

Classification of upper gastrointestinal carcinomas

In this paper, upper gastrointestinal carcinomas are classified as ESCC, AEG, and GNCC. Since endoscopy and biopsy has become the first and routine choice in the diagnoses of upper gastrointestinal cancers in the four counties since early 1990s, both topographic and morphological information are available for classification.

To register as an ESCC, the center of the tumor must be located in the esophagus and the histology must be a squamous cell carcinoma; distal esophageal adenocarcinomas are registered as AEG.

Siewert's classification (Sievert and Stein, 1996) is used for AEG. The group includes distal esophageal adenocarcinomas with the center of the primary tumor located within 1cm and 5cm above the EGJ (typeI); true gastric cardia adenocarcinomas with the center located within 1cm above and 2cm below the EGJ (type II); and sub-cardia gastric carcinomas with the center of the tumor located between 2 and 5 cm below EGJ (type III). Because cardia cancer is a common name to the local people, tumors shown in barium examination above-, at, and below- the EGJ are traditionally regarded as cardia cancer even before the routine use of endoscope and biopsy in diagnosis. In a sence, cardia cancer registered in the past is roughly the same as AEG today.

Mass endoscopic surveys and comparison between commune- and site-specific detection rates of precancerous and cancer lesions.

In the high-risk region of ESCC in China, mass surveys are frequently organized to detect high grade intraepithelial neoplasia and early cancers among the 40- to 69-year-old local residents on the commune level. One rural commune usually has 7 to 10 villages and a 20,000 to 30,000 population. The screening method used in the past was Balloon Cytology, and since the late 1980s it has been replaced by endoscope with iodine staining and biopsy. The mass surveys are country-supported programs but performed by us, with survey rates all above 70% on major sex-age strata of the chosen 40- to 69-year population. Therefore detection rates are comparable between communes. In this article, to confirm the geographic variation found with incidence rates, we also compared the site-specific detection rates of cancer and precancerous lesions between a Cixian commune survey and a Shexian commune survey, with each commune geographically representative of the county, and both surveys performed by us in 2002.

Analyses with incidence rates and screening detection rates

After age-specific incidence rates were calculated by dividing registered cases by the corresponding person-years for 1998 to 2002, the 1970 World Standard Population was used to calculate county-, site-, or histology-specific world ASRs. The ASRs were summed up for all UGICs, and the percentage taken by the UGICs among all-body-malignancies was calculated to show the clustering. Site- or histology-specific ASR for UGICs were compared between counties to show the geographic variations.

All analyses were performed using the SPSS 13.0 statistics package4. Mann-Whitney U-test was used to examine the difference between commune-site-specific detection rates of the two endoscope surveys (SPSS Incorporation, 2006).

Results

Total Crude incidence rates of upper gastrointestinal carcinomas

As shown in Table 1, a total of 18,337 incident UGIC cases were registered in a 2,384,000 annual population for

Table 1. World ASRs (1/100,000) for ESCC, AEG, and GNCC in Shexian, Linzhou, Yangcheng, and Cixian Counties in a High-risk Region in Northern China from 1998 to 2002 (/100,000)

Counties	Population (person-year)	No. UGIC	ESCC (%)	AEG (%)	GNCC (%)	Combined (1/100,000)	% of All
Male							
Cixian	1,593,265	2,917	164.9 (67.2)	46.7 (19.0)	33.9 (13.8)	245.5	70.6
Yangcheng	1,003,488	2,829	160.1 (49.3)	82.8 (25.5)	82.1 (25.3)	325.0	81.0
Linzhou	2,507,295	4,350	99.5 (47.3)	40.8 (19.4)	70.2 (33.3)	210.5	79.5
Shexian	595,771*	1,547*	124.9 (38.3)*	89.1 (27.3)*	111.8 (34.3)*	325.8*	82.1*
Female							
Cixian	1,532,864	1,787	104.6 (77.9)	14.0 (10.4)	15.7 (23.8)	134.3	65.9
Yangcheng	965,338	1,384	92.1 (61.4)	24.6 (16.4)	33.4 (22.3)	150.1	53.4
Linzhou	2,402,608	2,680	68.8 (58.6)	16.4 (14.0)	32.3 (27.5)	117.5	71.6
Shexian	551,713*	843*	70.8 (38.1)	37.6 (20.2)	77.3 (41.6)*	185.7*	77.0*

In Shexian County, the data are for 2000 to 2002; UGIC, upper gastrointestinal carcinomas; ESCC, esophageal squamous cell carcinoma; AEG, adenocarcinoma esophagogastric junction; GNCC, gastric noncardia carcinoma

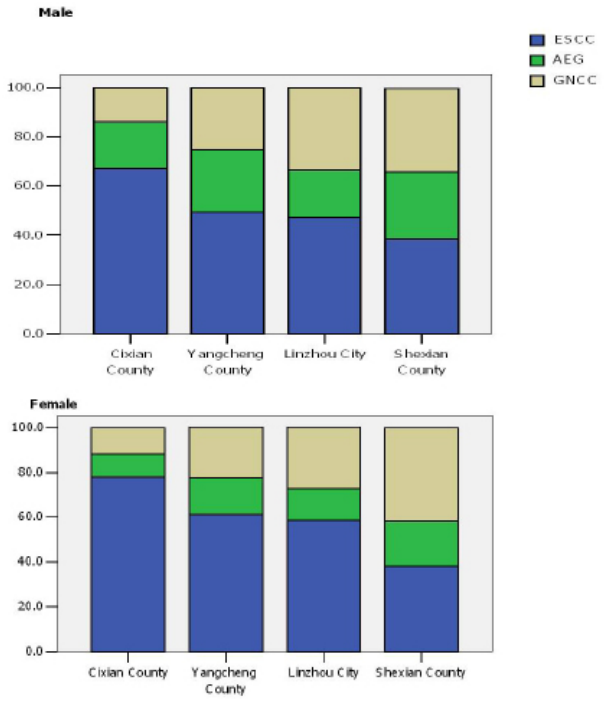

Figure 2. Geographic Variation in the Percentages of ESCC, AEG, and GNCC Among Upper Gastrointestinal Cancers 1998 to 2002 in Cixian, Yangcheng, Linzhou and Shexian Counties

1998 to 2002 in the four county.The total observed person-years was 5,699,819 in men and 5,452,523 in women. The crude incidence rates of UGIC for males is 204.3 per 100,000 (11,643/5,699,819), and for females is 122.8 per 100,000 (6,694/5,452,523). The crude incidence rates of ESCC, AEG and GNCC for males is 105.4, 44.6, and 54.3, and for females is 75.8, 17.6, and 33.4 respectively.

Clustering of upper gastrointestinal carcinomas in the region

As shown in Table 1, the county-specific ASRs of UGIC including ESCC, AEG, and GNCC reaches as high as 210.5 to 325.8 and 117.5 to 185.7 per 100,000 population, amounting to approximately 70.6 to 82.1 % and 53.4 to 77.0 % of all-body-malignancies in men and women respectively, demonstrating the clustering of UGIC in the region.

While in clustering, UGIC also show variation in county-specific ASR. The rates in Linzhou and Cixian, combined or separately, are generally lower than that of Yangcheng and Shexian, especially in men; but ESCC of Cixian is exceptionally higher than that of either Yangcheng or Shexian for both males or females.

Geographic variations across the counties

The geographic variation in topography/histology of UGICs is illustrated in Figure 2 by the percentage distribution of ESCC, AEG, and GNCC across the four counties. In the least mountainous county of Cixian, majority of the upper gastrointestinal cancers are ESCC: being 67.2% and 77.9% in men and women respectively; But in the more mountainous counties of Yangcheng and Linzhou, ESCC becomes less frequent, taking up 49.3% and 61.4%, and 47.3% and 58.6% of upper digestive cancers in men and women; Still in the most mountainous county of Shexian, ESCC takes only 38.3% and 38.1% of uppper digestive cancers in men and women, the lowest percentage among the four counties. In the same geographic direction but changing on the contrary in number, the percentage of AEG and GNCC, whether combined or separately, increases from Cixian to Yangcheng and Linzhou, and reaches the highest in Shexian County (Figure 2).

Table 2. A Comparison of Detection Rates for Esophageal/Cardia Cancerous and Precancerous Lesions Between a Cixian and Shexian Commune, by Mass-endoscope-surveys Among 40 to 69 Years-old Local Residents in 2002

Topography	Cixian (N=2013)	Shexian (N=1514)	Z	$P_{Mann-Whitney\ U}$
	N(%)	N(%)		
Esophagus				
Invasive cancer	14 (0.7)	6 (0.4)		
HGIE	88 (4.4)	48 (3.2)		
LGIE	175 (8.7)	106 (7.0)	-2.886	0.004
Gastric Cardia				
Invasive cancer	17 (0.8)	25 (1.7)		
HGIE	11 (0.5)	14 (0.9)		
LGIE	44 (2.2)	50 (3.3)	-3.257	0.001

Different detection rates of cancerous and pre-cancerous lesions on the esophagus and gastric cardia between a Cixian commune and a Shexian commune.

After performing mass endoscope survey for many years in Cixian and Shexian County of Hebei province, researchers from both Cancer Institute, Chinese Academ of Medical Science (CICAMS) in Peking and the Fourth Hospital of Hebei Medical University in Shijiazhuang gradually discovered that the detection rates of cancerous or precancerous lesions on the esophagus are higher in Cixian than in Shexian. On the contrary, on the gastric cardia the rates are lower in Cixian than in Shexian. For example, as shown in Table 2, among the 2013 subjects aged 40- to 69-years-old endoscopically surveyed in 2002, the detection rates of cancer, high- and low-grade intraepithelial neoplasia on the esophagus in a geographically smooth Cixian commune are 0.7, 4.4, and 8.7 % respectively, systemically and significantly higher than the corresponding 0.4, 3.2, and 7.0 % among 1514 subjects of the same age group surveyed in the same year in a mountainous Shexian commune (Z=-2.886, $P_{Mann-Whitney\ U}$=0.004); On the gastric cardia, however, the detection rates of cancer and precursors among the Cixian residents are systemically and significantly lower than that among the Shexian residents (0.8, 0.5, and 2.2 % versus 1.7, 0.9, and 3.3 % respectively, Z=-3.257, $P_{Mann-Whitney\ U}$=0.001). These different prevalence rates also indicate that while ESCC is more prevalent in Cixian than in Shexian, AEG is to the contrary. This is in agreement with the geographic variation found with incidence rates.

Discussion

Though ESCC is shown to be the main component of UGIC in any county in Table 1, AEG and GNCC are prevalent. Taking the World ASR of AEG and GNCC

in Cixian, for example, although the lowest of the four counties, were as high as 46.7 and 33.9 per 100,000 for men and 14.0 and 15.7 per 100,000 for women respectively from 1998 to 2002.

Clustering of UGIC in the region, formerly known for ESCC only, is also supported by the follow-up results of a famous international collaborative study performed in Linzhou City (formerly known as Linxian County).The Sino-USA nutritional intervention study had prospectively followed 29,584 adults for 15 year from 1986 to 1991. Among the 3410 cases of UGIC diagnosed, there were 1,089 gastric cardia, 363 gastric noncardia , as well as 1,958 esophageal cancer subjects: gastric cardia- and noncardia- cancers accounted for 31.9 and 10.6 percent respectively (Tran et al., 2005).

A question may be asked as to whether gastric cardia cancer, or AEG, like that of the western world, has been the result of rapid increase in recent years (Parkin et al., 2002). The answer seems unlikely if we divide the 15 year follow-up of the Sino-USA study into two periods and compare the results. In the first five-year, 34 percent of the UGIC (442/1180) were gastric cardia canecr, in comparison with a 29% (647/2230) in the latter ten-year period. Therefore, it seems that even in the past, cardia cancer or AEG had been prevalent in Linzhou City.

In contrast with AEG of the western world where the cancer is frequently associated gastroesophago refluxing syndrome or Barret esophagus (Parkin et al., 2002), AEG in the Chinese high-risk region shows a similar geographic variation as ESCC. Similar distribution may suggest common risks. This is also otherwise supported by the observation that in China, the percent of type IAEG is far less than that reported in western populations (Bai et al., 2006).

At this point, it is not unjusted in saying that although the southern Taihang mountains has long been known as a high-risk region for ESCC, populations there are actually at risk for all UGICs. Centralized occurrence of UGIC from the esophagus to the cardia and to the pyloric antrum, both in human and in chicken, may suggests the existence of common risk factors (even common environmental carcinogens) to the upper digestive tract.

In Table 1, the incidence rates of UGICs in Cixian and Linzhou are generally lower than that of Yangcheng and Shexian. One possible explanation may be that as two world-famous research fields, Cixian and Linxian have hosted many large preventive programs such as extensive drinking-water improvement and nutrition intervention in the past than in Yangcheng and Shexian. But this is not the main concern of this article.

What we are interested in here is the geographic variation as shown in Figure 2, or shown by the different detection rates in Table 2. Since the four adjacent counties are on a similar social- and economical- development level, it seems unlikely that uncomparable living-standards have contributed to the geographic variation in tumor topography or histology. Therefore, we tried to relate it to regional difference in kinds or richness of environmental carcinogens.

Past etiological studies on ESCC in the region have pinpointed nitrosamines and their precursors, fungus-infested food, nutritional deficiency, and genetic susceptibility as the main risk factors (Yang, 1980). Among the first three environmental risks, nitrosamines seem to play a central role for the following reasons. First, Nitrosamines can be synthesized either in vitro or in vivo from secondary amines and nitrites. Both precursors can be derived from nitrogenous compounds in food and water, and the content of these compounds in water and food is found to be higher in high- than in low-risk areas for esophageal cancer (Yang, 1980). In addition, a deficiency of molybdenum is observed in soil sample of high-risk places. Molybdenum is a cofactor of the enzyme Nitrate-reductase. Reduced molybdenum in soil therefore increases nitrite level in plant and food2; Secondly, the external amount of nitrosamine in food is usually increased when food become moldy (i.e. contaminated by fungi) (Yang, 1980); and thirdly formation of nitrosamines in the stomach is increased when there is a lack of nutrients or vitamins in the diet (Yang, 1980).

Nitrosamines are suspected as a possible reason underlying the geographic variation in topography or histology of UGICs because deep among the mountains, underground water resource is scarce than in hilly and level areas, people have historically relied on river water or raining water collected during raining season. Because the content of nitrogenous compounds in earth-surface water is much higher than deep-underground water, especially during the raining season when the surface-water supply is heavenly polluted by human and animal waste, water is the main source for nitrosamines and their precursors to enter into human body.

Although not necessarily relevant, variation in experimental tumors induced with N-nitrosamines on mice or rats previously performed in CICAMS may also serve as a reference. In the animal work, remarkable variations were observed in tumors with different nitrosamines, at different doses, or on different animal species. For example, in rats , N-nitrosamines with a symmetrically-structured molecular mainly induced liver tumor, but unsymmetrically-structured N-nitrosamines produced esophageal tumor. In one study, four groups of rats were fed with ditetranitrosamine at 75mg/kg, 37.5mg/kg, 20mg/kg, and 10mg/kg respectively. In the highest dose group, liver tumors were induced, but esophageal tumors appeared in the second and third dose groups, and in the fourth group, even bladder tumors developed (Lin and Gao, 1994).

Because the amount of nitrogenous compouds in underground water is much lower than in earth-surface water (Yang, 1980), beginning in the 1970s in the high-risk region, extensive efforts were made by the local and state governments to improve the drinking-water conditions by drilling deep wells or building up water-purification systems. Consquently, water condition for most people living in the mountains has been gradually improved. Meanwhile, a decrease in the incidence rate of esophageal cancer appeared. For example, in Linzhou City from 1984 to 2003, the annual world ASR of ESCC decreased from 187.0 to 90.2 for males and from 115.7 to 51.9 for females; and in Cixian county from 1983 to 2002, the annual world ASR for ESCC decreased from 220.7 to 169.5

for males and from 122.1 to 98.6 for females. Although other factors such as social-economical development may have contributed to the decrease, the effect of water improvement is widely exclaimed by Chinese researchers.

While the effect of environmental factors is apparent in the region, previous immigration studies also suggested genetic predisposition. On one hand, people who had emigrated from high- to low-risk places still showed significantly higher incidence rates of ESCC several decades later; and on the other, people who had immigrated into the high-risk region from low-risk places showed no increase 20 years later (Jiang and Zhang, 1997). Recently in a large hospital cohort, we found systematic differences in onset age, number of primary tumors and long-term survival rates between stage-adjusted familial and sporadic ESCC cases, proving the existence of inherited genetic predisposition (Denggui et al., 2006).

In addition to classic cancer genetics, progress in epigenetic epidemiology may help to explain the development of genetic predisposition from environmental risks (Jablonka, 2004); unlike experimental or occupational carcinogenesis in which tumor develops under a short intensified exposure, increased occurrence of UGIC on the population level in the region may have been the results of generation's exposure and risk accumulation. By evolution, epimutations accumulated from the past are continuously selected and promoted by environmental risks because cells carrying the epigenetic changes adapt better to the carcinogenetic environment (Vineis and Berwick, 2006). In this way, a high susceptibility is maintained in the population without significant mutation rates.

By the hypothesis, both an inherited predisposition and second environmental risk are prerequisite for emigrants to maintain high rates after leaving the high-risk place. If they are not exposed to similar environmental risk in the new place, their previously acquired susceptibility will not be selected and promoted, the rate will gradually go down. For example, although the ESCC mortality rate of the first generation of Chinese emigrants in USA is 2.94 times that of white Americans, the ratio became 1.91 in the second generation, and decreased further in later generations (King and William, 1973). As for immigrants come from low-risk places, their rate remains low despite many-year's living in a high-incidence place because they have no previous predisposition to be selected and promoted.

Therefore, for the sake of primary prevention in high-risk areas, the acquired or previously accumulated susceptibility will not take a heavy toll if similar exposure stops. But many years are needed before the effect become clear, just as emigrating to the U S A.

In summary, clustering of upper gastrointestinal carcinomas and the geographic variation in the high-risk region observed in recent years suggests effects of environmental carcinogens. Because nitrosamines are the mostly suspected agents and water is the main source for exposure, drinking-water improvement deserves emphasis for primary prevention. To study the development of a high susceptibility from evolutionary adaptation to a stressful environment, international collaborative research in this region may prove to be very fruitful.

References

Bai J, Yi L, Dang C (2006). Adenocarcinoma of the esophagogastric junction in China according to Siewert's classification. *Jpn J Clin Oncol*, **36**, 364-7.

Wen D, Wang S, Zhang L, et al (2006). Difference of onset age and survival rates in esophageal cancer cases with and without a family history of upper gastrointestinal cancer in a highrisk region in northern China. *Fam cancer*, **5**, 343-52.

Jablonka E (2004). Epigenetic epidemiology. *Int J Epidemiology*, **33**, 929-35.

Jiang BF and Zhang GN (1997). Migrant study of esophagus cancer. In: epidemiology, volume one. Geng GY, editor. p 303-307, People's health publishing house, Beijing.

King H, Haenszel W (1973). Cancer mortality among foreign- and native-born Chinese in the United States. *J Chron Dis*, **26**, 623-46.

Lin P, Gao F (1994). Prevention of esophageal cancer. In: Pathology and Prevention of Esophageal Cancer. Liu Fusheng, Lin Peizhong, editors. p 160-1, First ed. Geography Press, Beijing.

Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Sievert JR, Stein HJ (1996). Adenocarcinoma of the gastroesophageal juncton: classification, pathology and extent of resection. *Dis Esophagus*, **9**, 173-82.

SPSS Incorporation (2006). SPSS 13.0 for the Windows. SPSS Inc, Chicago.

Tran GD, Sun XD, Abnet CC, et al (2005). Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*, **113**, 456-63.

Vineis P, Berwick M (2006). The population dynamics of cancer: a Darwinian perspective. *Int J Epidemiology*, **35**, 1151-9.

Yang CS (1980). Research on esophageal cancer in China: a review. *Cancer Res*, **40**, 2633-44.

Zhang S, Chen W, Li L, et al (2006). Incidence and mortality rates of malignant tumors in a sample of Chinese towns and counties from 1998 to 2002. *Chinese J Tumor (in Chinese)*, **15**, 430-47.