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ORIGINAL PAPER

Drinking water: a risk factor for high incidence of esophageal cancer in Anyang, China

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Abstract Anyang is known to be a high-incidence area of esophageal cancer (EC) in China. Among a long list of risk factors, the quality of drinking water was evaluated. We have selected 3806 individuals and collected 550 drinking water samples correspondent with this not-matched case–control survey. There are 531 EC patients included based on Population Cancer Registry from 92 townships, of which 3275 controls with long-lived aged over 90 years and free from EC are used as controls in the same regions. Our result suggests that the quality of drinking water is a highly associated risk factor for EC. The residential ecological environment and the quality of water resource positively link with each other. The analysis of water samples also demonstrated that the concentrations of methyl ethylamine, morpholine, *N*-methylbenzylamine, nitrate and chloride in water from springs and rivers are higher than those in well and tap water ($P = 0.001$). Micronuclei formation tests show that well water and tap water in these regions have no mutagenicity.

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Introduction

Esophageal cancer (EC) is the sixth most common cause of cancer mortality in the world (Herszenyi and Tulassay 2010) and is the result of multiple risk factors (Wu and Li 2007). N-nitroso compounds have been suggested to be a causal factor in esophageal carcinogenesis (Islami et al. 2009; Habermeyer et al. 2015). In digestive tract, nitrate is reduced to nitrite which reacts with secondary amine, amide and nitrate to form two kinds of N-nitroso compounds, nitroso-amines and nitrite amide. N-nitroso compounds are considered as potent carcinogens (Bogovski and Bogovski 1981), which have the time- and dosage-dependent effect on intestines (Naimi et al. 2014). Contaminated drinking water might contain abundant nitrosation precursors above-mentioned. Our previous investigation showed the possible association between drinking water and the age-related incidence of EC (Xu et al. 2009), which suggested that nitrosation has cumulative carcinogenic effect on esophagus. We have conducted several investigations in Anyang, Henan province of China and advised the inhabitants to drink deep well water (Liu et al. 1983; Han et al. 2005; Han et al. 2007a, b; Xu et al. 2009). A retrospective study showed that EC incidence was declining (Han et al. 2007a, b). Recently, variation in water quality in China was driven by dramatic population growth, the rapid development of industrial and agricultural production, and the increase in township enterprises (Zhang et al. 2010). In Anyang, water resource also faces such environmental pressures. Consequently, the cancer incidence, including EC, showed an increasing trend in China (Chen et al. 2014; Ebenstein 2012). Studies on causal relationship between deteriorated water environment and cancer epidemiology have been extensively conducted (Mayne et al. 2001; Xu et al. 2007; Gao et al. 2011; Ren et al. 2015). However, the association between water pollution and digestive tract cancers has not been fully explored.

In this paper, we focused on the association between water quality and EC in Anyang, an ideal place to explore our investigation. Since the late 1980s, Chinese government began carefully monitoring both mortality and water pollution, which provides reliable data about the relations between water quality and EC in Anyang where most of the inhabitants still rely on springs, cistern, rivers, wells or tap water as their drinking sources. In China, population migration and immigration are strictly controlled by government regulations. Therefore, the location of residents at the time of observation will likely reflect their true lifetime drinking water pollution exposure in Anyang. In addition, Anyang's high rates of cancer and dramatic regional variation in water quality—driven in part by plausibly exogenous rainfall patterns—allow us to evaluate the effect of contaminated water on EC incidence (Ebenstein 2012).

In the present study, we selected 3806 individuals and collected 550 corresponding drinking water sources in 92 townships for a not-matched case–control survey. The cases included 531 EC patients, and the controls included 3275 long-lived aged over 90 years and free from EC. The geographical position and ecological character of 550 drinking water sources were investigated. In addition, we selected water samples for mutagenicity/contaminants analysis. The aim was to explore a link between the quality of drinking water sources and the reported high-incidence rate of EC in Anyang, China.

Materials and methods

Study area and the geological setting

The study area, Anyang, with a surface area of 7413 km^2 is located between 113°37′ and 114°58′ eastern longitudes and 35°12′ and 36°22′ northern latitudes. She lies in the north of Henan Province, west to Taihang Mountains and Zhanghe River and east to North China Plain. Most of Anyang regions fall in Haihe River basin and the transition zone of Taihang Mountains to North China Plain (Xin et al. 2011). The geomorphology is diverse, including plain, mountain, hill and basin. The climate of these regions is dry, and annual rainfall is very few. The rainfalls usually happen in July and August, and the amount of rainfall in this period is 57 % of annual average (Zhang et al. 2011). In east Taihang Mountains, richness in crust fault and lacking of good aquifer result in loss of surface water (Xin et al. 2011; Zhang and Huo 2010). It is difficult to detect deep groundwater resource because of the complex geologic structure. Therefore, the water resource is very poor, but coal resource is rich in Anyang. In Linzhou, the west–north regions of Anyang, water from Red Flag Canal originated from Zhanghe River was the only water resource for living drinking, agriculture and livestock drinking several decades ago.

Anyang is composed of a centralized city area of 5 counties at its outskirts, and 5 counties are composed of 92 townships. Studies found that EC incidence in Anyang decreases from west to south east. The order is the following: Linzhou City > Anyang County > Tangyin County > Neihuang County > Hua County (Han et al. 2007a, b). In contrast, the average lifetime in five counties is reverse to the EC incidence. People with age over 90 years in Linzhou are less than the other counties. Additionally, the EC incidence in area west to Weihe River is higher than that in the east. In West Weihe River region, there are few people aged over 90 years. In this paper, we selected all 92 townships in five counties as our study areas.

Study population and data collection

In this study, a total of 531 patients with histologically confirmed EC were recruited from 92 townships in Anyang region based on Population Cancer Registry during 2008. A control population including 3275 individuals with aged over 90 years and free from EC (without dysphagia) was selected from the same geographical areas based on Population Registry in Anyang. Individual expose data were collected by a structured questionnaire based on face-to-face interview, including age, gender, occupation, sources of drinking water, smoking and alcohol intake. Subjects with uncompleted information were excluded. All patients provided a written informed consent under an Institutional Review Board-approved protocol.

Investigation of geological and ecological characteristics of each water source, water sample collection and laboratory assays

Five hundred and fifty corresponding public drinking water sources were investigated in each township, and the geological and ecological characteristics of each water source were recorded. The drinking water resources in the study areas were springs, cistern (traditional water reservoir), rivers, wells (depth no <100 m) and tap water (supplied by pipelines). The former three were traditional drinking water resources which were used by inhabitants before 1980s, and they are still used in many remote villages. Wells and Tap water were new drinking water sources which are being used since 1980s.

We collected 51 water samples from four coal mines, seven Red Flag Canal water samples from different supply points and 40 traditional water sources in high-EC-incidence villages and 47 water samples from new water sources in low-EC-incidence villages. The low-/high-EC-incidence village was decided according to data provided by Anyang Center for Disease Control and Prevention. The standard for selecting new water source was described by Han et al. (2005). Each 7000 ml water sample was collected in precleaned (bathed in $KMnO_4$ solution), sterilized glass bottles in advance, numbered with double-blind method and stored in ice box (4 °C). pH was measured in situ using portable measuring devices and was adjusted to 2.0 with concentrated ultrapure hydrochloric acid (HCl) in the field. Each 2000 ml sample was concentrated to 200 ml with rotary evaporation and split into two fractions. The first fraction was used for anion analysis. The entrained solids were separated by vacuum filtering using >0.45 μm filter papers. The second fraction was for organic matters analysis. Fieldwork was carried out in December 2010 and January 2011.

The pollutants were detected according to Chinese standard examination methods for drinking water (GB/T 5750.1-2006). The kinds and concentration of organic matters were determined using gas chromatography-flame ionization detector (GC-FID), most suitable for analyzing natural waters. Advantages of using this technique include simultaneous multisubstance analysis, low detection limit, along with high accuracy, and precision.

Micronucleus test is a worldwide used technology for screening and monitoring environmental pollutants. For the advantages such as convenient, training materials, simply mastered technology and low cost (Minissi et al. 1998), we selected *Vicia faba* (*V. faba*) as the test plants. The methods for root tip preparing and micronucleus assaying were carried out with some modification, as described (Yi and Meng 2003). Dry *V. faba* seeds were soaked for 24 h in water samples and allowed to germinate between two layers of moist cotton. When the newly emerged roots were of 1.00–2.00 cm in length, they were used in the test. Five tips for each experimental group were scored blind. Micronucleus frequency was assessed in 1000 cells/tip.

Statistical analysis

For statistical analysis, categorical values are given in frequencies and percentages. Means, medians and standard deviations were calculated for numerical variables. T Distribution differences of mutagenicity and pollutant concentration of different water sources were tested by using Student's *t* test for continuous variables, as appropriate. To assess the risk factors for EC, univariate and multiple conditional logistic regressions were used. In addition, to assess the correlation between the drinking water type or geographic environment of water source and EC, nonconditional logistic regression was performed. The level of significance was set at 5 %. Analyses were performed using software SPSS version 19 and Stata/SE.

Results

Association between EC and demographic characteristics

In order to find out the other risk factors for EC besides drinking water, we surveyed the demographic characteristics of the participants, including gender, age, smoking and alcohol consumption (Table 1). Of EC patients, 330 (62.15 %) were male and the sex ratio was 100 males to 61 females. The long-lived included 728 males (22.23 %) and 2547 females (77.77 %), and the ratio of males to females was 1–3.50. The sex ratio difference was statistically significant ($P = 0.005$) between the case and the control. The unadjusted OR value suggested that male individual was susceptible to EC (OR 5.72/$P = 0.005$). The smoke and alcohol consumption had significant difference between cases and controls (OR 4.25/$P = 0.005$ and OR 2.09/$P = 0.005$, respectively). However, except male individuals with smoke consumption (OR 2.08/$P = 0.005$), the effect of gender on smoking and drinking had no statistical difference between two groups ($P > 0.05$). In the investigated regions, the majority of both populations were Han Chinese (over 99 %) and farmer (over 92 %). The ethnic/occupation had no statistical difference between two groups ($P > 0.05$), and the data are not shown in Table 1. Additionally, multivariate analysis demonstrated that drinking water quality, sex and tobacco consumption were independent factors in EC incidence (Table 2) (OR 1.41/$P = 0.001$, OR 4.54/$P < 0.001$ and OR 1.07/$P < 0.001$, respectively).

Association between EC and the drinking water type

Drinking water sources in present paper were the following: springs, cisterns, rivers, wells and tap water. We performed a statistically analysis with the aim to show a possible link between drinking water types and the cases/controls. The results showed that more control individuals had tap water and wells as drinking water sources (51.8 and 23.36 %, respectively), while more case individuals had springs, rivers and cisterns as drinking water resources (1.36, 21.89 and 6.2 %, respectively). The value of OR suggested that traditional drinking water resource was associated with EC (OR 3.53, 2.79 and 2.19, respectively; Fig. 1). In addition, there were 12.8 % cases and 10.4 % controls without fixed drinking water resource because of lackness of drinking water source in living areas.

Resident geographic environment effect on the quality of drinking water recourse

Geographic environment might have effect on the quality of drinking water resource. Anyang region has

Table 1 Socio-demographic data for EC cases and the controls and the univariate analysis according to sex, alcohol intake and tobacco consumption

Characteristic	EC cases	Control group	Univariate	
	$n = 531$	$n = 3275$	OR (95 % CI)	*P*
Age (years old)				
Low 60	14.31 (76)	0	No	No
60–70	39.36 (209)	0	No	No
70–80	23.16 (123)	0	No	No
Over 80	3.01 (16)	0	No	No
Sex				
Male	330 (62.15)	730 (22.29)	5.72 (5.64–5.75)	0.005
Female	201 (37.85)	2545 (77.71)	0.17 (0.16–0.17)	0.005
Smoking				
Total	156/509 (30.65)	300/3185 (9.42)	4.25 (4.18–4.26)	0.005
Male	153/315 (48.57)	222/711 (31.22)	2.08 (2.03–2.12)	0.005
Female	3/194 (1.55)	78/2474 (3.15)	0.48 (0.34–0.67)	0.250
Drinking				
Total	123/496 (24.79)	436/3201 (13.62)	2.09 (2.05–2.10)	0.005
Male	117/310 (37.74)	267/717 (37.24)	1.02 (0.99–1.03)	0.750
Female	6/186 (3.23)	169/2484 (6.80)	0.46 (0.38–0.54)	0.100
Water				
Traditional	52/516 (10.08)	107/3202 (3.34)	3.20 (2.26–4.64)	0.005
New	464/516 (89.92)	3095/3202 (96.66)	3.20 (2.26–4.64)	0.005

OR odds ratio, *No* no value. *CI* confidence interval. Traditional = traditional drinking water resources. New = new drinking water resources

Table 2 Multiple logistic regression for case–control study according to drinking water, sex, alcohol intake and tobacco consumption

Variables		OR (95 % CI)	*P*
Drinking water	Traditional versus news	1.41 (1.15–1.71)	0.001
Sex	Male versus female	4.54 (3.66–5.64)	0.000
Alcohol intake	Smoking versus no-smoking	1.07 (0.86–1.33)	0.543
Tobacco consumption	Drinking versus no-drinking	1.07 (0.98–1.53)	0.000

considerable geographic diversity. It consists of plain, mountain, hill and basin. In plain regions, the main drinking water source is tap water or well, while in remote mountain regions and hilly regions, the main drinking water source is springs or cistern water. In basin regions, the main drinking water source is river water. In order to detect the effect of diverse geographic character of water source on EC, next we surveyed the geographic environment of permanent participants and drinking water recourse. The majority of control population lived in plain regions (83.45 %), while most of the case population lived in mountain, hill and basin areas (42.33, 10.37 and 0.97 %, respectively). The value of OR gave us a hint that geological characteristics affect on the drinking water quality. In areas of mountain, hill or basin, EC incidence was higher than that in plain areas (OR 7.40, 3.35 and 8.03, respectively). The statistic difference was significant at the 0.01 level (Fig. 2).

Different water resources have mutagenic significance

In order to verify the potential harmful potency of different water resources, we carried out the mutagenicity test. Anyang has rich underground coal mine. A large number of discharged coal industry wastewater goes to underground and pollutes water resource. Red Flag Canal water is originated from Zhanghe River and used as the main water resource for agriculture in Anyang northwest area. Cistern was also the drinking water resource in many remote villages. So we collected water samples from coal mines, Red Flag Canal, cistern (in high-risk areas of EC), wells and taps (in low-risk areas of EC) in their villages to test mutagenicity with *V. faba* root tips. The results are shown with the number of micronucleus in every one thousand cells (Table 3). The data of each water resource were compared with that of negative control.

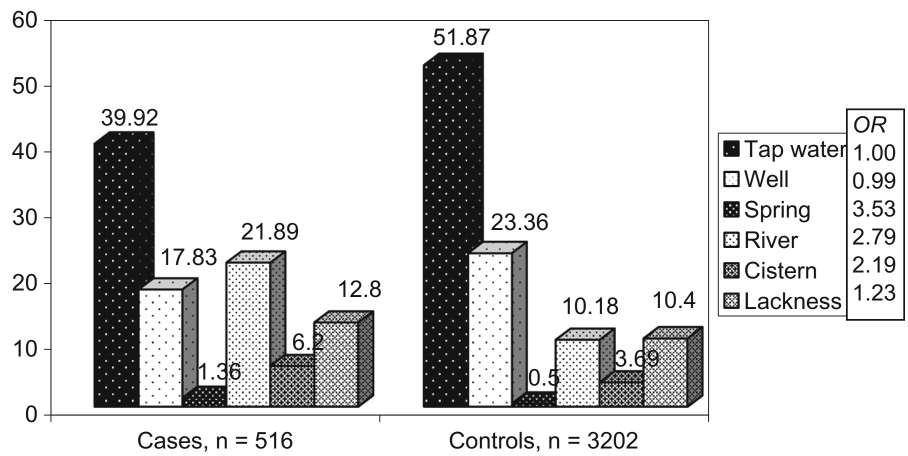

Fig. 1 Comparison of drinking water type between the cases and the controls. *Note*: *OR* odds ratio (univariate analysis)

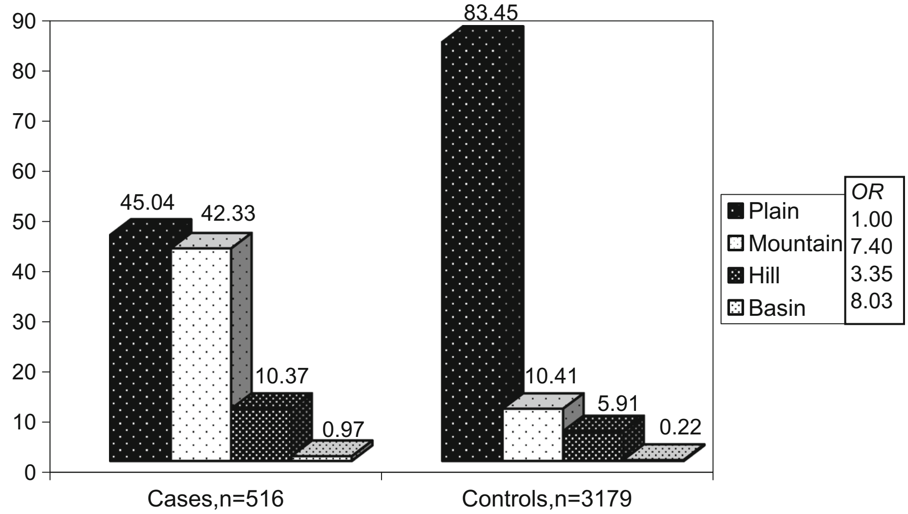

Fig. 2 Comparison of resident geographic environment between the cases and the controls

The micronucleus test results suggested that the mutagenicity order of water samples was coal industry > Red Flag Canal > Zhanghe River. Tap and well water hardly has mutagenicity.

Tap and Red Flag Canal water pollutant analysis

Water from Red Flag Canal had been the main drinking water resource for a long time. In order to find out carcinogens in drinking water, we analyzed wells and Red Flag Canal water samples. Summary of major pollutants in traditional and new water sources is presented in Table 4.

The results showed that there was significant difference ($P = 0.001$) for the concentration of three substances, methyl ethylamine, morpholine and *N*-methyl benzylamine between traditional and new water sources though there was no national guideline value of these compounds. Such substances were enriched in traditional water sources. The concentration of ammonia nitrogen in both two kinds of water source had no significance ($P = 0.5$) but was higher obviously than Chinese guideline value. However, the concentration of nitrate, nitrite, fluoride, chloride, total hardness and TDS in both water sources was lower than Chinese guideline value. The difference of nitrate, fluoride, chloride and TDS was significant ($P = 0.001$). It has no Chinese guideline value for OC, also. But the difference of OC between both water sources was significant too ($P = 0.001$).

Discussion

It is important for having a suitable method in epidemiologic study. In this paper, with not-matched case–control, we discovered the link between the quality of drinking water and high incidence of EC.

Table 3 Micronucleus test to detect the mutagenicity of each water resource

Sample source	Sample number	MN‰ (SD)	*t*	*P*
Coal wastewater	4	14.42 ± 2.28	10.17	0.001
Red Flag Canal	7	8.62 ± 1.58	9.19	0.001
Cistern	4	8.34 ± 1.74	6.43	0.002
Wells	7	2.81 ± 0.63	1.16	0.400
Tap	8	3.96 ± 1.96	2.12	0.100
Positive control	3	8.67 ± 0.88	10.39	0.002
Negative control	3	2.33 ± 0.58		

Positive control = potassium dichromate solution; negative control = distilled water. *MN* micronucleus

Table 4 Hydro-chemical analyses of traditional and new water sources of drinking water

Pollutants	Chinese guideline values	Traditional (n = 40) (mg/L)	New (n = 47) (mg/L)	t	P^a
Methyl ethylamine	No	7.07 ± 10.52	1.15 ± 5.15	17.430	0.001
Morpholine	No	12.77 ± 13.66	4.79 ± 23.26	10.419	0.001
N-methyl benzylamine	No	47.04 ± 33.31	39.49 ± 29.75	5.891	0.001
Ammonia nitrogen	≦0.02	0.20 ± 0.30	0.18 ± 0.11	0.721	0.5
Nitrate	10.00	6.40 ± 5.30	5.02 ± 1.67	5.779	0.001
Nitrite	≦0.02	0.00 ± 0.00	0.00 ± 0.00	1.784	0.1
Fluoride	1.00	0.30 ± 0.20	0.24 ± 0.04	14.363	0.001
Chloride	250.00	45.30 ± 122.40	16.02 ± 8.97	5.346	0.001
Total hardness	450.00	321.30 ± 81.90	324.79 ± 63.94	−0.785	0.5
TDS	1000.00	441.80 ± 207.60	342.13 ± 104.18	9.767	0.001
OC	No	1.3 ± 1.6	0.71 ± 0.33	7.706	0.001

The concentration of nitrite was low in both traditional and new drinking water, and the efficacious number after the point was all zero

TDS total dissolved solids, *OC* oxygen consumption. No = without guideline value

The difference to Chinese guideline is significant at 0.05 level; the difference to Chinese guideline is significant at 0.01 level

[a] The difference between traditional water source and new one

EC is the result of multiple risk factors including environmental, biologic, and genetic factors (Al-Haddad et al. 2014; Pelucchi et al. 2015; Keszei et al. 2013). Three previous case–control studies conducted by China Esophageal Cancer Collaborative Group in 1985, 1991 and 1997 had discovered multiple risk factors for EC, e.g., nutrition, moldy food, moodiness and hereditary. However, none of them discovered the association between drinking water and EC. The previous three control populations were all EC-free neighbors of the cases but not long-lived free EC aged over 90 years. The reason why drinking water was ignored as a risk factor for EC was that cases and their neighbors had the same drinking water resources. In the present study, the criteria for selecting controls were only that the individual was free from EC and age was over 90 years. According to Xu' hypothesis on N-cycle etiology of digestive system cancer, pollutant intake in the drinking water of controls was too low to suffer from EC for the controls during their lifetime (Xu 1986a, b).

With the case–control, the study found that population drinking polluted and mutagenic traditional water had higher incidences of EC than did population drinking relatively clean and nonmutagenic new source of water (OR 3.20, CI 2.26–4.64). This difference did not disappear after controlling for possible confounding factors such as sex, alcohol intake and tobacco consumption. This suggests that the quality of drinking water appears to be a risk factor for EC (OR 1.41, CI 1.15–1.71). In addition, the multivariate analysis demonstrates that males are more susceptible to EC. This study is consistent with some previous studies (Tao et al. 1999; Arnold et al. 2015; Golozar et al. 2015).

Some limitations to this study should be considered. The controls were only aged 90 years or more from Anyang region, so the result may not be truly representative of the risk of 5,173,000 persons in Anyang. In addition, there exist facts that number of female is larger than that of males and few female is smoking or drinking alcohol. Therefore, the strategy of selecting for controls might skew the distribution of other confounders. Two possible risk factors, smoking and alcohol drinking, might be masked in multivariate analysis by the disequilibrium attribution of gender. The biased overestimation of gender effect could result from with the strategy, also. However, the selection strategy for controls is helpful to verify the correlation between accumulation of pollutants in drinking water and age of suffering from EC.

With not-matched control population, this study discovered that pollutants in drinking water were associated with high risk of EC. The pollutants, such as nitrate and organic amines, are mutagens (Della-valle et al. 2014; Wu et al. 2014). These substances might form N-nitroso compounds (Bogovski and Bogovski 1981). The geographic, ecologic and economic factors might elevate the pollutant concentration in drinking water. In poor water resource areas, drinking water stored in cistern might accumulate nitrosation precursors (Alves et al. 2014). Pollutants from coal industry were intercepted by rivers and seep into groundwater to contaminate drinking water resources (Schilling et al. 2015). Therefore, in remote villages, without tap water provision and areas at river flow path turns, the EC incidence is higher than that in regions elsewhere (Han et al. 2008).

Our previous study discovered that the distribution of EC case in Linzhou, a county of Anyang, was in accordance with application of agriculture irrigation net. The EC incidence fluctuation was following water consumption and irrigation time (Han et al. 2007a, b). The areas along Zhanghe River are high-EC-incidence zone where drinking water is from rivers and springs all the time and the incidence remains high, while in villages where drinking water sources were altered to be from well or tap water, the EC incidence decreased from 107.51 to 75.80 per 100,000 after 5 years (Xu et al. 2009). These data were also supported by some previous studies (Xu 1986a, b; Han et al. 2007a, b; Xu et al. 2007).

The emergence of EC high-risk area is a result of multifactorial interaction (Xu 1986a, b). The hypothesis on N-cycle etiology of esophageal, gastric and liver carcinoma demonstrated the relationship between the pollutants, manure and wastewater, and these three cancers. The hypothesis pointed out that in semiarid and semihumid regions two kinds of carcinogen precursor, nitrate and nitrite in vadose zone and amine and amide in manure, migrated with river water flowing. Two kinds of precursors in drinking water synthesize two kinds of carcinogens, nitrosamine and nitrosamide, in metabolism. The high-cancer-incidence area emerges as soon as the efficacious polluted ratio is over 30 % (the individuals with efficacious pollutants intake were 30 % in population). We have succeeded in inducing pharyngo-esophageal, gastric and liver carcinoma in chicken with water polluted by manure and detected that the carcinogen was methylnitrosourea (MNU) (Xu et al. 2003). The hypothesis was supported by our study that the ratio of *p16* methylation and P16 protein expression had no significant difference in EC high-risk areas between North China and South China because the result suggested that the effect of hereditary factor on EC incidence had no difference in the two regions (Song et al. 2007).

Conclusion

The study investigated the relationship between quality of drinking water and EC risk with not-matched case–control design in Anyang, China. The results suggested that source of drinking water was an important risk factor for EC in addition to other known potential risk factors. It was found that traditional drinking water contained high concentration of carcinogens and would increase the risk of EC. In order to reduce EC incidence, it was necessary to improve quality of drinking water in EC risk areas.

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