

Study on environmental etiology of high incidence areas of liver cancer in China

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INTRODUCTION

China is a country with a high incidence of liver cancer in some areas^[1]. Liver cancer has a wide distribution and threatens human health seriously. A rough estimation shows that out of a population of 1.2×10^8 in liver cancer areas patients are more than 1.0×10^5 . The environment of the liver cancer area is very complicated and has different characteristics in different regions. But the epidemic regularity of liver cancer is obvious, and the environment in the cancer areas has also distinct characteristics that contribute to the study on the environmental etiology of liver cancer^[2-5].

THE EPIDEMIOLOGICAL CHARACTERISTICS OF LIVER CANCER

The liver cancer discussed here has epidemiological characteristics like endemic, comparison and trend. The general investigation of liver cancer all over the country of China or local area shows that the high rate of liver cancer has been found in some provinces, counties, towns, and islands with the background of the low death rate ($10/10^5$)^[1,6]. The main areas of high rate of liver cancer chiefly concentrate in the coastal areas such as Jiangsu, Guangxi, Fujian, Zhejiang, Guangdong Provinces, and Shanghai City^[7,8] (see Figure 1). Qidong in Jiangsu Province and Fusui in Guangxi Province are two counties of the highest death rate of liver cancer in China and the death rates are $47.76/10^5$ and $46.87/10^5$ ^[1,9]. As far as macroscopic environment is concerned, the risk area often

has focused distribution and has a strict and steady dividing line between light and non-liver cancer areas. The risk area has peculiar characteristics regarding landmark, geology, hydrogeology, and geochemistry^[9,10]. It is an important way to study the cause of high incidence of liver cancer from the angle of environmental etiology.

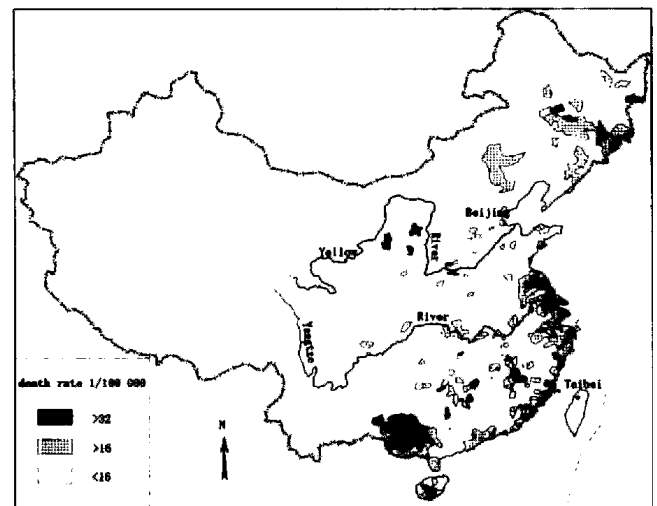


Figure 1 Sketch map of liver cancer in China.

The area of high incidence of liver cancer is adjacent to that of the low incidence area and the death rate has great disparity. For example, the death rate in Fusui is $46.87/10^5$ while that in Niming County is $7.47/10^5$, and the death rate in Qidong is $47.76/10^5$ while that of Rudong County adjacent to Qidong is $20.6/10^5$. The death rate in Tongxiang Town in Qidong County is $50.67/10^5$ while that in adjacent Xining Town is $17.28/10^5$. All these show that the carcinogens are distinctly different in the two adjacent environments^[9].

The three epidemic trends of liver cancer may be summarized as follows: the change in epidemic curve from low to high, parallel development or from high to low. The trend reflects the change in the intensity of carcinogenic factor with time, and the epidemic curve of many high incidence areas of liver cancer belongs to the first type. The curve rose in the 1970s, while it gently went down from the end of the 1980s to the beginning of the 1990s. We think that organic pollution of the drinking water may be the reason for the rising of the curve, while the downward trend of the curve may be the result of changed water.

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THE ECO-ENVIRONMENTAL GEOLOGICAL TYPES IN LIVER CANCER AREAS

The cancer of digestive system in China has wide distribution and threatens human health seriously and liver cancer is the most serious one of all^[1,11]. Distinct environmental characteristics were discovered in the high incidence areas of liver cancer according to a survey and analysis on a large scale. It reflects comprehensively the climate, hydrology, landmark, geology, geochemistry, drinking water, the degree of pollution, economic condition, the food custom and so on. However, the organic and reduction environment and the drinking water polluted by organisms are the most obvious and common characteristics. The high incidence areas are classified into five geo-environmental types^[10,12-14].

(1) The denuded mountain environmental type: it is mainly distributed at the junction of three provinces of Hebei, Henan, and Shanxi in south Taihang Mountain. Esophagus, liver and stomach cancer are the common cancers. The climate is dry and the rainfall is about 500 mm-600 mm. The slopes are bare and are made up of carbonate and clastic rock. The ground has sparse plantation and the surface water and groundwater are very scarce. The drinking water condition is poor, and only a few residents drink stream and spring water, while most have to drink pool and pond water polluted with organic waste.

(2) The Karst mountain environmental type: it is mainly distributed in Fusui and Longan County in Guangxi Province, the main cancers are liver and stomach cancer. The rainfall is sufficient about 1100 mm-1300 mm. The carbonate rock layer distributes extensively in the cancer areas belonging to Karst geographical area. Underground rivers are developed while surface water is very scarce. People here mainly drink the water from dirty ponds or wells besides the ponds.

(3) The river network plain environmental type: it is mainly distributed in Jianhu and Huai'an in the north of Jiangsu Province, Yangzhong and Taixing in the middle and lower reaches of Yangzi River. Main cancers are of the esophagus and liver. The area belongs to the alluvial and lake plains of the lower reaches of Yangzi River, and most of the cancer areas are in the lake-marsh depression which is rich in humus sludge, peat, and biological deposition and CH₄ is easily found escaping from the earth's surface. The surface water and groundwater is rich but the runoff is stagnated.

(4) The delta type: it is distributed in Qidong, Haimen, Rudong, Chongming Island in Yangzi River Delta and Nanhui County belonging to Shanghai City, Shunde, Jiangmen, and Foshan in the Zhujiang delta. Liver and esophagus cancer are the main cancers. The climate is humid with plenty rainfall. Most of the areas are sea and land mutual depositions that are mainly made up of sand, humus, peat, and biological deposition. The surface

water and groundwater flow is sluggish and is severely polluted by organisms.

(5) Coastal plain and island type: stomach, liver, and esophagus cancer are the main diseases. The cancer areas of coastal plain type are mainly distributed in Changle and Putian in Fujian Province. Most of them are sea and land mutual depositions of coastal plains that are made up of clay, soil, and biological deposition. The groundwater and surface water are rich, but severely polluted by organisms. Dongshan Island in Fujian and Nan'ao Island in Guangdong Province belong to the island type which is a rocky hill and is covered by thin Quaternary deposition, and fresh water is scarce.

The classification of eco-environmental geology has contributed towards a deep study and contrast between the macroscopic and microscopic characteristics in disease areas, and searching for questionable carcinogenic factors of environment, and giving comprehensive protective measures.

DRINKING WATER TYPES AND LIVER CANCER

Comparing the high incidence areas of liver cancer in China, we discovered that there exists a common faction in cancer incidence in these areas although the natural environment is different. It is that the groundwater or surface water is rich in humus, the water flow is stagnant and is in an organic and reduction environment consisting of pools, ponds, cellars, trenches, channels, and the groundwater in the swampland. The people in non-cancerous areas mainly drink groundwater or surface water which is not polluted by organisms. The water flow is smooth and is in an oxidation environment such as springs, rivers, and shallow or deep well water^[9]. Taking Fusui and Qidong as examples, we have constructed a figure that reflects the relation between the type of drinking water source and the death rate due to liver cancer (Figure 2). The figure illustrates that the death rate due to drinking the pond and pool water is the highest and due to deep well water is lowest.

RELATIONSHIP BETWEEN DRINKING WATER AND LIVER CANCER

After affirming a close relationship between drinking water type and liver cancer, we tested the inorganic and organic compositions of all kinds of drinking water. We did not find any peculiar contents regarding common and trace elements, but some cancer areas were low in minerals and Se in water^[13-16]. However the organisms in water were different and the death rate due to liver cancer was found to have a very close relationship with drinking water type and the degree of water pollution^[17-18] (Table 1).

From Table 1, it can be observed that water pollution indicator such as nitrate, nitrite, COD, and humic acid have an obvious relation with the drinking water type and death rate from liver cancer increases with a rise in the

above indicators. In order to study the relationship between death rate and water quality, 29 water samples that corresponded to death rate due to liver cancer were chosen. The death rate and COD, DO, BOD, NO_2^- , and humic acid were used to make a correlation analysis to study the relationship between the death rate and the five factors. The regression equation is $y = a + bx$, y stands for the death rate due to liver cancer, x stands for the five factors. The results of the analysis are listed in Table 2.

Table 1 The organic pollution indicators of drinking water and death rate from cancer

The drinking water type	Qidong in Jiangsu					Fusui in Guangxi		
	Pond	Channel	River	Shallow well	Deep well	Pond	River	Deep well
Death rate	61.53	58.17	41.99	18.80	0.0	115.05	37.49	0.0
Number of samples	20	18	22	21	16	7	18	25
COD	4.66	3.85	3.55	3.20	1.28	48.27	0.75	0.197
Humic acid	0.43	0.36	0.28	0.18	0.08	0.58	0.18	0.042
NO_3^-	14.52	18.20	21.46	67.91	1.53	0.74	0.75	0.480
NO_2^-	0.54	0.48	0.38	0.28	0.04	0.061	0.008	0.0096

The death rate is $1/10^5$ and the unit of NO_3^- , NO_2^- is ppm.

Table 2 The analysis between various drinking water factors and death rate due to liver cancer

Content PPM	Regression a	Coefficient b	Interrelation coefficient r
Humic acid	29.4985	78.6384	0.5981 ^b
NO_2^-	53.1249	75.9767	0.4232 ^a
COD	43.8098	0.4280	0.4881 ^b
BOD	45.0576	0.6231	0.4872 ^b
DO	191.8340	-19.0087	-0.7285 ^b

^a $P < 0.05$, ^b $P < 0.01$, vs control.

The results shows that humic, COD and BOD have a very remarkable positive relation with the death rate ($P < 0.01$), NO_2^- has a significant positive correlation. While DO has a very marked negative correlation ($P < 0.01$). That is to say, the lower the DO is in the water, the higher is the death rate. Pond water is severely polluted by organisms and is in a strong reduction environment lacking of DO. We postulate that the five factors given above can be used as important signs to judge the water quality and the death rate due to liver cancer.

THE RELATION BETWEEN NITROSAMINE AND LIVER CANCER

It has been affirmed that nitrosamine is carcinogenic. Nitrosamine contents were observed in water from high incidence areas of liver cancer in the 1970s and 1980s in China, but the test method used was not very sensitive for semi-quantify^[18].

We collected 24 water samples from cancer-prone villages and non-cancer-prone villages in Fushui County to quantify the contents of nitrosamine compound in water. Nitrosamine was not found in sixteen water samples taken

from river, stream, and deep well water except in 8 samples of pond water. Dimethyl nitrosamine was the main compound in the pond water samples, only three pond water samples contained diethyl nitrosamine. The death rate seems to have positive relation with the contents of nitrosamine (Table 3).

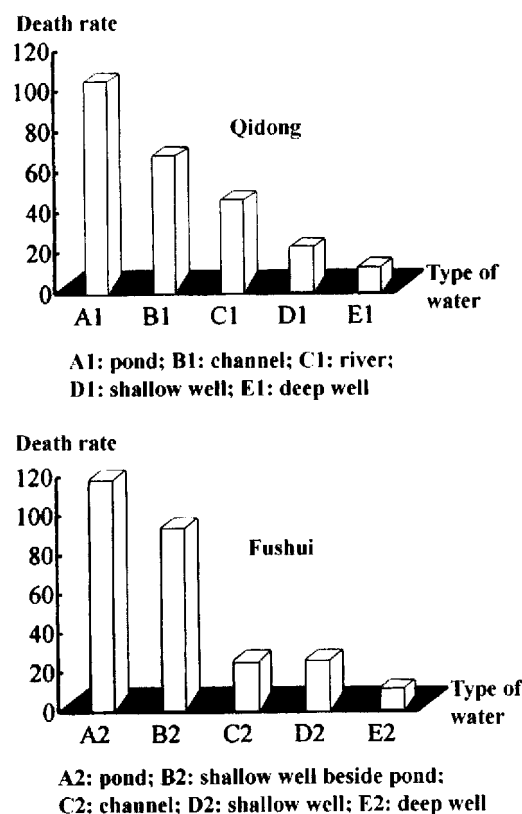


Figure 2 Relation between the types of drinking water source and the death rates from liver cancer.

Table 3 The content of nitrosamine in pond water and the death rate due to liver cancer in Fusui

Location of samples	Death rate of liver cancer $1/10^5$	Dimethyl nitrosamine ppb	Diethyl nitrosamine ppb
Sihe	74.96	3.8	
Jiuchen	35.42	3.2	
Yiliu	31.68	3.6	
Mumin	80.80	2.4	2.2
Qutun	112.59	5.6	
Zhongyuan	148.49	4.8	2.4
Lailu	95.36	4.2	
Jiuta	18.38	0.8	0.4

MUTATION TEST OF DRINKING WATER

Professor De Long Su^[11] holds that the high incidence of liver cancer has relation with water polluted by micro organisms. He carried out an Ames test on the drinking water in Qidong disease area and got a positive result. Li Sheng Zhang^[19] carried out a micronucleus test using Zilu Grass from America on pond water in Fusui disease area and extracted liquid from the pond mud. His results show

that high pollution degree corresponds to high micronucleus rate of plant cell and high death rate due to liver cancer. He also found that the micronuclei in clean deep well water in Karst area and corresponding water are very low.

Following some studies^[19-24], we decided to carry out an HHPL mutation test on pond water, shallow well water, and deep well water. Distilled water was used as a blank contrast.

The first test was the cell micronuclei test and the results showed that HHPL micronuclei rate found in the water that has been poisoned had a dose-effect relationship with the density of the samples and the higher the density of samples content was, the higher the micronuclei rate was. The micronuclei rate had a marked difference (pond water > shallow well water > deep well water ≥ blank). On evaluation by *t* test, the micronuclei rates of poisoned pond water and shallow well water were significantly different ($P < 0.001$).

The second test used was the mutation test of cell chromosome malformation test. The results showed that the mutation rate of chromosome aberration of HHPL has dose-effect with the density of each polluted water sample. Rates of chromosome aberration caused by polluted water are statistically significant and similar to micronuclei test as evaluated by *t* test, $P < 0.001$ (Table 4). This can be an important test for studying environmental etiology of liver cancer.

Table 4 Result of cell mutation test and polluted water samples

Water source type	Cell micronuclei rate %	Cell chromosomal aberration rate %
Pond water 1	63.34	6.42
Pond water 2	59.66	4.76
Shallow well water 1	48.32	3.76
Shallow well water 2	42.66	3.21
Deep well water	3.30	0.75
Blank contrast	2.43	0.17

STUDY ON THE WATER QUALITY BEFORE AND AFTER THE CHANGE IN WATER SOURCE

It has been accepted that liver cancer has close relations with the polluted drinking water. The changed water project has been made in many cancer prone areas since 1980's, especially in Fusui County, the changed water project has been implemented on a large scale, and the present water source is from the limestone layer. The depth of well is about 100 m-200 m. Most cancer prone villages have used this supply of water with beneficial results. We chose nine villages supplied with changed water and observed the change in the water quality and human health before and after. Before the water was changed, the pond water was severely polluted, and the color of water was brown and grey green, the water smelled terrible, and residents had many unhealthy symptoms such as pale cheeks, fatigue, distension of abdomen, menoxenia and liver cancer. After the water was

changed, the deep well water was clear and sweet, the symptoms noted above gradually disappeared, residents felt sound and the liver cancer death rate lowered. The results of water quality before and after the water was changed and mutation test are listed in Table 5.

Table 5 Contrast in water quality before and after the change in water

Test item (ppm)	NO ₂ ⁻	Humic acid	COD	DO	NH ₄
1	0.0224	0.53	44.24	6.10	0.34
2	0.0106	0.05	0.34	8.21	0.07
Test item (ppb)	Se	Fe	Mn	Zn	nitrosamine
1	0.56	1110.88	198.33	9.29	4.20
2	0.39	164.60	10.14	50.47	0
Test item	Plant cell micronuclei rate/%	HHPL			
		micronuclei rate/%	chromosome aberration rate/%		
1	10.34	59.61		4.76	
2	5.96	3.30		0.75	

Note: 1. pond water, 2. deep well water.

From Table 5 it can be observed that the water quality of deep well is better than that of pond water. Thus using a change in water source and additional treatments, an improvement in human health and prevention in the occurrence of liver cancer^[25-32] may be observed.

REFERENCES

- 1 Lini NF. Medicine environment geochemistry. Changchun City: Ji Lin Science and Technology Publishing House; 1991:242-256
- 2 Gu GW, Zhou HG, The new concept of the cause of liver cancer. *Shijie Huaren Xiaohua Zazhi*, 1998;6:185
- 3 Liu WW, The study on etiology of hepatocytic liver cancer. *Shijie Huaren Xiaohua Zazhi*, 1999;7:93-95
- 4 Wu Y, Liu E, Zhang BC. The analysis of family history in the patients of primary liver cancer in different areas. *Shijie Huaren Xiaohua Zazhi*, 1998;6:178
- 5 Zhou HG, Gu GW, The study on molecular epidemiology of liver cancer. *Shijie Huaren Xiaohua Zazhi*, 1998;6:432
- 6 Chen WS, Qiu JW, Cai SS, Lin K, Yuan H, Guo LM, Lin GB, Wan XA. Epidemiologic survey of liver cancer in Jieyang City of Guangdong Province. *Shijie Huaren Xiaohua Zazhi*, 1995; 3:39-41
- 7 Wang ZQ, He J, Chen W, Chen Y, Zhou TS, Lin YC. Relationship between different sources of drinking water, water quality improvement, and gastric cancer mortality in Changle County; - A retrospective cohort study in high incidence area. *World J Gastroentero*, 1998;4:45
- 8 Cai Lin, Yu SZ, The study on molecular epidemiology in Changle County of Fujian Province. *Shijie Huaren Xiaohua Zazhi*, 1999; 7:652-655
- 9 Tang J, Lin NF. Relationship between drinking water quality and high frequency of the liver cancer in Fusui County in Guangxi. *Huanjing Kexue Xuebao*, 1996;Vol.16:287-293
- 10 Yang KY, Tu JT, Li HM, Wang YQ, Zhi SP, The relationship between the distribution of stomach cancer and Tertiary stratum. *Shijie Huaren Xiaohua Zazhi*, 1996;4:695-697
- 11 Chung S. Chinese diet in the causation and prevention of cancer. *World J Gastroentero*, 1998;4(Suppl 2):36
- 12 Wei XF, Cai YX. The dialectical diagnose of stomach cancer. *Shijie Huaren Xiaohua Zazhi*, 1993;1:31-32
- 13 Ruan CC, Chen YH, Zhang ZQ. Drinking water and liver cancer. *Shijie Huaren Xiaohua Zazhi*, 1997;3:47
- 14 Liue, Zhang QN, Li WG. Effect of various drinking water on human micronucleus frequency in high risk population of PHC. *World J Gastroentero*, 1998;4:183
- 15 Woman HJ, Lin F, Mamiya N, Mustacchia PJ. Molecular biology and the

- diagnosis and treatment of liver diseases. *World J Gastroentero*, 1998;4:185
- 16 Wang GT, Tang ZY, Wu Z, Zhu FL. The study on the relationship between 141 patients of liver disease and trice elements. *Shijie Huaren Xiaohua Zazhi*, 1993;1:134-136
- 17 Ci ZC. Liver disease and the metabolism of Ca and P. *Shijie Huaren Xiaohua Zazhi*, 1996;4:1-2
- 18 Liu HQ, Ren CY, Jia LS, Yao XX, Ren XL. Effects of acute hepatic dam age on natriuresis and water excretion after acute normal saline loading in rats. *Shijie Huaren Xiaohua Zazhi*, 1996;4:176-178
- 19 Cai JM, Zheng XL, Luo CJ, Gao JG, Cheng TM. The characteristics of D NA repair synthesis induced by DNA polymerase β in hepatoma cells after γ rays irradiation. *Shijie Huaren Xiaohua Zazhi*, 1997;5:705
- 20 Xiao WH, Liu WW, Liu YY, Li Z. Control cancer gene p53 mutate of He patoma cells cancer. *Shijie Huaren Xiaohua Zazhi*, 1997;5:573
- 21 Du QS, Fang DC, Luo YH, Lu Y, Liu WW. The study on N ras gene mutate in primary liver cancer. *Shijie Huaren Xiaohua Zazhi*, 1997;5:650
- 22 Liu QF, Lou D, Shu JJ, Gove C, Williams R. The study on HBV-infect and Nras gene mutate of liver cancer in Guangxi Province. *Shijie Huaren Xiaohua Zazhi*, 1998;6:467
- 23 Lee JH, Ku JL, Park YJ, Lee Ku, Kim WH, Park JG. Establishment and characterization of four human hepatocellular carcinoma cell lines containing hepatitis B virus DNA. *World J Gastroentero*, 1999;5:2 89-295
- 24 Yakoob J, Hu GL, Fan XG, Zhang Z. Telomere, telomerase and digestive cancer. *World J Gastroentero*, 1999;5:334-337
- 25 Sun JJ, Zhou XD, Liu YK, Zhou G. Phase tissue intercellular adhesion molecule 1expression in nude mice human liver cancer metastasis model. *World J Gastroenterol*, 1998;4:314
- 26 Yang BH. The current situation of early phase diagnose and treatment in liver cancer in China. *Shijie Huaren Xiaohua Zazhi*, 1993;1:133
- 27 Wu MC. Clinical research advances in primary liver cancer. *World J Gastroentero*, 1998;4:471
- 28 Li ZQ. Traditional Chinese medicine for primary liver cancer. *World J Gastroentero*, 1998;4:360
- 29 Tang ZY. Schmid advances in clinical research of hepatocellular carc inoma in China. *World J Gastroentero*, 1998;4(Suppl 2):4
- 30 Tang CY. Clinical research advances in liver cancer, China. *Shijie Huaren Xiaohua Zazhi*, 1998;6:1013
- 31 Gu GW, Zhou HG. Chinese medicine to prevent liver cancer. *Shijie Huaren Xiaohua Zazhi*, 1999;7:80-81
- 32 Zou HG, Gu GW. Compound of vitamin to prevent liver cancer. *Shijie Huaren Xiaohua Zazhi*, 1999;7:82-83

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