ORIGINAL RESEARCH

Urban-Rural Disparity in *Helicobacter Pylori* Infection–Related Upper Gastrointestinal Cancer in China and the Decreasing Trend in Parallel with Socioeconomic Development and Urbanization in an Endemic Area

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Abstract

BACKGROUND Globally China has the largest urban-rural disparity in socioeconomic development, and the urban-rural difference in upper gastrointestinal cancer (UGIC) is similar to the difference between developed and developing countries.

OBJECTIVES To describe urban-rural disparity in UGIC and to emphasize prevention by socioeconomic development and urbanization in China.

METHODS Age-standardized incidence rates (ASRs) of cancers in 2012 were compared between urban Shijiazhuang city and rural Shexian County, and trends from 2000-2015 in Shexian County were analyzed.

FINDINGS Compared with urban Shijiazhuang city, the ASR of gastroesophageal cancers in rural Shexian County was 5.3 times higher in men (234.1 vs 44.2/100,000, $P < .01$) and 9.1 times higher in women (107.7 vs 11.8/100,000, $P < .01$). This rural-urban disparity in UGIC is associated with differences in socioeconomic development in annual gross domestic product (GDP) per capita of US\$2700 vs US\$6965, in urbanization rate of 48% vs 100%, and in adult *Helicobacter pylori* infection prevalence of 75% vs 50%. From 2000-2015, the GDP per capita in Shexian County increased from US\$860 to US\$3000, urbanization rate increased from 22.4% to 54.8%, and prevalence of *H pylori* infection among 3- to 10-year-old children decreased from 60% to 46.1% ($P < .01$). Meanwhile, the biennial ASR of esophagogastric cancer decreased 42% in men, from 313.5 to 182.1 per 100,000 ($P < .01$), and 57% in women, from 188.6 to 80.4 per 100,000 ($P = .00$). However, lung, colorectal, and gallbladder cancers and leukemia in both sexes and breast, ovary, thyroid, and kidney cancer in women increased significantly. Despite this offset, ASR of all cancers combined decreased 25% in men (from 378.2 to 283.0/100,000, $P = .00$) and 19% in women (from 238.5 to 193.6/100,000, $P = .00$).

CONCLUSIONS Urban-rural disparity in UGIC is related to inequity in socioeconomic development. Economic growth and urbanization is effective for prevention in endemic regions in China and should be a policy priority.

INTRODUCTION

In China, the former Soviet Union–style central economy planning system implemented from 1949 until 1980 had invested more in urban industry development than in rural living condition improvement. This has created multidimensional urban-rural inequalities in social determinants of health. According to the National Health Service Survey 2003, safe drinking water is available to 96% of the population of large cities but to <30% in poor rural areas. Ninety percent of residents in large cities have sanitation toilets, compared with <10% in poor rural areas.[1] Although economic reform has lifted millions of people out of extreme poverty in recent decades, the urban-rural income gap has widened, with the rural residents having an annual average per capita disposable income less than a third of urban residents in 2010 (US$898 vs US$2900).[2] These inequities are associated with significant differences in prevalence of *Helicobacter pylori* infection. As reported by a nationwide collaborative survey in China between 2002-2004, the prevalence of *H pylori* infection among rural and urban residents was 73.4% vs 65.4% ($P < .01$).[3] A more recent systematic review reported that the mean prevalence of *H pylori* infection was 66% for rural Chinese populations and 47% for urban Chinese populations.[4] Because *H pylori* infection has been established as the most important carcinogen of upper gastrointestinal cancer (UGIC),[5] a huge urban-rural disparity in *H pylori* infection–related cancers has been reported. For example, in China, although the age of rural populations was significantly younger and the population numbered 149.1 million less than the urban population by the middle of 2015 (611,060,000 vs 760,160,000),[6] the numbers of newly diagnosed esophageal and gastric cancer cases in 2015, as estimated by the Chinese National Cancer Registry (CNCR), were 3 and 2 times more among rural than among urban populations (364,100 vs 113,800 and 444,000 vs 235,200, respectively).[7] The urban-rural disparities in these *H pylori* infection–related cancers are significantly larger than that in all cancers combined, which was 213.6 vs 191.5 per 100,000.[7] CNCR also estimated that the 5-year relative survival for new cancer cases diagnosed between 2003 and 2005 in rural China was about half that of their urban counterparts for all cancers combined (21.8% vs 39.5%), because of a scarcity of medical resources for early diagnosis and adequate treatment.[8] Despite such grave social inequities, specific policy is lacking. Using age-standardized incidence rates by population-based tumor registration, this paper describes the urban-rural disparity in *H pylori* infection–related cancers in relation to unfair distribution of social determinants of health and examines the hypothesis that a decreasing trend of these cancers is associated with socioeconomic development and urbanization in an endemic region. Our aim is to emphasize the role of socioeconomic development among disadvantaged populations and make it a policy priority.

MATERIALS AND METHODS

Shexian County. Shexian County of Hebei Province is located 250 km southwest of Shijiazhuang city in the Taihang Mountain range, from 36° 17' to 36° 55' north latitude (Supplementary Fig. 1 in the online version at doi:10.1016/j.aogh.2017.09.004). Its population was 408,995 in 2012. It is a northern neighbor of Linxian County and a northwestern neighbor of Cixian County. All 3 counties have been noted for endemic rates of esophagogastric cancers.[9] Shexian consists of a county town and 580 villages. The economy of the county town relies on employment in the industry of power generating and steel making, agricultural product refinery, food manufacture, and tourism, and the rural population is engaged in growing rice, wheat, persimmon, Chinese prickly ash, and walnut. A quarter of the Shexian population, mainly young or middle-aged villagers, move between the village and the county town doing seasonal jobs. Diet in Shexian consists of a self-made staple foods of rice or steamed buns flavored by dishes of vegetables, pork, or eggs. Physical activities for villagers mean manual labor. But in the county town, people aged 60 or older walk or jog in the morning or evening.

As in most of China, health care in Shexian has been hospital centered. From 1949 until 2010, only government or public employees were protected by public medical insurance programs. For villagers, only basic medicine was provided free of charge by a rural corporative medical program.

Shijiazhuang City. Shijiazhuang is the capital city of Hebei Province, located 270 km south of Peking at the cross point of the north-south–bound Peking-Wuhan railway and the east-west–bound Dezhou-Taiyuan railway, at the foot of Taihang Mountain. The registered urban population in 2012 was 2,374,827. Shijiazhuang was not a city before 1953. It used to consist of several dozen villages. Its urbanization began as late as 1953, when it was chosen by the Chinese central government as the capital city of Hebei Province and as one of the cities with development priority during the first national 5-year program (1953-1957). During implementation of the program, the North China Pharmaceutical Corporation, which is the biggest antibiotic factory in Asia, and 5 modern textile plants were established in Shijiazhuang city. In 60 years, its registered urban population increased from 182,188 in 1953 to 2,374,827 in 2012. In 2012 the gross domestic product (GDP) per capita of Shijiazhuang city was US$6964.80, ranking 119th among the 150 Chinese cities with a GDP higher than the average of US$6102 out of a total of 293 prefecture-level cities.[10]

Cancer Registration in Shexian County and Shijiazhuang City. Population-based cancer registration was established in Shexian County in 1999 and in Shijiazhuang City in 2011, under the agreement of the Chinese National Cancer Registration Center and International Association of Cancer Registration (IACR). The 2 registries are run by the same team according to the principles of the IACR. The Ministry of Health of China provides a running budget. Cancer diagnoses are reported to registries from multiple sources, including local hospitals and community health centers, as well as the Urban Resident Basic Medical Insurance program and the New Rural Cooperative Medical Scheme, both of which are public insurance programs gradually established after the severe acute respiratory syndrome epidemic in 2003 with universal coverage of local registered urban or rural residents achieved by 2010. Data quality of cancer registration is assessed annually by CNCR before publication. On July 21, 2017, the incidence data of Shexian Cancer Registry for 2008-2012 were accepted by IACR for inclusion in the Cancer Incidence in 5 Continents Vol. XI.

Surveillance on the Prevalence of *H Pylori* Infection among Children Aged 3-10 Years in Shexian County From 2000-2015 as an Indication of Improved Sanitation Associated with Socioeconomic Development and Urbanization. To examine the effect of improved sanitation associated with socioeconomic development and urbanization between 2000 and 2015 on the prevalence of *H pylori* infection, we surveyed the prevalence of *H pylori* infection among a random sample of children aged 3-10 years in 2000 and 2015, which may serve as a more sensitive outcome indicator than adult prevalence. The prevalence of infection was assessed by ^{13}C urea breath test. Sampling was made by 1/100 sampling from the register book of all Shexian preschool and school children aged 3-10 years edited by the Shexian Department of Education Administration. If the sampled child could not be found or refused, a nearby child was invited. Administration of the ^{13}C-labeled urea pill, collection of the breath sample, and measurement of the ^{13}C-labeled CO_2 in the collected breath sample were performed by X.D.W., D.G.W., Y.Y., Y.T.C., and G.Y.W.

Statistical Methods. Gender- and age-specific cancer incidence rates were calculated, and the Segi standard world population (modified by Doll) was used to calculate age-standardized incidence rates (ASRs).[11] ASRs of major cancers were compared between Shijiazhuang and Shexian and the difference was tested by the approximate method.[12] The trends of biennial ASR of cancer in Shexian between 2000 and 2015 were analyzed using Join Point Analysis 4.2.0.2.[13] The study was approved by the Institutional Ethics Review Board of 4th Hospital of Hebei Medical University.

RESULTS

Contrasting Cancer Pattern between Rural Shexian County and Urban Shijiazhuang City in 2012. Although the population age distribution was younger in rural Shexian than in urban Shijiazhuang (Supplementary Fig. 2 in the online version at doi:10.1016/j.aogh.2017.09.004), the former had a crude incidence rate of all cancers combined that was significantly higher in both men (359.5 vs 269.1/100,000, $P < .01$) and women (274.2 vs 207.6/100,000, $P < .01$) (Table 1). The rural excess in ASR of all cancers combined was even larger, 1.7 times higher in men (325.2 and 187.5, $P < .01$) and 1.5 times higher in women (230.7 and 150.4, $P < .01$) (Table 1). The significantly higher incidence rate of all cancers combined in Shexian County was caused by clustering of esophagogastric cancer, which accounts for 72% and 46% of all cancer in men and women, respectively (Fig. 1). The ASR of esophagogastric cancer alone in Shexian is higher than that of all cancers combined in Shijiazhuang in men (234.1 vs 187.5/100,000), although not in women (107.7 vs 150.4/100,000). Gastric or esophageal cancer has always been the first or the second most common
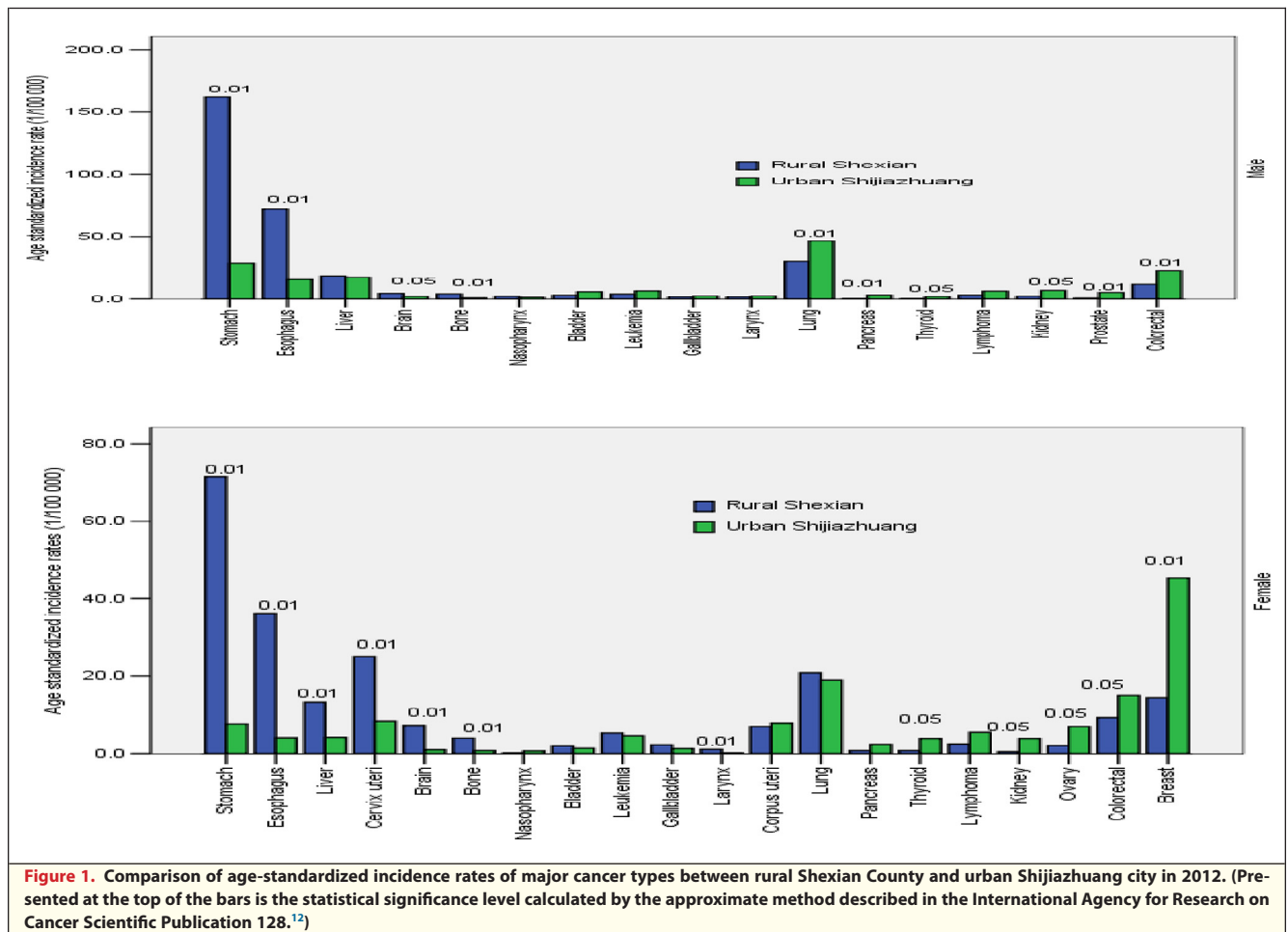
Table 1. Comparison of Age-Standardized Incidence Rates of Major Cancer Types Between Urban Shijiazhuang (USZ; Men 1,157,390, Women 1,217,437) and Rural Shexian County (RSX; Men 211,579, Women 197,416) in 2012

Tumor site	Cases USZ	Cases RSX	Ranks USZ	Ranks RSX	Incidence rate (1/10^5) USZ	Incidence rate (1/10^5) RSX	Percentage (%) USZ	Percentage (%) RSX	ASR World (1/10^5) USZ	ASR World (1/10^5) RSX	P*
Male											
Lung (C33-34)	786	72	1	3	67.9	33.4	25.2	9.3	46.5	30.0	<.01
Stomach (C16)	469	389	2	1	40.5	180.4	15.1	50.2	28.5	162.0	<.01
Colorectal (C18-21)	381	29	3	5	32.9	13.5	12.2	3.7	22.7	11.8	<.01
Liver (C22)	279	46	4	4	24.1	21.3	9.0	5.9	17.4	18.5	
Esophagus (C15)	266	172	5	2	23.0	79.8	8.5	22.2	15.7	72.1	<.01
Kidney (C64-66,68)	114	5	6	8	9.9	2.3	3.7	0.6	6.9	2.2	<.05
Prostate (C61)	106	2	7	10	9.2	0.9	3.4	0.3	5.3	0.7	<.01
Leukemia (C91-95)	104	9	8	6	9.0	4.2	3.3	1.2	6.5	4.0	
Bladder (C67)	101	5	9	8	8.7	2.3	3.2	0.6	5.8	3.0	
Lymphoma (C81-85,88,90,96)	100	8	10	7	8.6	3.7	3.2	1.0	6.3	3.1	
Pancreas (C25)	50	0	11	11	4.3	0.0	1.6	0.0	3.1	0.1	<.01
Larynx (C32)	39	4	12	9	3.4	1.9	1.3	0.5	2.4	1.6	
Gallbladder (C23-24)	38	4	13	9	3.3	1.9	1.2	0.5	2.4	1.6	
Thyroid (C73)	29	0	14	11	2.5	0.0	0.9	0.0	1.9	0.1	<.05
Brain (C70-72)	27	9	15	6	2.3	4.2	0.9	1.2	2.0	4.5	<.05
Nasopharynx (C11)	21	5	16	8	1.8	2.3	0.7	0.6	1.3	2.1	
Bone (C40-41)	14	9	17	6	1.2	4.2	0.4	1.2	0.9	4.1	<.01
All Male Cancer	3114	775			269.1	359.5	100.0	100.0	187.5	325.2	<.01
Female											
Breast (C50)	726	36	1	5	59.6	18.1	28.7	6.6	45.3	14.4	<.01
Lung (C33-34)	346	46	2	4	28.4	23.1	13.7	8.4	19.0	20.8	
Colorectal (C18-21)	260	22	3	7	21.4	11.0	10.3	4.0	15.0	9.3	<.05
Stomach (C16)	137	166	4	1	11.3	83.2	5.4	30.3	7.7	71.5	<.01
Cervix (C53)	132	64	5	3	10.8	32.1	5.2	11.7	8.4	25.0	<.01
Corpus uteri (C54)	126	18	6	8	10.4	9.0	5.0	3.3	7.9	7.0	
Ovary (C56)	112	6	7	11	9.2	3.0	4.4	1.1	7.0	2.1	<.05
Lymphoma (C81-85,88,90,96)	93	6	8	11	7.6	3.0	3.7	1.1	5.5	2.5	
Esophagus (C15)	79	86	9	2	6.5	43.1	3.1	15.7	4.1	36.2	<.01
Liver (C22)	74	30	10	6	6.1	15.0	2.9	5.5	4.2	13.3	<.01
Leukemia (C91-95)	66	8	11	10	5.4	4.0	2.6	1.5	4.6	5.3	
Thyroid (C73)	60	2	12	15	4.9	1.0	2.4	0.4	3.9	0.8	<.05
Kidney (C64-66,68)	60	1	12	16	4.9	0.5	2.4	0.2	3.9	0.5	<.05
Pancreas (C25)	44	2	13	15	3.6	1.0	1.7	0.4	2.4	0.8	
Bladder (C67)	21	4	14	13	1.7	2.0	1.7	0.2	1.4	2.0	
Gallbladder (C23-24)	20	5	15	12	1.6	2.5	0.8	0.9	1.3	2.3	
Brain (C70-72)	12	18	16	8	1.0	9.0	0.5	3.3	1.0	7.3	<.01
Bone (C40-41)	11	9	17	9	0.9	4.5	0.4	1.6	0.8	4.0	<.01
Nasopharynx (C11)	9	0	18	17	0.7	0.0	0.4	0.0	0.7	0.0	
Larynx (C32)	1	3	19	14	0.1	1.5	0.0	0.5	0.1	1.1	<.01
All female cancer	2527	547			207.6	274.2	100.0	100.0	150.4	230.7	<.01

* By the approximate method for the comparison of incidence of a disease in 2 groups as described in Cancer Research Volume IV: Descriptive Epidemiology.[12]

cancer in Shexian. Compared with urban Shijiazhuang, the ASR of stomach cancer in rural Shexian is 5.7 times higher in men (162.0 vs 28.5/100,000, $P < .01$) and 9.3 times higher in women (71.5 vs 7.7/100,000, $P < .01$); esophageal cancer is 4.6 times higher in men (72.1 vs 15.7/100,000, $P < .01$) and 8.8 times higher in women (36.2 vs 4.1/100,000, $P < .01$); liver cancer is 3.2 times higher in women (13.3 vs 4.2/100,000, $P < .01$). In addition to UGIC, the ASR of cervical cancer is 3 times higher among Shexian than Shijiazhuang women (25.0 vs 8.4/100,000, $P < .01$). All 4 of these are infection–related cancers associated with disadvantaged socioeconomic development.

Figure 1. Comparison of age-standardized incidence rates of major cancer types between rural Shexian County and urban Shijiazhuang city in 2012. (Presented at the top of the bars is the statistical significance level calculated by the approximate method described in the International Agency for Research on Cancer Scientific Publication 128.[12])

The predominance of UGIC was no longer identified 250 km away in Shijiazhuang city. The proportion of esophagogastric cancer was only 24% in men and 9% in women, contrasting with the corresponding percentage of 72% and 46% in Shexian County. On the contrary, lung and breast cancers became the most commonly diagnosed cancers in men and women in Shijiazhuang city. The ASR of lung cancer in Shijiazhuang city was significantly higher than in rural Shexian in men (46.5 vs 30.0/100,000, $P < .01$), although not in women (19.0 vs 20.8/100,000), and the ASR of female breast cancer was more than 3 times higher in Shijiazhuang than in Shexian (45.3 vs 14.4/100,000, $P < .01$). After lung and breast cancer, significant urban excess was also noted with colorectal (22.7 vs 11.8/100,000, $P < .01$ in men and 15.0 vs 9.3/100,000, $P < .05$ in women), kidney (6.9 vs 2.2/100,000, $P < .05$ in men and 3.9 vs 0.5/100,000, $P < .05$ in women), pancreas (3.1 vs 0.1/100,000, $P < .01$ in men), thyroid (1.9 vs 0.1/100,000, $P < .05$ in men and 3.9 vs 0.8/100,000, $P < .05$ in women), prostate (5.3 vs 0.7/100,000, $P < .01$), and ovarian cancers (7.0 vs 2.1/100,000, $P < .05$).

Socioeconomic Development and Urbanization and the Changing Risk of Cancer From 2000-2015 in Rural Shexian County. Shexian has been a traditional rural agrarian county, but as is the case in most parts of eastern and central China, rapid socioeconomic development and urbanization has been taking place since 1978. From 2000 through 2015, the booming of real estate development has led the economy to rebalance from agricultural and heavy industry toward services and tourism. As a result the annual net income of the Shexian people increased from US$600-US$1500 per person. Overall, the annual GDP per capita increased from US$860-US$3000.[14-17] Along with increasing income and market supply of manufactured food, a diet transition took place, with the staple starch food of steamed buns or rice formerly eaten gradually replaced by increasing proportions of animal food such as saturated fat, meat, eggs, and milk.

From 2000-2015, more than 100,000 young or middle-aged villagers had migrated from the villages to live and work in the county town. The proportion of urban residents increased from 22.4% (85,000/380,000) to 54.8% (230,000/420,000). In 16 years the urban population increased by 170%, with an annual increase of 10.7%. Because pipe water, flush toilets, and central sewage treatment systems are available in the county town, public hygiene and environmental sanitation are greatly improved.

In addition to rural-urban migration, in situ urbanization also has been in progress since 1978. Because water has been historically scarce in this mountainous land, a key act of in situ urbanization has been the construction of safe drinking water systems. Since the 1980s, a growing budget has been maintained by the government to improve drinking-water conditions, by drilling deep wells, often 400-500 meters underground, to tap underground water, or building up water purification systems in underground water resource–scarce areas. Consequently, water conditions for most people living in the mountainous county has been gradually improved: The percentage of people drinking rainwater has been reduced from 80% in the 1970s to 10% in 2010. Meanwhile, the prevalence of *H pylori* infection by ^{13}C urea breath test decreased significantly from 60% (240/400) to 46.1% (190/412) (χ^2 = 15.8, $P < .001$) among children aged 3-10 years.

Meanwhile, the county has experienced rapid population aging. The proportion of people aged 60 or older grew from 7.9% in 2000 to 13.9% in 2015.

Trends of Upper Gastrointestinal Cancer Versus Westernization-Related Cancers From 2000-2015 in Rural Shexian County. Incidence of UGIC decreased significantly in parallel with socioeconomic development and urbanization. As shown in Table 2 and Figure 2, between 2000 and 2015, the biennial ASR of stomach cancer decreased 33.7% from 196.1 to 130.1 per 100,000 among men (averaged biennial percent change (ABPC) = −3.4%, P = .00) and 59.5% from 114.5 to 46.4 per 100,000 among women (ABPC = −6.0%, P = .00); esophageal cancer decreased 55.7% from 117.4 to 52.0 per 100,000 in men (ABPC = −6.0%, P = .00) and 54.1% from 74.1 to 34.0 per 100,000 among women (ABPC = -5.5%, P = .00); liver cancer decreased 22.3% from 20.6 to 16.1 per 100,000 among men (ABPC = −2.4%, P = .20) and 55% from 13.1 to 5.9 per 100,000 among women (ABPC = −7.1%, P = .00). In addition to UGIC, larynx cancer also decreased significantly from 5.5 to 1.9 per 100,000 among men (ABPC =−4.4%, P = .00) and from 1.4 to 0.5 per 100,000 among

women (ABPC = −10.0%, P = .00). As shown in Figure 3, the decrease in incidence from 2000-2015 has been evenly distributed across all age groups for both esophageal and stomach cancer in Shexian County.

In contrast, there have been small but significant increases in the ASR of westernization-related cancers, including the cancer of the lung, colorectal cancer, gallbladder cancer, and leukemia in both sexes and breast, ovarian, thyroid, and kidney cancer in women (Table 2, Fig. 2), although the absolute increase in these cancers is far less compared with the decrease in UGIC. Of these increases, the ABPC among men was statistically significant for lung cancer (ABPC = +2.8%, P = .05), colorectal cancer (ABPC = +6.0%, P = .00), leukemia (ABPC = +7.4%, $P < .00$), and gallbladder cancer (ABPC = +28.7%, P = .00), and the ABPC among women was significant for lung cancer (ABPC = +3.4%, P = .00), colorectal cancer (ABPC = +5.5%, P = .00), breast (ABPC = +10.2%, P = .00), leukemia (ABPC = +7.9%, $P < .00$), gallbladder cancer (ABPC = +15.6%, P = .00), bone carcinoma (ABPC = +24.5%, P = .00), kidney cancer (ABPC = +16.2%, P = .00), ovarian cancer (ABPC = +12.4%, P = .00), and thyroid cancer (ABPC = +23.4%, P = .00).

DISCUSSION

Socioeconomic status is one of the most important determinants of cancer distribution.[18] In developed countries, because the difference in urban-rural socioeconomic development is limited, the urban-rural disparity in cancer is small.[18] But in China, urban-rural inequity in socioeconomic development is so large that the urban-rural difference in cancer distribution is similar to the difference between developed and developing countries.[7,8,19] In addition, an urban excess in overall cancer incidence is often found in western countries because of a surplus of industrial pollutants, population aging, and a more sedentary life-style[18]; but in China, the incidence rate of *H pylori* infection–related cancers associated with disadvantaged socioeconomic conditions are so high among the rural population that their overall cancer burden is higher than in urban population. On this point our finding is in agreement with that reported by Chen et al in 2016.[7]

Our study indicates a contrasting cancer pattern between a rural and a nearby urban setting (Fig. 1). In rural Shexian, a predominance of *H pylori* infection–related gastroesophageal cancers was noted, whereas in urban Shijiazhuang westernization-related cancers such as lung, colorectal, and female

Table 2. **Biennial Age-Standardized Incidence Rates of Major Cancer Sites Between 2000-2015 and Averaged Biennial Percent Change (ABPC) and Trends in Shexian County***
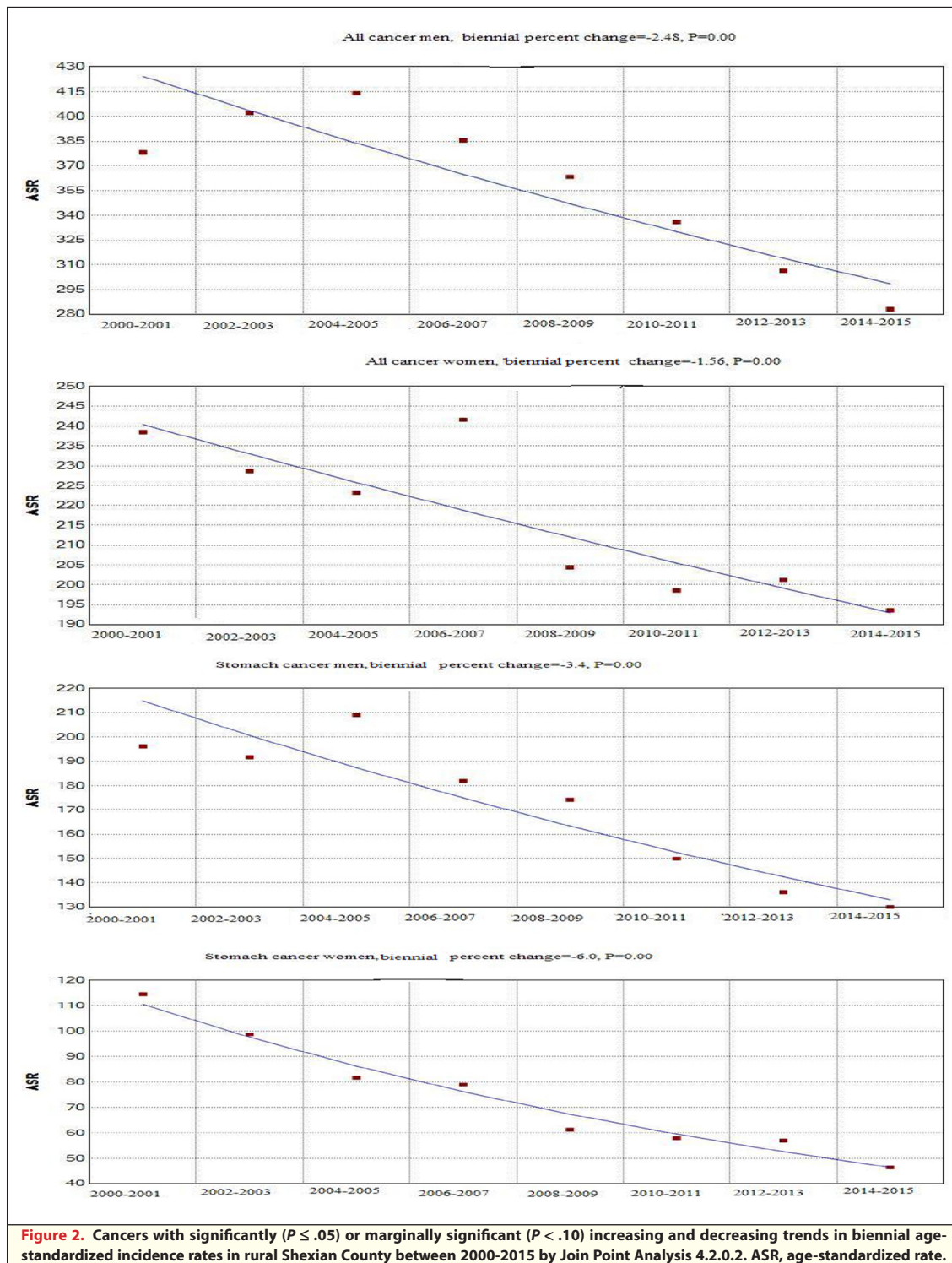
| Cancer Types (ICD-10) | Age-Standardized Incidence Rates (1/100,000) | | | | | | | | ABPC$_{1-8}$* | P |
	2000-2001	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	2014-2015		
Male										
All cancer	378.2	402.6	414.1	385.6	363.4	336.1	306.4	283.0	−2.5	<.00
Stomach (C16) 37.5%	196.1	191.8	209.0	181.9	174.2	150.0	136.1	130.1	−3.4	<.00
Esophagus (C15)	117.4	128.5	108.9	94.1	84.8	75.2	61.3	52.0	−6.0	<.00
Liver (C22)	20.6	25.5	28.5	33.0	24.1	23.6	20.8	16.0	−2.4	
Lung (C33-34)	15.9	24.6	32.3	32.6	29.5	28.3	31.6	34.7	2.8	<.05*
Colorectal (C18-21)	6.6	8.6	11.5	10.2	18.5	20.5	16.4	15.9	6.0	<.00
Larynx (C32)	5.5	3.8	2.7	4.2	3.6	4.0	2.9	1.9	−4.4	<.00
Brain (C70-72)	3.9	3.3	4.6	4.9	3.9	4.3	6.9	3.3	2.0	
Leukemia (C91-95)	2.8	4.3	2.1	3.8	3.9	5.2	5.9	7.7	7.4	<.00
Pancreas (C25)	1.9	0.9	0.7	1.6	2.4	2.5	2.0	3.4	6.5	
Bladder (C67)	0.6	2.1	3.0	2.8	3.7	2.1	3.0	2.3	0.4	
Lymphoma (C81-85,88,90,96)	1.6	1.9	3.5	3.8	3.2	4.3	3.3	2.9	3.0	
Bone (C40-41)	1.0	1.5	0.7	4.3	1.8	4.1	2.8	2.1	4.2	
Prostate (C61)	0.6	0.3	0.3	0.6	1.5	1.2	0.7	1.2	6.4	
Nasopharynx (C11)	0.4	0.6	1.1	1.3	0.8	2.3	1.4	0.5	0.4	
Kidney (C64-66,68)	0.2	0.3	2.1	1.3	1.3	1.3	2.1	2.9	9.0	
Thyroid (C73.9)	0.2	0.3	0.9	0.2	0.5	0.8	0.8	1.5	3.2	
Gallbladder (C23-24)	0.1	0.2	0.5	0.7	2.3	0.4	2.3	2.4	28.7	<.00
Female										
All cancer	238.5	228.6	223.2	241.6	204.4	198.6	201.2	193.6	−1.6	<.00
Stomach (C16)	114.5	98.7	81.7	79.0	61.3	57.9	57.0	46.4	−6.0	<.00
Esophagus (C15)	74.1	55.9	58.0	59.0	40.0	38.8	34.1	34.0	−5.5	<.00
Liver (C22)	13.1	17.6	15.1	14.6	10.4	9.0	6.3	5.9	−7.1	<.00
Cervix (C53)	11.3	19.9	19.4	28.3	27.2	28.4	27.7	23.5	2.2	
Lung (C33-34)	9.6	10.9	10.0	14.4	12.5	10.9	13.9	16.7	3.4	<.00
Colorectal (C18-21)	4.0	5.7	8.9	7.7	9.4	8.4	11.1	11.7	5.5	<.00
Breast (C50)	2.8	5.5	5.5	12.6	15.1	15.5	18.1	17.3	10.2	<.00
Leukemia (C91-95)	2.3	2.2	2.5	3.9	2.9	3.4	5.1	6.2	7.9	<.00
Larynx (C32)	1.4	1.5	2.3	1.6	0.5	0.7	0.7	0.5	−10.0	<.00
Uterus (C54-55)	0.8	3.2	4.2	3.6	5.8	2.5	4.7	4.6	7.8	
Bladder (C67)	0.3	0.7	0.9	2.1	0.5	0.2	1.6	0.9	5.7	
Pancreas (C25)	0.8	0.3	0.6	1.1	1.1	1.5	1.0	1.0	4.1	
Brain (C70-72)	0.7	0.6	4.1	2.8	3.3	5.6	4.9	5.2	18.5	
Lymphoma (C81-85,88,90,96)	1.0	2.6	2.2	2.1	2.8	2.3	1.8	2.3	1.2	
Gallbladder (C23-24)	0.3	0.6	0.4	0.4	1.4	2.1	1.4	2.7	15.6	<.00
Bone (C40-41)	0.1	0.9	1.6	1.2	1.0	1.0	1.4	0.7	24.5	<.00
Nasopharynx (C11)	0.2	0.6	0.6	0.9	0.3	0.5	0.6	0.6	0.10	
Kidney (C64-66,68)	0.0	0.2	0.6	0.9	0.7	0.9	1.7	2.4	16.2	<.00
Ovary (C56)	0.2	0.3	1.7	1.2	3.5	2.7	3.3	4.3	12.4	<.00
Thyroid (C73.9)	0.2	0.2	1.5	0.9	2.5	1.5	2.1	4.2	23.4	<.00

ICD-10, International Statistical Classification of Diseases and Related Health Problems.
* Averaged Biennial Percent Change by Join Point Analysis 4.2.0.2.

breast cancer prevail. Because Shexian County is an endemic area for UGIC, the urban-rural difference in esophagogastric cancer in our study is greater than that reported by a Chinese national analysis in 2012 between 74 urban and 119 rural registries.[20] However, the differences in westernization-related cancers are about the same. In the national study the urban-rural difference in colorectal cancer was 23.8 vs 16.1 in men and 17.1 vs 11.6 in women, and our results was 22.7 vs 11.8 in men and 15.0 vs 9.3 in women;

Figure 2. Cancers with significantly (*P* ≤ .05) or marginally significant (*P* < .10) increasing and decreasing trends in biennial age-standardized incidence rates in rural Shexian County between 2000-2015 by Join Point Analysis 4.2.0.2. ASR, age-standardized rate.

the national urban-rural difference for female breast cancer was 36.5 vs 23.1; our results was 45.3 vs 14.4. Our finding is also indirectly supported by the most recent national annual cancer incidence analysis, in-

cluding 255 cancer registries covering 226,494,490 populations for 2013. In the analysis a significantly negative correlation was found between ASR and urbanization rate (the proportion of nonagricultural
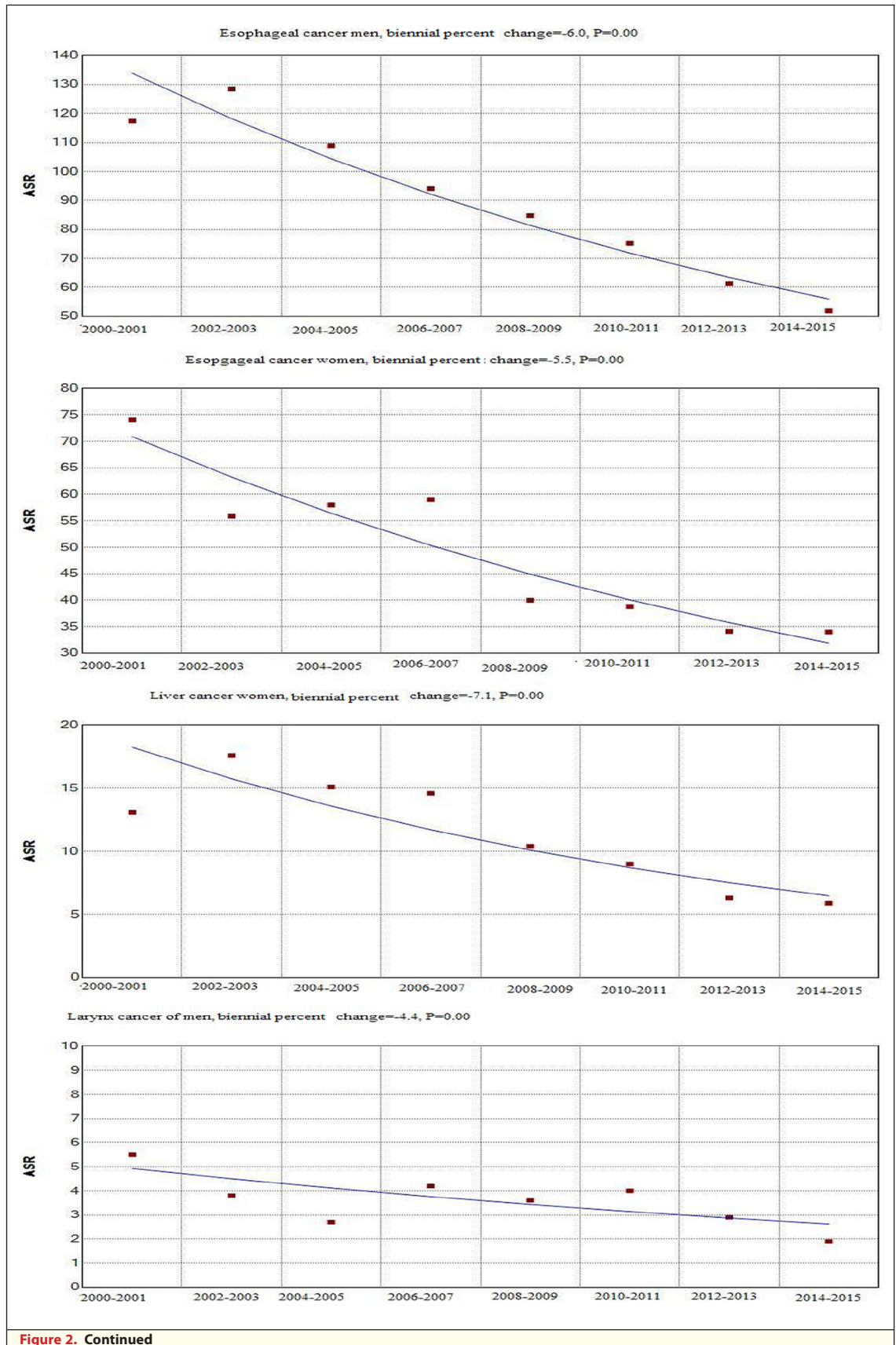
Figure 2. Continued
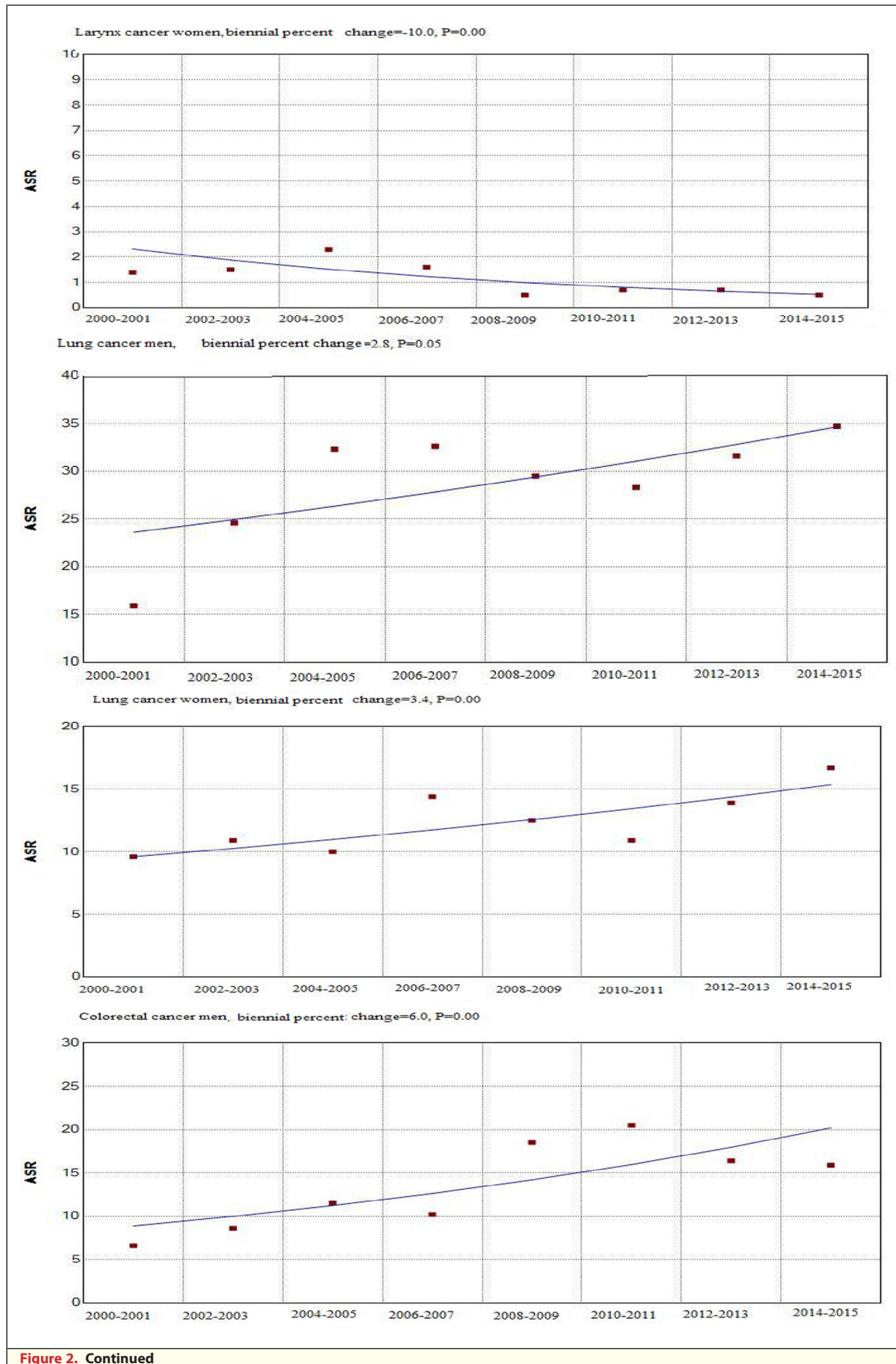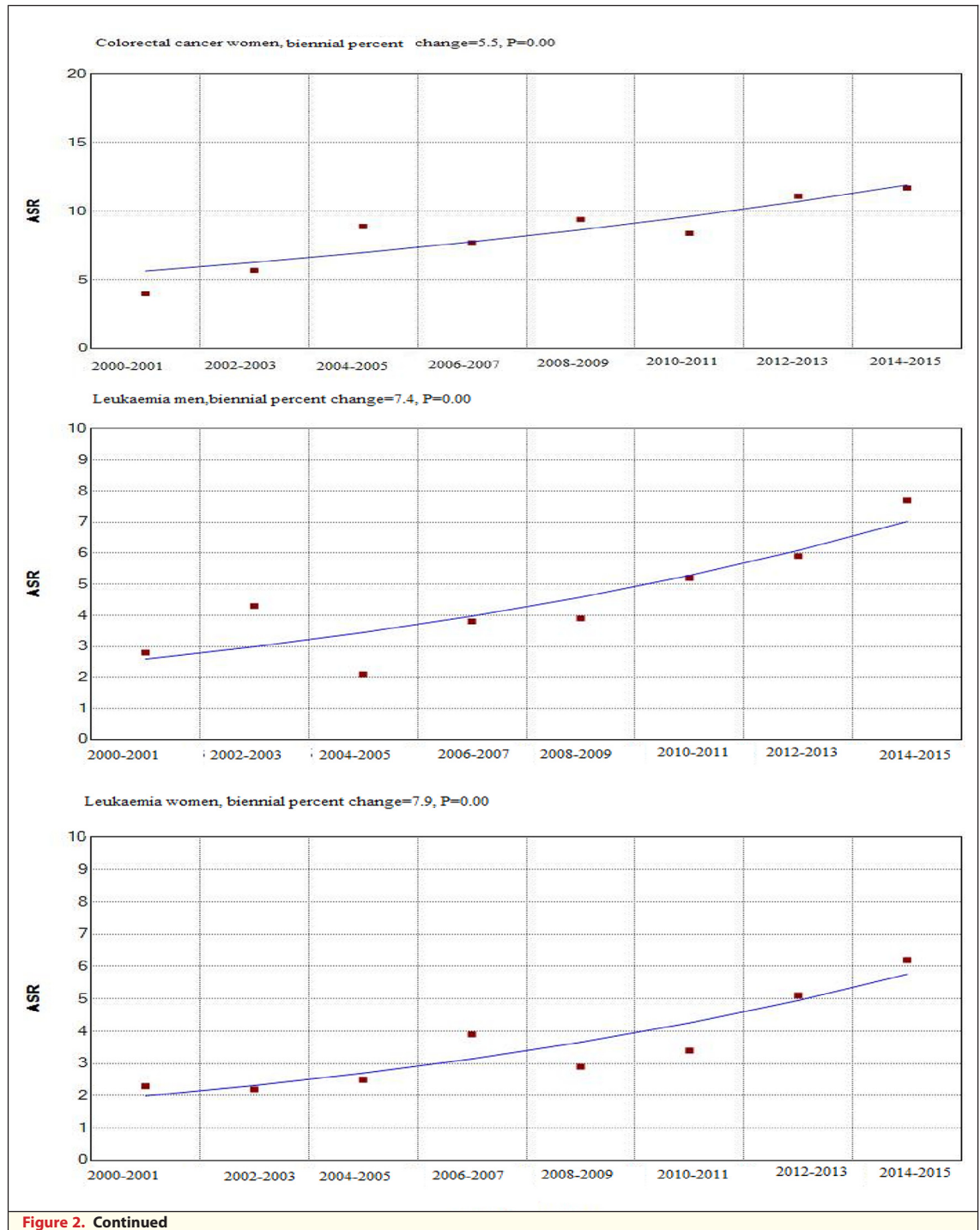
Figure 2. Continued

Figure 2. Continued

population) in both sexes for stomach, esophagus, and liver cancers and in women for cervix cancer, but a significant positive correlation was found in both sexes for colorectal cancer; in men for lymphoma, bladder, and pancreatic cancers; and in women for breast, uterus, and thyroid cancers and tumors of the central nervous system.[21]

Regarding the underlying causes of urban-rural disparity in UGIC, we think inequity in socioeconomic development contributes the most. Although
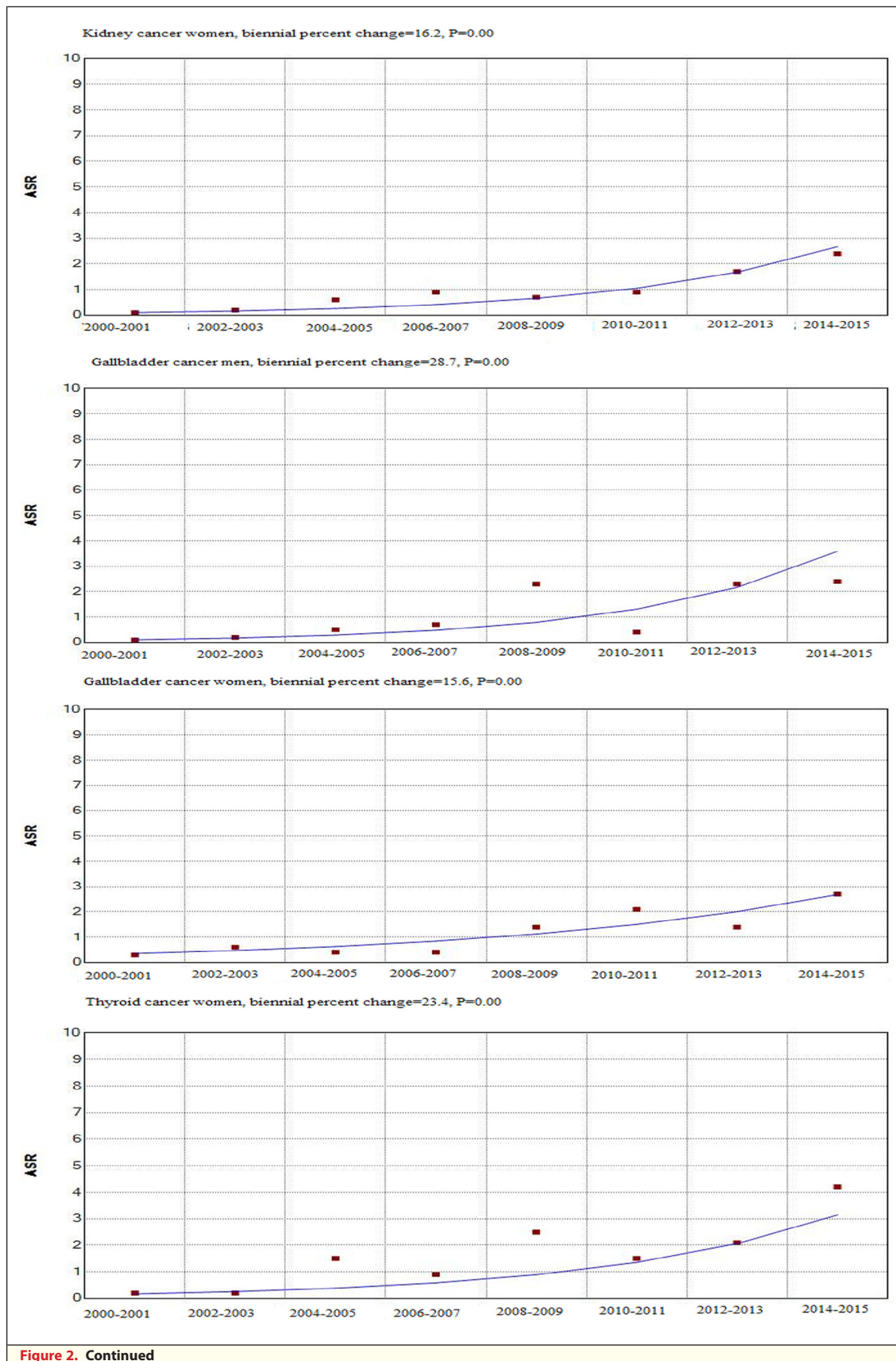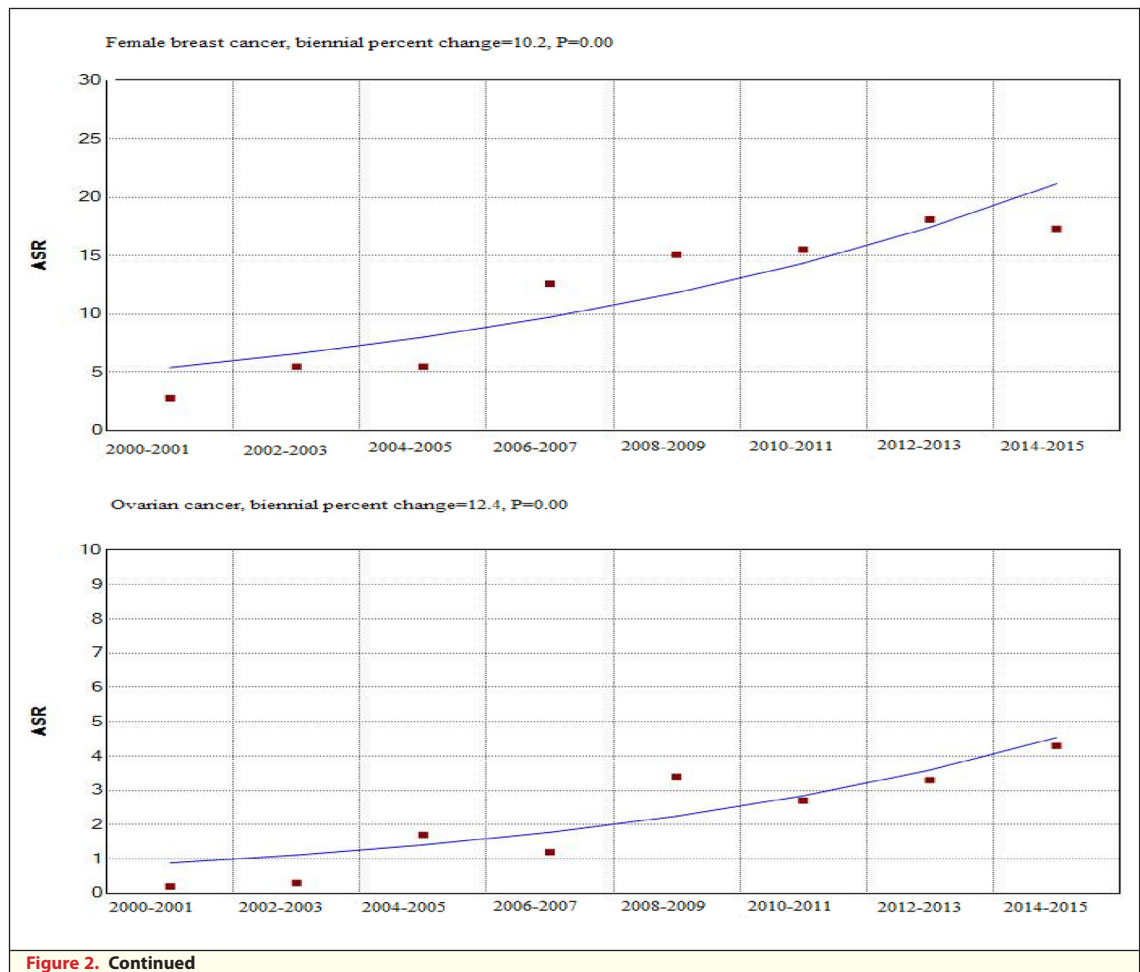
Kidney cancer women, biennial percent change=16.2, P=0.00

Gallbladder cancer men, biennial percent change=28.7, P=0.00

Gallbladder cancer women, biennial percent change=15.6, P=0.00

Thyroid cancer women, biennial percent change=23.4, P=0.00

Figure 2. Continued

Figure 2. **Continued**

developed from a similar rural agrarian background 60 years ago, with people in both areas being from the Han ethnic group descending from common ancestors living along the Taihang Mountain range for thousands of years, Shexian County is considerably underdeveloped compared with Shijiazhuang city. As shown in Table 3, in 2012 the GDP per capita was 2.6 times higher in urban Shijiazhuang than in Shexian county (US$6964.80 vs US$2700).[10,14-17] Regarding living conditions, all Shijiazhuang people were living in an urban setting, having access to chlorinated pipe water and sanitation toilets,[10] whereas 52% of Shexian people were living in rural villages, drinking unchlorinated well water, without sanitation toilets and sewage systems.[14-17] The prevalence of *H pylori* infection was significantly higher in Shexian than in Shijiazhuang city in 2000 (75% vs 42.2%,[22] *P* < .01).[10,14-17]

Inequity in social determinants of health between Shexian and Shijiazhuang city has existed since the

establishment of the People's Republic of China in 1949 under the Soviet Union–style central economy planning system (1949-1979), which emphasized urban industry investment over on rural living condition improvement, like the 1953-1957 first national 5-year development program choosing Shijiazhuang city as the site to build Asia's largest antibiotic factory and 5 modern textile plants. Under the centralized economic system, urban residents work in public factories or enterprises and received a monthly salary, whereas rural agricultural populations live on grains produced themselves. Preferred development of big cities brought about significant inequalities between large cities and rural counties in the form of employment, income, education, sanitation, health service infrastructure, and so on.

The prevalence of *H pylori* infection is closely associated with local socioeconomic development and sanitation, and this infection has been classified as a group 1 carcinogen for gastric cancer by the IARC.[5]
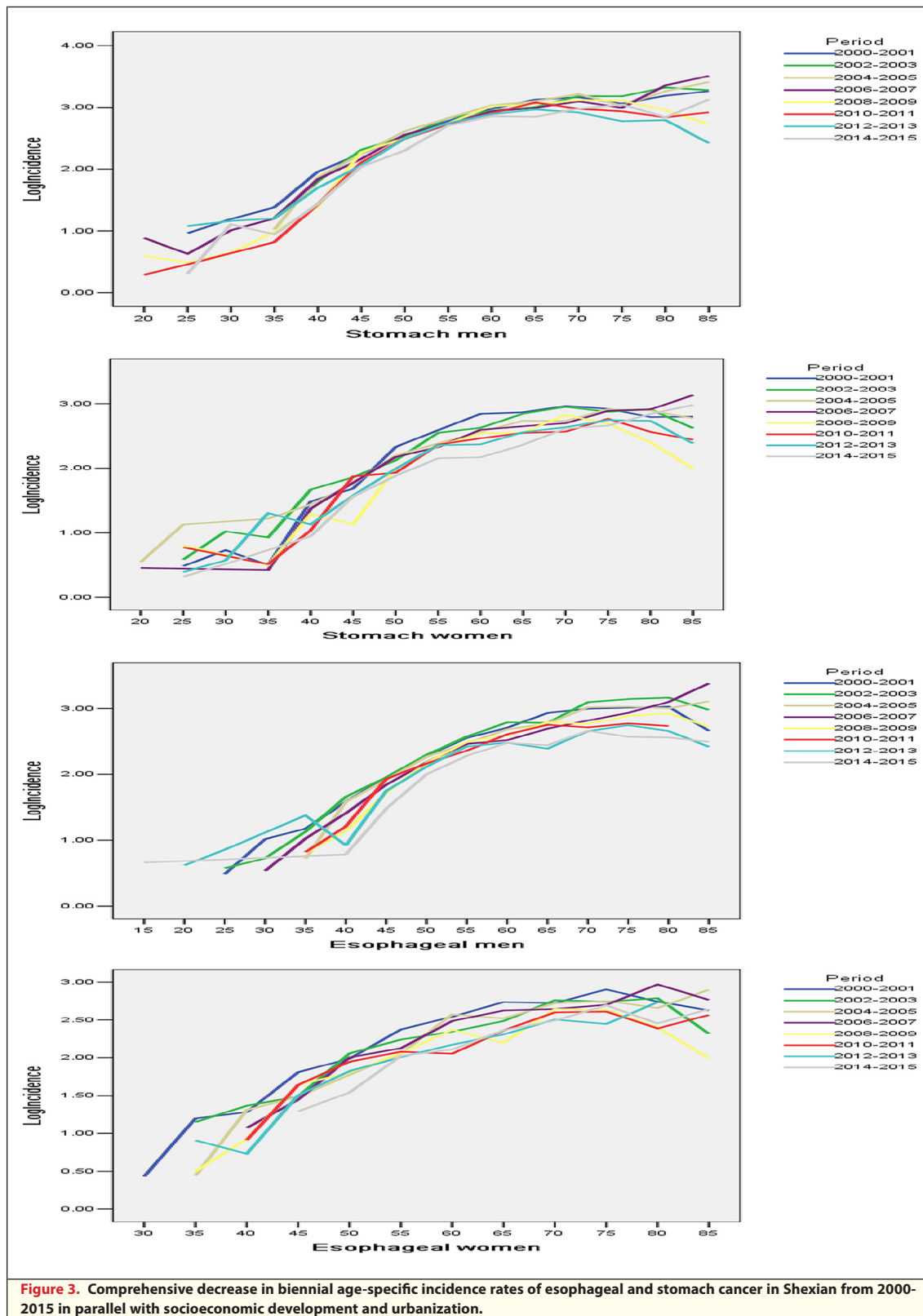
Figure 3. Comprehensive decrease in biennial age-specific incidence rates of esophageal and stomach cancer in Shexian from 2000-2015 in parallel with socioeconomic development and urbanization.

Table 3. Urban-Rural Disparity in Socioeconomic Development and Urbanization Between Shijiazhuang and Shexian*

Demographic	Urban Shijiazhuang	Rural Shexian
Population, 2012	2,374,827[10]	408,995[14-17]
% Urban population, 2012	100%[10]	48%[14-17]
Area	455.8 km²	1509 km²
Urban area (%)	455.8 km² (100%)[10]	91.8 km² (6.1%)[14-17]
Altitude (m above sea level)	30-100 m above sea level	1000 m above sea level
Latitude N	37°27′ ~ 38°47′	36°17′ ~ 36°55′
GDP per capita, 2012 (US$)	6964.8[10]	2700[14-17]
Annual net income per person, 2012 (US$)	3000[10]	1200[14-17]
Life expectancy, 2012 (y)	75[10]	71[14-17]
Chlorinated pipe water, 2015	100% population[10]	48% population[14-17]
Unchlorinated raining water, 2015	0%[10]	10% population[14-17]
Unchlorinated well water, 2015	0%[10]	42%[14-17]
Sewage system, 2015	100%[10]	48%[14-17]
Solid waste treatment, 2015	100%[10]	48%[14-17]
Prevalence of *Helicobacter pylori* infection in adults, 2000	42.2%[22]	75%[our data]
Household automobile, 2015	40%[10]	12%[14-17]
Household mobile phone, 2015	100%[10]	90%[14-17]
Household refrigerator, 2015	100%[10]	60%[14-17]
% Overweight (BMI >24 kg/m²) 18-69 y, men, 2004	43.7[22-24]	30.2[23]
% Overweight (BMI >24 kg/m²) 18-69 y, women, 2004	36.7[22-24]	35.4[23]
% Obese (BMI 28 kg/m²) 18-69 y, men, 2004	19.9[22-24]	14.5[23]
% Obese (BMI >28 kg/m²) 18-69 y, women, 2004	23.2[22-24]	17.1[23]

BMI, body mass index; GDP, gross domestic product.
* Reference number in the reference list containing the data.

Recently, viable *H pylori* has been identified in drinking water supplies by cultural and molecular techniques.[25] Using DNA fingerprint analyses, Karita et al[26] found that most *H pylori* transmission in Japan is waterborne and that infection is strongly associated with the duration of the history of drinking well water. In Shexian County, because of elevated altitude and other geographic and climate conditions, underground water resources have been scarce from ancient times. People traditionally rely on rainwater collected during the rainy season by "dry wells" or underground pits. The water is stored for use throughout the year. Because sewage systems are unavailable, water in the pits is easily polluted in the rainy season by human and animal waste. The water is infested with microorganisms. In addition, unaccustomed to the smell, people do not add disinfectant to the water. In the Linxian-Cixian-Shexian area, the prevalence of *H pylori* infection among adults has been reported as high as 80%-90%.[9] Epidemiologically, source of drinking water has been found to be significantly associated with the prevalence of *H pylori* infection.[9] In 2000 we found the prevalence of *H pylori* infection among a representative sample of Shexian children aged 3-10 years to be 60% by ^{13}C urea breathe test, and 50% of children who drank rainwater were infected by the age of 5 years. The age-specific prevalence of *H pylori* infection was significantly lower in pipe water than in rainwater drinking areas.

In addition to urban-rural disparity, trend analysis found the biennial ASR of esophagogastric cancer decreased 42% in men, from 313.5 per 100,000 in 2000-2001 to 182.1 per 100,000 in 2014-2015 (*P* < .01), and 57% in women, from 188.6 per 100,000 in 2000-2001 to 80.4 per 100,000 in 2014-2015 (*P* = .00). Regarding the causes of decreased UGIC, although many factors are involved, improvement in drinking water and sanitation by migration from villages to the county town and improved nutrition status may have contributed most significantly. Largely because of the building of drinking water network and sanitation toilets associated with urbanization, the prevalence of *H pylori* infection among children aged 3-10 years decreased significantly from 60% in 2000 to 46.1% in 2015 in Shexian County. This hypothesis is supported by a recent systematic review that found, on the basis of study time, that the prevalence of *H pylori* infection has been decreasing significantly in China from the 1980s to 2010s (*P* = .00).[4] Meanwhile, the incidence of stomach cancer has also been found to be decreasing in China.[4]

Zhou[27] reported that the stomach cancer ASR in China decreased from 1988-2007 by one-third in Peking (from 12.2 to 8.0/100,000), by 42% in Shanghai (from 25.2 to 14.5/100,000), by 24% in Linxian (from 79.1 to 60.3/100,000), and by 7% in Qidong. The largest absolute decrease (18.8/100,000) was noted in Linxian, which is a neighboring area of Shexian.

The UGIC preventive effects of socioeconomic development and urbanization may require a more integrated approach than reducing *H pylori* infection alone. Esophageal cancer is much less associated with *H pylori* infection than is gastric cancer,[5] but the incidence of this cancer also decreased significantly. Zhao et al[28] reported that from 1989-2008, the trends in ASR of esophageal cancer had been falling significantly in rural areas from 65.51 to 47.33 per 100,000 (AAPC = –2.1%, *P* < .05) in men, and from 36.89 to 25.02 per 100,000 (AAPC = –2.5%, *P* <.05) in women, but the decrease in urban areas was minimal, only from 14.01 to 13.02 per 100,000 (AAPC = –0.2% *P* > .05) in men and from 5.72 to 3.91 per 100,000 (AAPC = –1.5%, *P* > .05) in women.

It is surprising to witness a 42% and a 57% decrease in biennial ASR of esophagogastric cancer in men and women over a 16-year period in Shexian. The war on esophagogastric cancer in the Taihang Mountain high-risk region in China began as early as 1959 when the endemic of hard-swallowing disease attracted the attention of late primer Zhou Enlai.[29] Since then many scientists have visited the Linxian-Cixian-Shexian region to study esophagogastric cancer. Fighting the endemic disease has been placed on the top list of nationally supported championships. When Sino-US relations thawed in 1972 after Chairman Mao and US President Richard Nixon met, scientists from National Cancer Institute of the United States arrived in Linxian to carry out a population-based randomized nutrition intervention trial.[30] After decades of vigorous study, Chinese scientists concluded that high levels of nitroso compounds in drinking water, fungus infection in food, nutritional deficiencies, and genetic predisposition were implicated.[29] To control the endemic, mass movements such as drying grain and water in the sunshine, marketing of riboflavin-intensified salt, balloon cytology, and endoscopic screening have been successively tried. But never before has a systemic and persistent decrease in the incidence of esophagogastric cancer, similar to what we have just mentioned here, been reported, even in the Sino-US joint population-based intervention trial.[30] This example indicates that assigning causation of poverty-related UGIC solely to biological anomalies has not been wholly successful in accounting for all of the relevant factors in the pathogenesis and progression, because it has been the disadvantaged social conditions that predisposed the population to the onset of pathogenesis. In this sense, social inequalities are fundamental causes of the cancer. Social determinants of health can never be ignored or regarded as secondary to biological factors.

The effect of socioeconomic development is most pronounced when the population is severely disadvantaged. It is perhaps largely because of the disadvantaged socioeconomic status along the Taihang Mountain range in China that we got this opportunity to witness the strength of this connection. Indeed, rural populations in China have been severely and are continually being disadvantaged. The Chinese National Tumor Prevention and Control Office conducted a nationwide cancer mortality survey in 1974-1976.[29] It identified several dozen of rural areas with extraordinarily high mortality rates of specific cancer, such as the Linxian-Cixian-Shexian region for esophageal cancer, Qidong County in Jiangsu province for liver cancer, and Qingan County in Jiangxi province for cervical cancer, and so on. This is the origin of so-called high-risk cancer regions in China. Most of these high-risk regions are located in remote or geographically disadvantaged mountainous areas with low levels of socioeconomic development, and the prevalent cancer is often infection-based, poverty-related cancer. During the 1970s, when chemical carcinogenesis theory was popular, strenuous efforts were made by scholars to identify chemical carcinogens in the local environment, and mass movements were launched to curb the suspected carcinogens. However, cancer rates of these high-risk regions had little or only moderate reduction. Only after rapid socioeconomic development began in the 1980s did significant reductions begin to appear, suggesting that cancer control among marginal groups depends on social progress as a whole. This is particularly relevant to a country as vast and unevenly developed as China.

The effect of socioeconomic development on UGIC is sustainable. Even after a decade of progressive decline, the rural excess of esophagogastric cancer in 2012 in Shexian vs Shijiazhuang was still as large as 234.1 vs 44.2 per 100,000 in men (*P* < .01) and 107.7 vs 11.8 per 100,000 in women (*P* < .01), and this disparity was accompanied by a difference in GDP per capita of US$2700 vs US$6965, in an urbanization rate of 48% vs 100%, and in an adult *H pylori* infection prevalence of 75% vs 50% (Table 3).
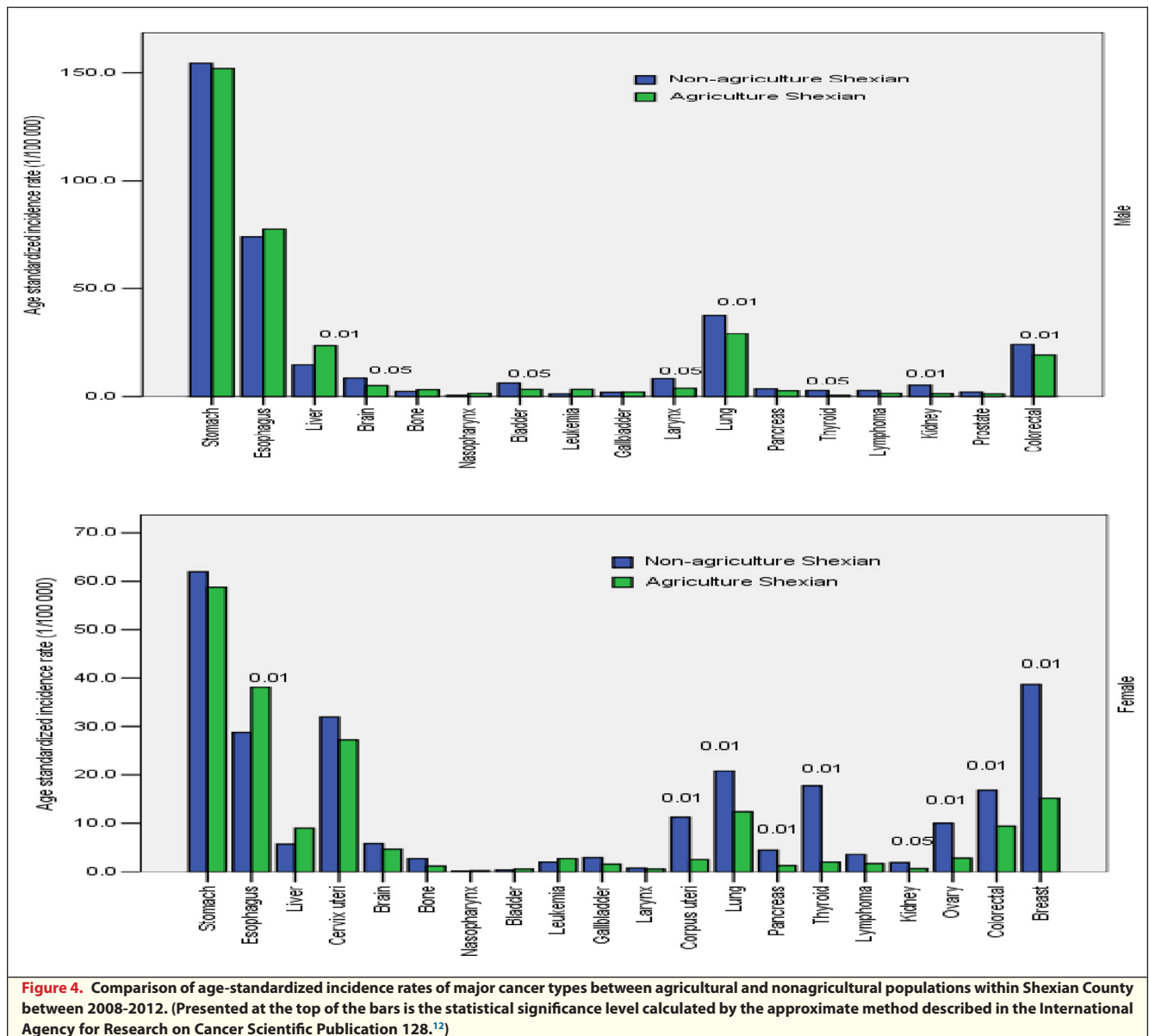
These local figures are in agreement with national data. According to the World Factbook published by the US Central Intelligence Agency, even as of 2015, 7% and 36.3% of rural population in China had unimproved drinking water and sanitation.[30] Although 55.6% of Chinese people are living in urban cities, people living in rural villages located far from cities generally have no access to chlorinated pipe water and sanitation toilets.[31] Therefore, there is a long road ahead of the Chinese government to reduce the urban-rural gap in distribution of socioeconomic determinants of health. If this goal is achieved, the so-called high-risk cancer regions may gradually disappear.

Reducing urban-rural inequality in social determinants of health can achieve more health outcomes than cancer in China. A 2006 review by the China Ministry of Health and several United Nations agencies found large inequalities in maternal and child mortality rates between the poorest rural counties and urban areas in 2004,[31] and more recent data indicate that the maternal mortality ratio in 2006 and newborn mortality rate in 2007-2008 in the poorest rural type IV counties both remained around 5 times higher than in urban areas.[32,33] Therefore, government commitments to social equity are bound to achieve extensive health outcomes.

Our study has a few merits. First, previous studies on urban-rural disparity in cancer in China often defined urban or rural population according to the administration level.[32] If it is from a prefecture-level city (eg, province-governing city) or a municipality, the population is considered urban; if it is from a county or county-level city, the registry is regarded as rural. However, in addition to the urban population, a typical Chinese prefecture-level city also includes several rural counties. When these people are misclassified as urban, the real urban-rural difference is diluted. This may explain the contradictory results previously reported in China.[7,32] Regarding this, we compared the ASR between a pure urban and a rural county. Second, although previous studies have noted declining trends in UGIC in parallel with socioeconomic development in Chinese high-risk areas,[27,28] synchronous increasing trends of urbanization-related cancer are rarely reported. Conversely, previous studies on cancer transition in developed countries usually focus on the increase in westernization-related cancer,[33,34] but the decrease in UGIC was less described, because such observations occur only among disadvantaged population in endemic regions. Along with socioeconomic development and urbanization in an endemic area, we noted contrasting trends of dramatically decreasing UGIC as opposed to steadily increasing westernization-related cancers over a 16-year period. Our study reveals a more realistic view regarding the effect of socioeconomic development and urbanization on cancer transition. Third, in Shexian County, cancer screening programs have never been implemented for lung, colorectal, female breast, and cervical cancers. With UGIC, <5% of the incident cases may be discovered by endoscopic screening. Therefore, an increasing trend in the incidence of westernization-related cancers and a decreasing trend in UGICs should not have been influenced by screening.

Our study has a limitation in study design. Ideally, urban-rural disparity in cancer incidence in Shexian should be assessed by comparing the ASR of the county town to that of the 580 villages, rather than choosing Shijiazhuang as the urban site for comparison, because the population would be more similar but with different urbanization rates. However, as we described earlier, socioeconomic disparity in China exists mainly between people in prefecture cities (province-governing cities) or higher-level cities and people in rural counties. Regarding urban-rural disparity between the county town and villages within a county, because the county town is usually not assigned a development priority under the central planning economic system and there are few factories or enterprises located there, the number of nonagricultural salary-receiving people is very small. Only government employees or workers in public sectors are paid with a monthly salary. For example, the total number of salary-receiving people and their families accounts for only 22% of the population (44,000/196,318) living in the county town of Shexian. The remaining 78% used to be registered rural residents. They have migrated into the county town in recent years. These "floating" people had been of agrarian origin and were still counted as rural residents in the Chinese National Census. We compared the ASR of cancers between nonagricultural and agricultural Shexian people for the time between 2008-2012, As shown in Figure 4, although the ASRs of westernization-related cancers are higher among nonagricultural than among agricultural people, with significant differences noted in women for breast, colorectal, lung, kidney, thyroid, pancreas, ovarian, and corpus uterine cancers, and in men for lung, colorectal, kidney, bladder, larynx, and thyroid cancers and brain tumors, the ASRs of UGIC cancers among agricultural people were not significantly higher than among nonagricultural populations, except for male liver and female esophageal cancer, suggesting agricultural and

Figure 4. Comparison of age-standardized incidence rates of major cancer types between agricultural and nonagricultural populations within Shexian County between 2008-2012. (Presented at the top of the bars is the statistical significance level calculated by the approximate method described in the International Agency for Research on Cancer Scientific Publication 128.[12])

nonagricultural populations in Shexian County have had similar levels of risk for UGIC under a common macroenvironment.

Another limitation may related to the representativeness of our findings. Because Shexian County has been an endemic region for esophagogastric cancers, the rural excess of UGIC may be much greater than that in other places in China. However, as described in the Introduction, although the age of the national rural population was significantly younger and the population size was considerably smaller than their national urban counterpart,[6] the newly diagnosed esophageal and gastric cancer cases were 3 and

2 times more common, respectively, among rural than among urban population in 2015.[7] In this aspect our estimate is representative of the rural excess of UGIC in China.

In summary, by noting urban-rural disparity in UGIC in relation to unfair distribution of social determinants of health, and the trends of deceasing UGIC in parallel with rapid socioeconomic development and urbanization, this paper hopes to call the attention of policymakers to the extraordinary urban-rural disparity in cancer in China and stress the role of socioeconomic development in tackling the rural excess of *H pylori* infection–related cancers.

SUPPLEMENTARY DATA

Supplementary figures accompaying this article can be found in the online version at doi:10.1016/j.aogh.2017.09.004.

REFERENCES

1. Ministry of Health. National Health Services Survey 2003. Beijing, China: Peking Union Medical University Press; 2004.
2. The Team of Collaboration of Helicobacter pylori research in China, Zhang WD, Hu FL, Xiao SD, Xu ZM. Prevalence of Helicobacter pylori infection in China. Mod Dig Interv 2010;15:265–70. [in Chinese].
3. Cheng LW, Tan L, Zhang L, et al. Chronic disease mortality in rural and urban residents in Hubei Province, China, 2008-2010. BMC Public Health 2013;13:713–22.
4. Nagy P, Johansson S, Molloy-Bland M. Systematic review of time trends in the prevalence of Helicobacter pylori infection in China and the USA. Gut Pathog 2016;8:8.
5. Schistosomes, liver flukes and Helicobacter pylori. IARC working group on the evaluation of carcinogenic risk to humans. Lyon, 7-14 June 1994. IARC Monogr Eval Carcinog Risks Hum 1994;61:1–241.
6. National Bureau of Statistics China. National data. Beijing, China: National Bureau of Statistics of the People's Republic of China. Available at: http://data.stats.gov.cn/easyquery.htm?cn=C01. Accessed March 20, 2017.
7. Chen WQ, Zheng RS, Baade P, et al. Cancer statistics in China 2015. CA Cancer J Clin 2016;66:115–32.
8. Zeng H, Zheng R, Guo Y, et al. Cancer survival in China, 2003-2005: a population-based study. Int J Cancer 2015;136:1921–30.
9. Wen DG, Zhang N, Shan B, Wang S. Helicobacter pylori infection may be implicated in the topography and geographic variation of upper gastrointestinal cancers in the Taihang mountain high-risk region in northern China. Helicobacter 2010;15:416–21.
10. Gross domestic production in Chinese cities in 2012. Development history of Shijiazhuang city. Available at: http://tieba.baidu.com/p/2417841476. Accessed October 21, 2017.
11. Doll R, Payne P, Waterhouse J, eds. Cancer Incidence in Five Continents: A Technical Report. Berlin, Germany: Springer-Verlag; 1966.
12. Esteve J, Benhamou E, Raymond L, eds. Techniques for the analysis of cancer risk. Cancer Research, Vol. IV. Descriptive Epidemiology. IARC Scientific Publications 128. Lyon, France: IARC Press; 1994:74–7.
13. Joinpoint Regression Program, Version 4.2.0.2. Washington, DC: Statistical Research and Applications Branch, National Cancer Institute; 2015. Available at: http://surveillance.gov/joinpoint. Accessed May 16, 2017.
14. Socioeconomic development in Shexian (2011-2015). Available at: http://www.docin.com/p-511099233.html. Accessed May 15, 2017 (in Chinese).
15. Website of Shexian County. Available at: http://shexian.hebnews.cn/node_26370.htm. Accessed October 21, 2017 (in Chinese).
16. China Shexian. Available at: http://www.sx.hd.gov.cn/sxxq/sxgk.htm. Accessed May 15, 2017 (in Chinese).
17. Shexian County Website. Available at: http://www.sxsxw.cn/. Accessed May 15, 2017 (in Chinese).
18. Doll R. Urban and rural factors in the etiology of cancer. Int J Cancer 1991;47:803–10.
19. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
20. Chen W, Zheng R, Zuo T, Zeng H, Zhang S, He J. National cancer incidence and mortality in China, 2012. Chin J Cancer Res 2016;28:1–11.
21. Chen W, Zheng R, Zhang S, et al. Cancer incidence and mortality in China in 2013: an analysis based on urbanization level. Chin J Cancer Res 2017;29:1–10.
22. Chen S, Zhang G, Li C, Zhao D. A survey on the Helicobacter pylori infection among Shijiazhuang residents with ^{13}C urea breathe test. Chinese Gen Med 2004;7:1241–3. [in Chinese].
23. Li H, Wang L, Zhu J, Zhang J, Zhang Z. An analysis of body mass parameters of urban and rural adults residents in Hebei province in 2004. Chin J Prev Contr Chron Non-Commun Dis 2006;14:250–3. [in Chinese].
24. Ma X, Ma W. Prevalence of risk factors of non-communicable chronic disease in a community in Shijiazhuang City. Hebei Med J 2010;32:3556–7. [in Chinese].
25. Santiago P, Moreno Y, Ferrus MA. Identification of viable Helicobacter pylori in drinking water supplies by cultural and molecular techniques. Helicobacter 2015;20:252–9.
26. Karita M, Teramukai S, Matsumoto S. Risk of Helicobacter pylori transmission from drinking well water is higher than that from infected intrafamilial members in Japan. Digest Dis Sci 2003;48:1062–7.
27. Zhou XN. Gastric cancer. In: Zhao P, Chen WQ, Kong LZ, eds. National Cancer Center, Disease Prevention Bureau of the Ministry of Health. Cancer incidence and mortality in China 2003-2007. Beijing: Military Medical Science Press; 2012: 54–65.
28. Zhao J, He YT, Zheng RS, Zhang SW, Chen WQ. Analysis of esophageal cancer time trends in China, 1989-2008. Asian Pacific J Cancer Prev 2012;13:4613–7.
29. Yang CS. Research on esophageal cancer in China: a review. Cancer Res 1980;40:2633–44.
30. Qiao YL, Dawsey SM, Kamangar F, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. J Natl Cancer Inst 2009;101:507–18.
31. World Factbook. Washington, DC: Central Intelligence Agency; 2017. Available at: https://www.cia.gov/library/publications/resources/the-world-factbook/geos/ch.html. Accessed May 3, 2017.
32. Wang N, Yuan YN, Zheng RS, et al. An analysis on difference of cancer incidence between urban and rural areas in China, 2009. China Cancer 2013;22:168–73. [in Chinese].
33. Vineis P, Wild CP. Global cancer patterns: causes and prevention. Lancet 2014;383:549–57.
34. Fidler M, Soerjomataram I, Bray F. A global view on cancer incidence and national levels of the Human Development Index. Int J Cancer 2016;139:2436–46.