

Geographic variations of predominantly hepatitis C virus associated male hepatocellular carcinoma townships in Taiwan: identification of potential high HCV endemic areas

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Abstract

Purpose The proportion of B-HCC cases in Taiwan has progressively decreased over the last 20 years. It was not really due to an overall decrease in B-HCC but due to an increase in HCV-related HCC. The identification of

potential HCV endemic areas in Taiwan has consequently become important.

Methods Data were collected retrospectively from eight Taiwan medical centers from 1981 to 2001, the geographical variations of male C-HCC townships in Taiwan were illustrated on maps. Goodness of fit was used to compare the anti-HCV prevalence in townships and cities, with the mean anti-HCV prevalence for Taiwan as a whole. Township-, city-, and county-specific prevalence of anti-HCV was presented as the median, ranges, and SMRs.

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Results Geographic variation can be analyzed in only 263 townships and cities. The maps were designed on the basis of different SMRs. The mean anti-HCV prevalence for male HCC patients in Taiwan was 31.9% (95% confidence interval: 30.7–33.0). Twenty-five townships distributed throughout central-western and south-western Taiwan have significantly higher prevalence ($P < 0.05$) (12 townships $SMR \geq 2$; 13 townships $1.5 \leq SMR < 2$). Twenty-two townships have significantly lower prevalence ($P < 0.05$) (6 townships $0.5 \leq SMR < 1$; 16 townships $SMR < 0.5$). Four different patterns of geographic variation in different counties were also noted and demonstrated.

Conclusion We successfully highlighted some potential high HCV endemic townships in Taiwan.

Keywords Hepatocellular carcinoma · Hepatitis B virus · Hepatitis C virus · Geographic variation Taiwan

Abbreviations

B + C-HCC	HBV-HCV-related HCC
B-HCC	HBV-related HCC
C-HCC	HCV-related HCC
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
NBNC-HCC	Non-HBV-non-HCV-related HCC
SMR	Standardized mortality ratio

Introduction

Chronic HBV and HCV infections are the two major etiologies of HCC in Taiwan [1]. To control HBV infection, a mass immunization program in Taiwan was launched on 1 July 1984, dramatically decreasing HBV carrier rates and childhood B-HCCs [2, 3]. The average annual incidence of HCC in children 6–14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990 and to 0.36 between 1990 and 1994 [3]. A further 80–85% decrease in HCC among Taiwanese adults can be expected within the next 3–4 decades [4]. There is still no effective vaccine to control HCV infection, but interferon-based combined treatment may cure the infection and thereby prevent later complications of HCCs [5]. We recently reported an increase in C-HCC in Taiwan over the last 20 years [6]. To gain better control of HCC in Taiwan, it is important to know the trends and gain a more detailed understanding of possible high HCV endemic areas to implement a cost-effective strategy to eradicate

HCV infection. The major viral etiology in male Taiwanese HCC patients is HBV [1, 6]. We have shown in an earlier study that HBsAg prevalence is more closely correlated with HCC mortality than anti-HCV prevalence among male subjects [7]. Hence, those areas having higher HCV-related male HCC patients could potentially be HCV endemic areas. Our previous report focused only on variations between different counties [6], but this variation was noted even among different townships within the same county. Using the same cohort, we further report on these townships.

Materials and methods

Patients and data collection

This is a retrospective multicentric study. The methods of patient enrollment and items recorded have been reported elsewhere [6, 7]. Eight medical centers participated in this study. Patient medical records from 1994 to 2001, with a diagnosis of *International Classification of Diseases, Ninth Revision*, code 155, were retrieved from the computer database of each hospital. Hepatologists and experienced, well-trained specialized nurses in each hospital then reviewed the medical records. Only patients diagnosed with HCC were enrolled. Each patient's name, medical record number, national citizen identification number, birthday, sex, residency, ZIP code, diagnostic criteria for HCC, definitive diagnosis date, HBsAg status, and anti-HCV status were recorded. We included patients from 1994 to 2001 for analysis because anti-HCV data were not universally available in Taiwan before 1994. Because patients might have made multiple visits to different hospitals, we used their national citizen identification numbers to eliminate any potentially duplicated records.

Diagnosis of HCC

We arbitrarily divided the diagnostic criteria of HCC from 1 to 4. Criterion 1 applied to a diagnosis of HCC verified by either pathology or cytology. Criterion 2 involved a diagnosis of HCC based on α -fetoprotein levels higher than 400 ng/ml, plus at least 1 imaging study that showed a typical HCC image. Criterion 3 was used for the diagnosis of HCC that did not fit criteria 1 or 2 initially but fit either criteria 1 or 2 during the follow-up period. Criterion 4 was used when the diagnosis of HCC was based on typical imaging studies but did not fit criteria 1–3. HCC patients with diagnostic criteria 1–3 were grouped in the definite diagnosis group. A total of 6,654 patients were enrolled for further analysis.

Data analysis

Foxpro® (Version 5.0) was used to create the database and SPSS® (Version 10.0) for statistical analysis. We used goodness of fit to compare the anti-HCV prevalence in townships and cities, with the mean anti-HCV prevalence for Taiwan as a whole. Statistical significance was defined as $P < 0.05$.

There are 16 counties in Taiwan’s main island and in total 356 townships and cities. Geographic variation could be analyzed in only 263 townships and cities; 93 other townships and cities could not be analyzed because of the number of patients enrolled was fewer than 5. The major cause of inadequate enrollment was due to the small population of these townships. Anti-HCV prevalence and 95% confidence intervals were calculated. Township-, city-, and county-specific prevalence of anti-HCV was presented as median, ranges, and SMRs. SMR (herein represented as relative proportion of HCV-associated HCC) is defined as anti-HCV prevalence of HCC patients of a certain city or county divided by anti-HCV prevalence of HCC patients in Taiwan as a whole.

Results

The mean anti-HCV prevalence for male HCC patients in Taiwan was 31.9% (95% confidence interval: 30.7–33.0). Figure 1 presents the geographic variation of different townships in Taiwan as a whole. Twenty-five townships located in different counties throughout central-western Taiwan and southwestern Taiwan have significantly higher prevalence rates (Table 1). $SMR \geq 2$ was noted in 12 townships, Lucao (Chiayi), Mailiao (Yunlin), Guantian (Tainan), Lioujia (Tainan), Zihguan (Kaohsiung), Jhuci (Chiayi), Siluo (Yunlin), Jhongpu (Chiayi), Liouying (Tainan), Gukeng (Yunlin), Singang (Chiayi), and Houli (Taichung), whereas $1.5 \leq SMR < 2$ was noted in 13 townships, Siaying (Tainan), Yuanli (Miaoli), Dongshih (Taichung), Yijhu (Chiayi), Lunbei (Yunlin), Minsyong (Chiayi), Sinying (Tainan), Chiayi City, Yanshuei (Tainan), Alian (Kaohsiung), West district (Taichung City), Caotun (Nantou), and Sihu (Changhua). Another 11 townships, Fangshan (Pingtung), Sanyi (Miaoli), Jiasian (Kaohsiung), Dapi (Yunlin), Baojhong (Yunlin), Sikou (Chiayi), Yuanchang (Yunlin), Sinyi (Keelung City), Dalin (Chiayi),

Fig. 1 Different relative proportion of HCV associated HCC (SMR) among male HCC patients in different townships of Taiwan

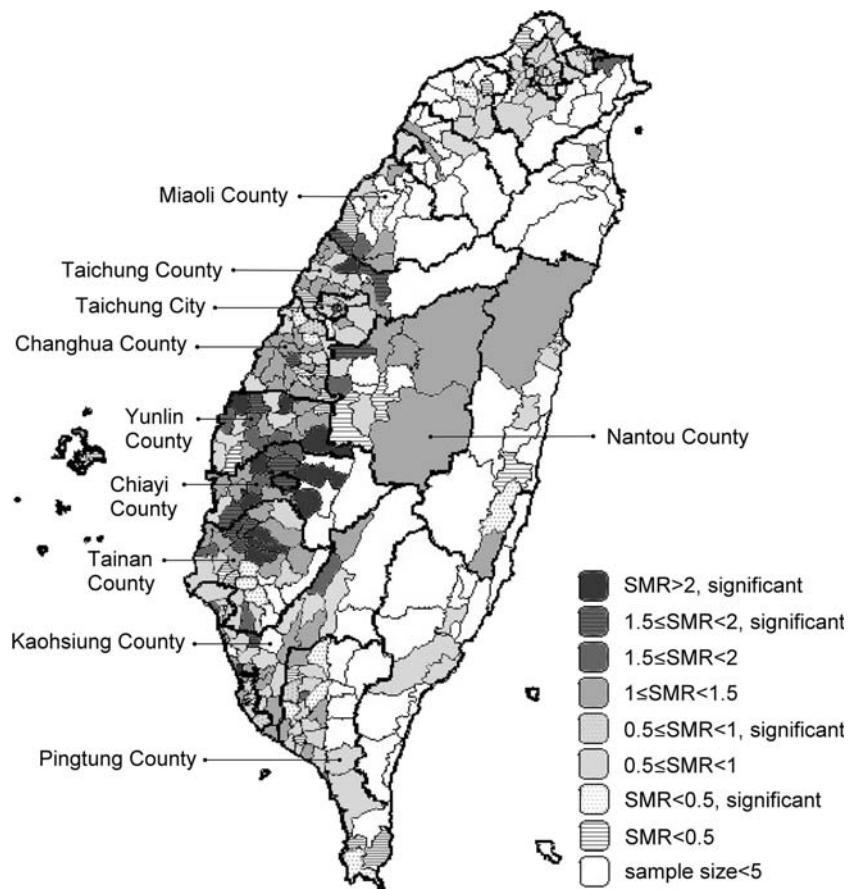


Table 1 Different townships and counties stratified according to HCV SMR

SMR	Test results (township number)	Townships (sorting by prevalence of anti-HCV in descending order)
≥ 2 (12 townships)	Significantly higher (12)	Lucao (Chiayi) ^a , Mailliao (Yunlin) ^a , Guantian (Tainan) ^a , Lioujia (Tainan) ^a , Zihguan (Kaohsiung) ^a , Jhuci (Chiayi) ^a , Siltuo (Yunlin) ^a , Jhongpu (Chiayi) ^a , Liouying (Tainan) ^a , Gukeng (Yunlin) ^a , Singang (Chiayi) ^a , Houli (Taichung) ^a
$1.5 \leq \text{SMR} < 2$ (30 townships)	Not significantly different (0)	None
	Significantly higher (13)	Siaying (Tainan) ^a , Yuanli (Miaoli) ^a , Dongshih (Taichung) ^a , Yijhu (Chiayi) ^a , Lunbei (Yunlin) ^a , Minsyong (Chiayi) ^a , Sinying (Tainan) ^a , Chiayi City, ^a Yanshuei (Tainan) ^a , Alian (Kaohsiung) ^a , West district (Taichung City), Caotun (Nantou), Sihu (Changhua)
	Not significantly different (17)	Fangshan (Pingtung) ^a , Sanyi (Miaoli) ^a , Jiasian (Kaohsiung) ^a , Dapi (Yunlin) ^a , Baojhong (Yunlin) ^a , Sikou (Chiayi), Yuanchang (Yunlin) ^a , Sinyi (Keelung City) ^a , Dalin (Chiayi) ^a , Tatbao (Chiayi) ^a , Taisi (Yunlin) ^a , Rueifang (Taipei), Anping (Tainan City), Jiangyun (Tainan), Gueiren (Tainan), Mingjian (Nantou), Linluo (Pingtung)
$1 \leq \text{SMR} < 1.5$ (69 townships)	Significantly higher (0)	None
	Not significantly different (69)	Not listed
	Significantly lower (6)	Changhua (Changhua), Siaoang (Kaohsiung City), Wanhua (Taipei City), Situn (Taichung City), Pingtung (Pingtung), Banciao (Taipei)
$0.5 \leq \text{SMR} < 1$ (114 townships)	Not significantly different (108)	Not listed
	Significantly lower (16)	Jhonghe (Taipei), Wandan (Pingtung), Wurih (Taichung), Neipu (Pingtung), Jhongli (Taoyuan), Huatan (Changhua), Lujhou (Taipei), Hemei (Changhua), Shanhua (Tainan) ^b , Sinhua (Tainan) ^b , Sinsih (Tainan) ^b , Yuli (Hualien) ^b , Hengchun (Pingtung) ^b , Gaoshu (Pingtung) ^b , Gongguan (Miaoli) ^b , Nuannuan (Keelung City) ^b
Sample size <5	Not significantly different (22)	Not listed
	93 townships	Not listed

^a Prevalence of anti-HCV in 33 townships was more than 50%

^b Prevalence of anti-HCV was 0%

Taibao (Chiayi), and Taisi (Yunlin), have anti-HCV prevalence rates of more than 50%, but there are no statistically significant differences. Twenty-two townships have significant lower rates of prevalence, including 6 townships Changhua (Changhua), Siaogang (Kaohsiung City), Wanhua (Taipei City), Situn (Taichung City), Pingtung (Pingtung), and Banciao (Taipei) with $0.5 \leq \text{SMR} < 1$. Sixteen townships, Jhonghe (Taipei), Wandan (Pingtung), Wurih (Taichung), Neipu (Pingtung), Jhongli (Taoyuan), Huatan (Changhua), Lujhou (Taipei), Hemei (Changhua), Shanhua (Tainan), Sinhua (Tainan), Sinshih (Tainan), Yuli (Hualien), Hengchun (Pingtung), Gaoshu (Pingtung), Gongguan (Miaoli), and Nuannuan (Keelung City), were found to have SMR of less than 0.5.

There were four different patterns (Fig. 1) regarding the geographic variations of different townships in each county. The first pattern included Yunlin, Chiayi, and Tainan counties. In each county, there were at least four more significantly high prevalence townships with anti-HCV prevalences for male HCC patients. The second pattern included Miaoli, Taichung, and Nantou counties. There was only a limited number of high to significantly high prevalence townships that seemed to be neighbors, although located in different counties. The third pattern included Taichung City as well as Changhua and Kaohsiung counties. Only one significantly high prevalence township was identified in each county and city. The fourth pattern included other counties except those mentioned above (e.g., Pingtung County). There were either no significantly high prevalence townships or else the information was inadequately enrolled there.

Discussion

It has been observed that a recent increase in HCC in Western countries was related to HCV infections acquired 2–4 decades ago and that C-HCC incidents are likely to continue increasing over the next decade [8, 9]. The same trend has also been observed in Taiwan, as reported in recent study [6], as well as noted in Japan [10]. HBV and HCV are the two major viral etiologies of HCC patients in Taiwan [6]. Our previous case-control study found that chronic HCV infection was the major cause of excess mortality from HCC in an HBV-HCV endemic area [11]. The same finding was shown later in a large-scale community-based survey [7]. The predominant etiology of male HCC was HBV. The male-to-female ratio in B-HCC was 6.4, whereas it was 1.7 in the C-HCC [6]. Hence, those areas having higher HCV-related male HCC patients could potentially be HCV endemic areas. Further analysis has revealed geographic variations among different townships with regard to anti-HCV prevalence of male HCC patients.

These variations exist both among different counties and among different townships within the same county. Four different patterns were identified in different parts of Taiwan. In contrast to the fourth pattern, the first pattern indicated the areas with the greatest HCV prevalence, that is, central-western to southwestern Taiwan, including Chiayi, Yunlin, and Tainan counties. This finding correlated well with several high-incidence HCV infection areas in Taiwan reported in previous smaller studies. This was especially true in southern Taiwan [7, 11, 12]. It is interesting to note that some significantly low prevalence townships still exist in these high-incidence HCV prevalent counties. Together with the second and the third patterns, the geographical distribution strongly suggests common shared factors for those patients living in these areas. Previously identified risk factors associated with high HCV infection might include iatrogenic routes of infection. For example, local customs and medical treatment seeking behaviors, such as frequent intravenous injections for minor illnesses and incomplete disinfection of medical equipment in the past, may have contributed to the high prevalence of HCV [13, 14]. In view of the high HCV rates among male HCC patients, especially in central-western and southwestern Taiwan counties, further field investigation to search for other risk factors responsible for the transmission of this disease may still be warranted. We also tried to see whether this geographic variation existed in B-HCC patients. As shown in Fig. 2, SMR for geographic variation of B-HCC patients mostly ranged between 0.5 and 1.5. In comparison with C-HCC patients, it was much less significant ($P < 0.001$) (Fig. 3).

Several potential biases do exist in this study, such as the study being based on hospital cases only. Different HCV prevalence among different townships may be varied because of different transmission routes. We failed to address this issue due to lack of data of risk factors in these patients. For townships with particular high HCV prevalence, further investigation of the risk factors in these areas may still be justified to see whether there are active, common, shared risk factors that we seek to prevent. Also, the HCC patients of the clinical diagnosis group were not included in the analyses of geographic variations and exclusion of such patients might have created a potential bias. The population of patients residing in mountainous areas was usually relative small and led to inadequate enrollment and patient information. However, this integrated population is likely to represent the largest target population of male HCC patients ever reported in Taiwan. Our observations correlated well with the recently published results of the community-based screening program carried out by the Liver Disease Prevention and Treatment Research Foundation in Taiwan [15] [a wide variation in crude HCV seroprevalence was noted, ranging from 0.4 to

Fig. 2 Different relative proportion of HBV associated HCC (SMR) among male HCC patients in different townships of Taiwan

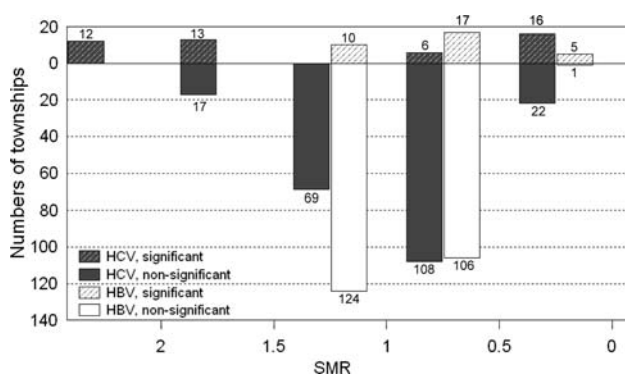
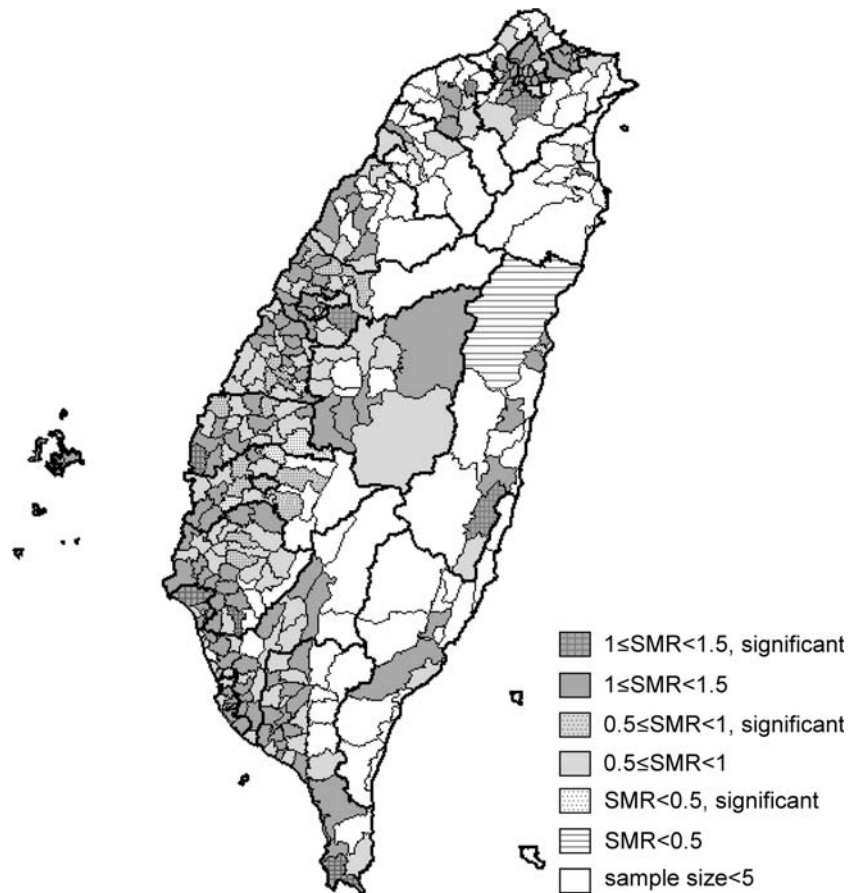


Fig. 3 Comparison of SMR among male HCC patients in different townships of Taiwan using relative proportion of HCV and HBV associated HCC

10.5%. The analysis of age-adjusted HCV seroprevalence revealed that Miaoli County (7.6%) had the highest HCV prevalence, followed by Chiayi County (6.1%), Chiayi City (6.0%), Yunlin County (4.8%), Tainan County (4.0%)], and provided more detailed data regarding townships' HCV prevalence rates revealed by the larger survey. In addition to the nationwide community survey, we also conducted a massive screening of about 60,000 adult residents in Tainan County and reported the township- and

village-specific prevalence [16], which proved the correlation between township HCV-prevalence and HCC mortality rate [7]. This study may therefore be worth using as a guide for further investigations of the true prevalence rates of these endemic areas.

HCV infection takes 2–4 decades to lead to HCC [8, 9]; thus, the geographic variations of male C-HCC patients do not represent the current state of infection but rather the past state of infection in those areas. This may be why we failed to demonstrate any geographical variation in metropolitan areas such as Taipei and Kaohsiung cities, because a large proportion of people living in these places come from different parts of the country and have had relatively shorter periods of residency.

Furthermore, because this study enrolled only HCC patients, we may have missed some endemic areas where HCV is a newly introduced infection. In this regard, active screening methods are still warranted to identify HCV-infected endemic areas, especially in those areas where some high-risk behaviors still exist.

Interferon-based antiviral treatment has achieved success in eradicating HCV infection in Taiwan [5] and other countries [17]. However, many people with chronic HCV infection may not realize that they carry this infection

unless screening blood tests are undertaken. It is well known that the yield from targeted screening, particularly among intravenous drug users, would be substantially higher than for the general population [18]. Identifying these potential high HCV endemic townships has made these areas ideal targets for a more cost-effective screening strategy. This large cohort study may provide a guide for identifying the possible high HCV endemic areas in Taiwan as a whole and aid in further implementation of cost-effective strategy in carrying out further surveillance. Because the cost of disease surveillance and prevention is always high and financial resources are always limited, a high priority for doing survey work in these endemic areas may be more cost-effective and help the government to save money.

In conclusion, our study has designed maps to illustrate some potentially high HCV endemic townships in Taiwan. Prevention of new HCV infections and treatment of chronic hepatitis C are now major public health issues. A nationwide, multicenter study in Taiwan using interferon or interferon/ribavirin to treat chronic HCV infection had been proven to reduce HCC and improve survival rates. Pegylated interferon-based antiviral treatment is now well known to be better and more cost-effective [19] than traditional interferon therapy. Such treatment should lead to further decreases in HCC incidence in the near future, but further efforts should be made to further validate our observations.

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