行政院國家科學委員會專題研究計畫 成果報告

應用 GIS 及 GPS 工具初探台灣西南沿海鄉鎮肝癌死亡率聚集原因

研究成果報告(精簡版)

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Introduction

Hepatocellular carcinoma (HCC) is the leading cause of cancer death in males and the second leading cause in females in Taiwan (Cancer Registry Annual Report 2001). In Taiwan, 70–90% of HCC patients have chronic hepatitis B virus (HBV) infection or antibodies to hepatitis C virus (HCV) (Yu and Chen 1994). A hepatitis B vaccination program was launched in Taiwan in 1984, and it has effectively reduced the prevalence of HBV infection, chronic HBV infection rate, and incidence of HCC in children (Chang et al. 1997; Chen HL et al. 1996). However, to date, the incidence and mortality of HCC in the overall Taiwanese population remain high.

From the public health viewpoint, an immediate challenge in cancer prevention and control is the reduction of incidence rate for those people who live at high risk areas for developing cancer. For this purpose, detecting a high-mortality cluster and suggesting possible prevention strategies in addition to HBV vaccination have gained considerable importance. In Taiwan, in addition to HBV and HCV infections, other major factors associated with an increased HCC risk include aflatoxin exposure, low consumption of vegetables, low serum levels of retinol, cigarette smoking, alcohol consumption, and iron overload (Chen CJ et al. 1996; Chen et al. 1991; Chen et al. 1993; Hoshuyama T et al. 2006; Huang 2003; Stevens et al. 1986; Yu et al. 1995).The major factor besides HBV and HCV infections that should be selected for the formulation of a prevention strategy to lower the incidence of HCC in Taiwan remains in question. The geographical distribution of cancer provides valuable clues for studying its etiology and will help generate hypotheses that can be tested in analytical studies (Glattre 1989). In a previous study, an atlas of cancer mortality in Taiwan from 1968 to 1976 led to a series of comprehensive cancer epidemiology studies in an endemic area of blackfoot disease. A dose-response relationship between high-arsenic artesian well water and internal organ cancers was documented (Chen et al. 1988). Therefore, to prevent HCC in Taiwan, this study aims to map the geographical distribution of liver cancer and then generate potential etiological hypotheses.

Materials and Methods

The number of certified deaths from HCC [International Classification of Diseases (ICD) code 155] stratified by sex and 5-year age groups were published annually from 1992 to 2001 by the Taiwan Department of Health, according to the ninth revision of the ICD. Age-standardized rates (ASRs) were calculated by the direct method using the 1976 world population as the standard (Esteve et al. 1994) and 5-year groups of 0 to 4, 5 to 9, 10 to 14, . . . 80 to 84, and 85 years or more. ASRs are expressed as the average number of annual deaths per 100,000 population.

In order to illustrate and compare the liver age-adjusted mortality rates in the study areas by sex, different colors were used to denote the groups of the rates ranked by percentile. The result of this comparison of the township-specific rates to the overall rate in Taiwan and the ranking of the township rates were used to determine the following color categories for mapping.

(1) Red: the highest 10% of all township rates in Taiwan and significantly higher than the overall rate in Taiwan

(2) Purple: not among the highest 10% of all township rates in Taiwan but significantly higher than the overall rate in Taiwan

(3) Orange: among the highest 10% of all township rates in Taiwan but not significantly higher than the overall rate in Taiwan

(4) Green: within 10–90% of all township rates in Taiwan and not significantly higher than the overall rate in Taiwan

(5) Gray: among the lowest 10% of all township rates in Taiwan but not significantly lower than the overall rate in Taiwan

(6) Yellow: not in the lowest 10% of all township rates in Taiwan but significantly lower than the overall rate in Taiwan

(7) White: among the lowest 10% of all township rates in Taiwan and significantly lower than the overall rate in Taiwan

Township-specific ASRs for HCC were calculated using the SAS statistical package (SAS, version 8.2; SAS Institute, Inc., Cary, NC), and cancer maps were prepared using the Geographical Information System (GIS) tool (ArcView GIS-The Geographic Information System for Everyone; Environmental Systems Research Institute, New York, NY). After mapping the geographical variation in cancer mortality, a preliminary study of the hot spots in the geographical distribution was conducted to enable the generation of potential etiological hypotheses.

Results

The distributions of male and female liver cancer mortality rates from 1992 to 2001 ranked by percentile are shown in Figures 1 and 2, respectively. The most striking cluster was observed on the southwestern coast of Taiwan, and it clearly depicts a marked coastal gradient pattern for men; however, no such trend was observed for women. The apparently highest rate per 100,000 person years in the red category for males was observed in the northern and southern regions of the western coastal townships including the following: Fangyuan (60.82) and Dacheng (60.89) townships in Changhua County; Mailiao (80.43), Taisi (83.47), Sihhu (69.30), and Kouhu (65.42) townships in Yunlin County; Dongshih (60.34) and Budai (61.97) townships in Chiayi County; and Beimen (66.61), Jiangiyun (73.04), and Cigu

(63.52) townships in Tainan County. For females, the mortality rate per 100,000 person years was 17.67 for Fangyuan and 15.1 for Dacheng (Changhua County); 19.74 for Mailiao, 20.14 for Taisi, 16.03 for Sihhu, and 17.25 for Kouhu (Yunlin County); 10.89 for Dongshih and 9.82 for Budai (Chiayi County); and 15.35 for Beimen, 12.88 for Jiangiyun, and 14.61 for Cigu (Tainan County). All these coastal townships with red hot spots are located in the Changhua, Yunlin, Chiayi, and Tainan counties; they form the largest agricultural county cluster and are the most serious land subsidence areas in Taiwan.

Discussion

Our experience suggests that aggregations of cancer on a small-area scale may provide clues to identify environmental or lifestyle risk factors. As expected, it is important to be cautious about fluctuations in diagnosis, reporting, survival time, migration, and mobility. Since any sociodemographical event including birth, death, or migration is mandatorily registered in Taiwan, the demographical data reported by the Household Registration Offices in Taiwan are essentially complete and accurate. In Taiwan, it is mandatory to submit death certificates to household registration offices; therefore, the death certificate registry in this country is basically complete. In this study, we found that the age-adjusted mortality rates were significantly higher in townships on the southwestern coast than in other townships. The difference in mortality rates between the southwestern coastal townships and the other townships could not merely be due to a variation in survival times because the prognosis of liver cancer in Taiwan is very poor (Lee et al. 1986). Therefore, the hot spot in the map merited further exploration and was suitable for use in generating potential etiological hypotheses.

Why was the most striking cluster of HCC mortality rate in males detected in the southwestern coastal regions (including the Changhwa, Yunlin, Chiayi, and Tainan counties) of Taiwan? A series of epidemiological studies of the major risk factors for liver cancer in Taiwan has been carried out. Both HBV and HCV infections are major risk factors for HCC in Taiwan (Chang et al. 1994; Chen CJ et al. 1997; Chen et al. 1990; Chen et al. 1991; Chen et al. 1993; Lu et al. 1988; Sun et al. 1996; Yu et al. 1991). On the other hand, previous studies have demonstrated that the mortality rate of liver cancer is strikingly higher in the Matzu islets (located near the north coast of Fukien Province of mainland China and separated from Taiwan Island by the Taiwan Strait), Penghu islets, and the endemic area of arseniasis in southwestern Taiwan; however, the seroprevalence of HBsAg among the residents of these areas was similar or only slightly higher than that in the general Taiwanese population (Chen et al. 1995; Chen SY et al. 1997; Lu and Chen 1991; Wang et al. 1993).

Moreover, the seroprevalence of anti-HCV antibodies in Matzu was even lower than that in the general Taiwanese population (Chen SY et al. 1997). These results suggest the involvement of other major risk factors besides HBV and HCV infections in the etiology of liver cancer, and these factors are responsible for the high liver cancer mortality in the Matzu and Penghu islets, and in southwestern Taiwan.

Therefore, which major risk factor besides HBV and HCV infections is involved in the etiology of liver cancer and is responsible for the most striking geographical clustering observed in southwestern Taiwan? The incidence of HCC varies greatly in different areas of the world, suggesting the involvement of environmental etiological factors.

Why the clustering of liver mortality rates was observed for males but not for females is an important question raised in our study. Which potential environmental etiological factors could explain this gender difference in the HCC mortality rate clustering in southwestern Taiwan?

Groundwater is a major water resource in southwestern coastal Taiwan due to the shortage of surface water that is mainly obtained from a few creeks and rivers. The over pumping of groundwater for aquaculture has caused serious land subsidence in southwestern coastal Taiwan (Liu et al. 2001). Serious land subsidence areas are located in the counties of Changhwa and Yunlin in the southwestern part of the alluvial fan of the Chou-Shui River (Fig 3). We compared data regarding untreated tap water between serious land subsidence areas (tap water source from groundwater) and non-land subsidence areas and found the iron concentration to be 1.01 and 0.3 mg/l, respectively (Table 1). The supply rates of tap water in Changhwa and Yunlin are the lowest among all the counties in Taiwan, these values were less than 36.95% and 52.51% in 1975 and 1981, respectively (Taiwan Water Supply Corporation 1975, 1981). According to a WHO report, the concentrations of iron in drinking water are normally less than 0.3 mg/l (WHO 1996). From the above statements, we conclude that the residents of the serious land subsidence areas had used a large quantity of groundwater with high iron concentration for drinking and for aquaculture and fishponds over several decades. Table 1 shows that the average ASR of HCC for males and females is significantly higher among the residents of serious land subsidence areas than among those of non-serious/non-land subsidence areas.

Unlike arsenic, a confirmed human carcinogen, the carcinogenicity of iron is debatable. However, increasing evidence summarized below shows that iron overload can contribute to cancer development either as an initiator or a promoter (Huang 2003). The toxicity of iron is largely based on Fenton and Haber-Weiss chemistry wherein catalytic amounts of iron are sufficient to yield hydroxyl radicals ($OH^{\cdot}$) from superoxide ($O_2^{\cdot -}$) and hydrogen peroxide (H_2O_2), collectively known as "reactive oxygen intermediates" (ROIs). Importantly, ROIs are inevitable byproducts of aerobic respiration and are generated by incomplete reduction of dioxygen in mitochondria (Haliwell and Gutteridge 1990; Papanikolaou and Pantopoulos 2005).

According to Blumberg et al. (1981), chronic HBV carriers who develop primary hepatocellular carcinoma (PHC) may have higher iron stores than those who do not develop PHC. Serum ferritin was thought to be related to body iron stores (Cook et al. 1974; Finch and Huebers 1982; Forman and Vye 1980). Iron can catalyze the production of oxygen radicals that may be proximate carcinogens (Ames 1983; Halliwell and Gutteridge 1984). The results of a study conducted in Taiwan by Stevens et al. (1986) were consistent with the hypothesis that increased iron stores increase the risk of PHC. Moreover, the serum ferritin concentration, which is widely used clinically as an index of body iron stores, was predominantly influenced by sex, blood donation, and age. The serum ferritin concentration tends to be lower among women and regular blood donors. Moreover, the increase in ferritin concentration parallels expected physiological changes, for example, the concentrations in women remain low until after menopause (Leggett et al. 1990).

This difference in body iron stores is responsible for the gender difference in the HCC mortality rate clustering in southwestern Taiwan.

The data from this study demonstrated the geographic clustering of male HCC mortality and an apparent overall consistency of this clustering with the geographical variation in serious land subsidence in Taiwan; this suggests that iron overload in drinking water may be a particularly interesting risk factor for etiologic investigations of HCC. Iron can catalyze the production of oxygen radicals that may be proximate carcinogens. Moreover, iron may be a limiting nutrient for the growth and replication of cancer cells. Therefore, our study showed that the effect of iron overload on liver carcinogenesis cannot be ruled out and warrants further investigation.

Conclusions

The most interesting finding of this study is that the geographical variation in HCC clearly depicted a marked coastal gradient pattern for men, whereas no such trend was observed for women. This study suggests the hypothesis that iron overload in drinking water may play an important role in HCC.

Acknowledgements

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Abbreviations: HBV: hepatitis B virus

HCV: hepatitis C virus

HCC: hepatocellular carcinoma

ASRs: age-standardized rates

GIS: geographical information system

ICD: international classification of diseases

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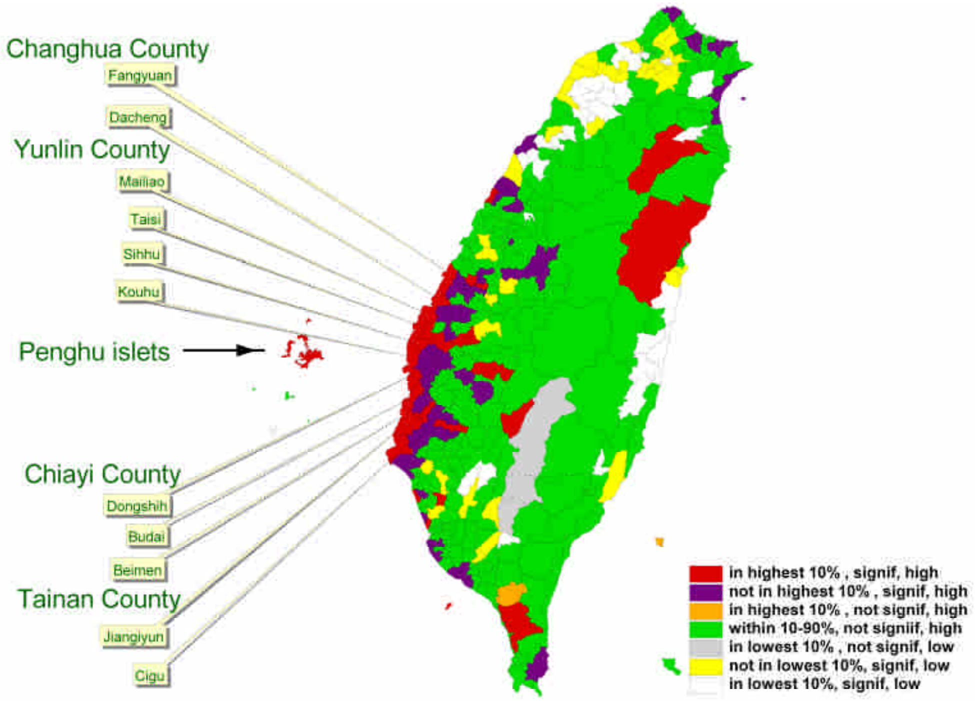

Figure 1: A mortality map for males based on the township-specific age-adjusted mortality by rank for hepatocellular carcinoma in Taiwan (1992–2001).

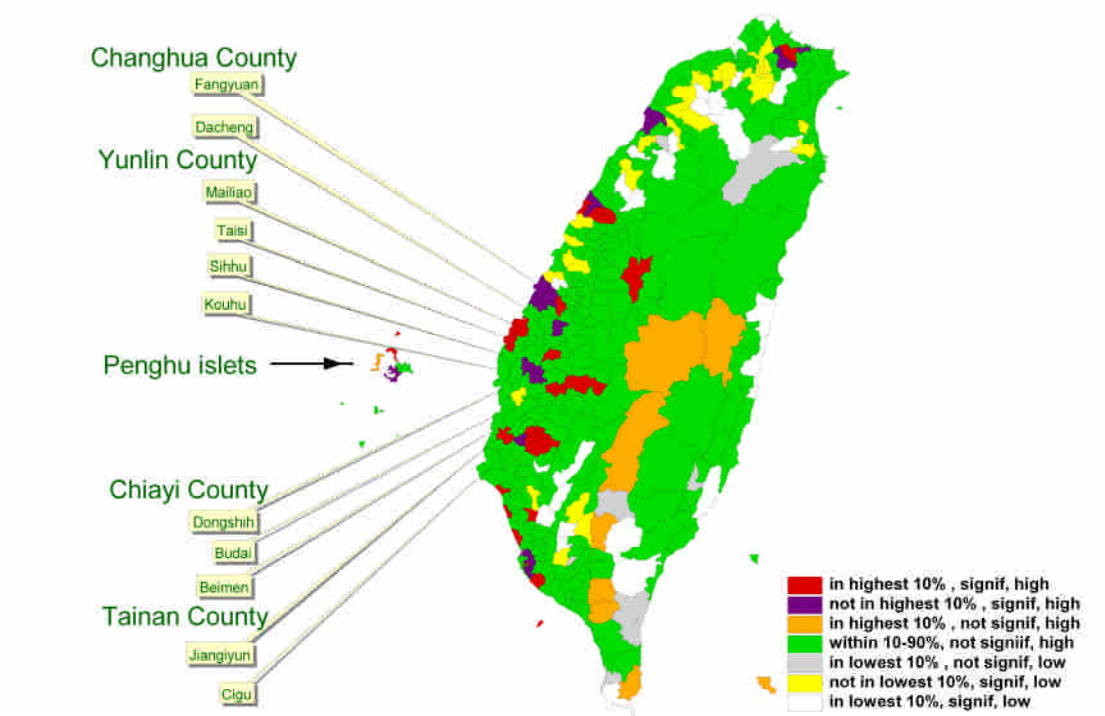

Figure 2: A mortality map for females based on the township-specific age-adjusted mortality by rank for hepatocellular carcinoma in Taiwan (1992–2001).

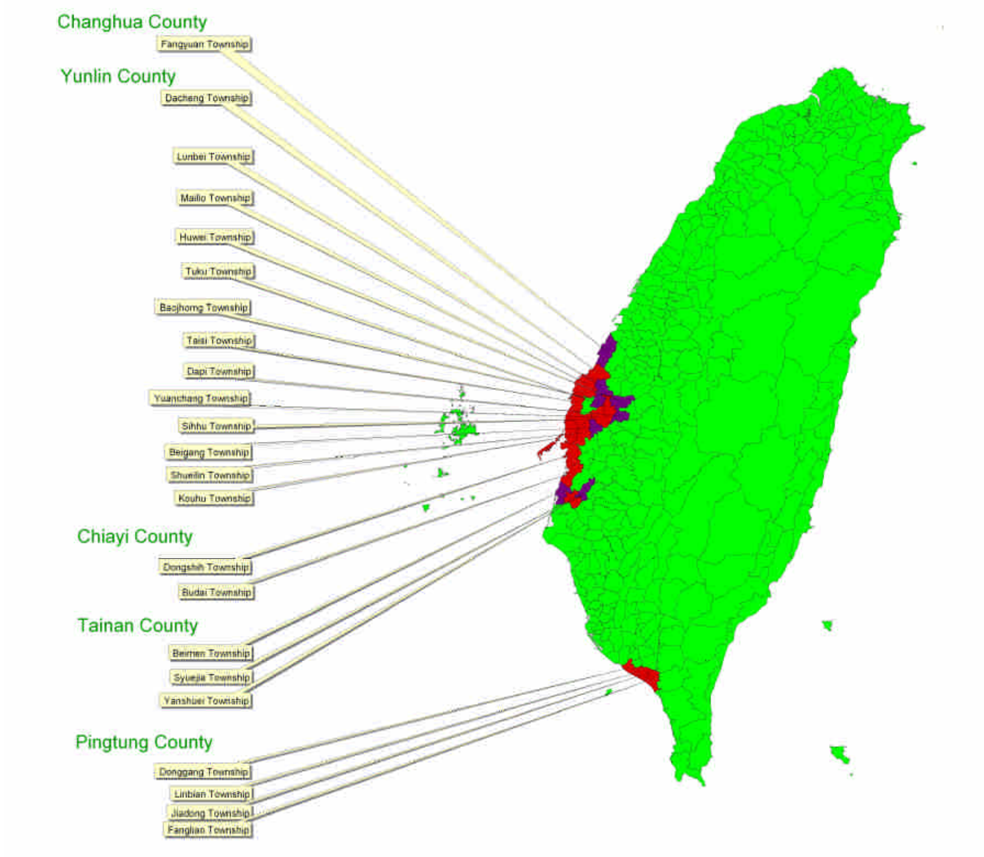

Figure 3: Serious land subsidence townships are located in the Changhua, Yunlin, Chiayi, Tainan, and Pingtung counties in Taiwan.

Table 1. Average iron concentration in untreated tap water and HCC mortality rate (per 100,000 person years) in both serious land subsidence areas and non-serious/non-land subsidence areas.

		Serious land subsidence	Non-serious/non-land subsidence	P-value
Average iron concentration (mg/l)		1.01	0.30	0.0003
HCC mortality rate (per 100000)	Males	61.35	37.10	<0.0001
	Females	16.86	11.16	0.0003

HCC: Hepatocellular carcinoma

結果自評：本成果與原計畫方向符合度幾近百分之百，然而在立論上仍須有更多之証據給予加強假說之建立。未來將朝體內鐵濃度與 B 型肝炎、C 型肝炎對肝癌的交互作用進行研究。