
RESEARCH COMMUNICATION

Estimate of the Incidence of Hepatocellular Carcinoma Among Carriers of HBsAg (+) in the General Population of Hanoi, Viet Nam from 1991-93

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Abstract

Background: The estimated number of carriers of HBsAg (+) in the world significantly increased from 120 to 350 million from the 1970s to the 1990s. Eighty per cent of liver cancers are estimated to be due to chronic HBV infection. However, only limited data are available regarding liver cancer rates among carriers of HBsAg (+). The aim of the present study was to estimate the incidence of liver cancer among carriers of HBsAg (+) in the general population of Hanoi City, Viet Nam.

Method: Data were derived from published reports for incidence of liver cancer (population-based cancer registry), the risk of HBV infection for liver cancer (case-control study), and the prevalence of HBV infection (stratified random sampling of the general population) in the same population of Hanoi City. The Method of Indirect Estimation in a Case Control Study was used in this study.

Results: Crude incidence rates per 100,000 were 114 and 37 for carriers of HBsAg (+) in males and females, respectively. The age-standardized incidence rate per 100,000 among carriers of HBsAg (+) for liver cancer was 166 in males and 58 in females, (ASR, world population). The annual incidence of liver cancer among carriers of HBsAg (+) was strongly correlated with increased age in both males and females: the estimated value sharply increased from 6 to 655 per 100,000 for persons aged 0-9 and 50+, respectively, in males. Similarly, the estimated incidence of liver cancer also sharply increased from 8 to 233 per 100,000 for the age groups 10-19 and 50+, respectively, in females.

Conclusion: The present results indicate a high age-dependent incidence of liver cancer among carriers of HBsAg (+) in a general population. These results for Hanoi City, Viet Nam point to the magnitude of the problem and provide a basis for intervention.

Key words: Viet Nam- cancer incidence - HCC - HBV infection - estimate

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Background

The estimated number of carriers of HBsAg (+) worldwide increased from 120 million in the 1970s to 350 million in the 1990s, (Kane, 1995; Szmuness, 1975; Van Damme et al., 1995). Moreover, the estimated number of people suffering from liver cancer demonstrated a marked increase from 251,100 in 1980 to 314,900 in 1985, and 437,400 in 1990 (Parkin et al., 1988; Parkin et al., 1993;

Parkin et al., 1999). Eighty per cent of liver cancers are estimated to be due to chronic HBV infection throughout the world (World Health Organization, 1983). However, only limited data are available regarding the incidence of liver cancer among people with chronic HBV infection in the general population, based on published reports. Among carriers of HBsAg (+) among specific populations, crude truncated incidence rates of liver cancer per 100,000 have been reported to vary widely from 37 to 657 in males. And

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it was also widely ranked from 21 to 130 in females, (McMahon et al., 1990; McMahon et al., 1999; Oshima et al., 1984; Sakuma et al., 1982; Sherman et al., 1995; Tokudome et al., 1987; Tokudome et al., 1988). The age standardized incidence rate of liver cancer among population with carriers of HBsAg (+) among the general population has not been documented yet. Estimates of the incidence of HCC among carriers of HBsAg (+) in the general population of Hanoi City, Viet Nam from 1991-93 were the aim of the present work.

Materials and Methods

The method of Indirect Estimation in Case Control Study was used in this study, (MacMahon & Trichopoulos, 1996). That is, the incidence of liver cancer in the those exposed to HBV infection (I_e) is linked to the corresponding incidence among non-exposed persons (I_o) through the odds ratio (OR) as: $I_e = OR * I_o$. The overall incidence of liver cancer in the population of Hanoi City (I_t) is: $I_t = I_e * P + I_o * (1-P)$, (P is the proportion of carriers of HBsAg (+) among this population). To calculate I_o , the following formula is used: $I_o = I_t / (OR * P + (1-P))$. Data of risk factors (OR) of HBV infection for HCC, incidence of liver cancer (I_t), and proportion (P or prevalence of HBV infection) of carriers of HBsAg (+) were derived from previous published reports. For risk factors of HBV infection, one published report in English studied the role of HBV infection and HCC in the population of Hanoi City from 1989-92, (Cordier et al., 1993). A total of 152 males with liver cancer (HCC) were recruited from two hospitals. All subjects were born before January 1st 1953. HBsAg was detected in the sera of these cancer patients as a marker for HBV infection by using a second generation ELISA test. The same method was done for 241 hospital controls without HCC who were comparable to HCC patients in characteristics such as sex, age, hospital and residence. A questionnaire was used to collect information on socio-demographic factors, smoking and alcohol habits, diet and exposure to pesticides. HBsAg (+) was observed in 92.6% (138) of HCC patients and in 18.3% (44) of hospital controls, giving an odds ratio of 61.7, 95% CI = 30-128. This is the first available data that confirms the relationship between chronic HBV infection and HCC in the population of Hanoi City, Viet Nam.

General cancer incidences and incidence of liver cancer in particular have also been available for the population of Hanoi City from 1991-93, based on the population-based cancer registry, that we used to analyze in the present study, (Anh et al., 1997).

The prevalence of HBV infection in the population of Hanoi City was systematically investigated in 1986 and written up in Vietnamese, (Tuan, 1986). It was a cross sectional study. The sample method was Stratified Random Sampling. The number of subjects was 1,304 (672 males and 632 females) who were randomly selected from the general population of Hanoi City (2,935,866 in 1986). The number of subjects for each specific group was calculated

by proportional allocation for males and females. For age group 0-14, subjects were randomly selected from 6 places, such as child-care center, kindergarten, elementary school, and high school. Subjects aged 15-60 were randomly selected from 16 places when they entered the pre-enrolment school health examination for professional training, pre-employee health check up, and periodic health examination for workers. Also subjects over 60 years of age were selected from persons at the health check up for retirees and aged persons. All subjects were randomly recruited from 8 of all 9 districts of Hanoi City. Study was conducted in 1986 from January to June. Blood samples were collected by trained research assistants and nurses. These collected samples were frozen before being transported to the laboratory. All serum samples were analyzed in the Laboratory of the Institute of Clinical Research in Tropical Medicine, Bach Mai Hospital, Hanoi, Viet Nam. HBsAg was detected by the Reversed Passive Haemagglutination (RPHA) Method. The kit was developed by the Wellcome Trust Center. Thirteen five-year age groups were examined for the prevalence of chronic HBV infection in 1986, that is, from 0-4 to 60+. Five years later in 1991, members of these 13 age groups had become 5 years older, that is, from 5-9 to 65+. For the age group 0-4 in the period from 1991-93, we used the same estimated prevalence as those in 1986 because there was no available vaccination program for children with HBV vaccine at birth.

The results of the estimated incidence of liver cancer were presented for the six 10-year age groups from 0-9 to 50+ for both males and females. In addition, these results were also present in males for seven 10-year age groups from 0-9 to 60+. Confidence interval for the proportion (prevalence rate) was calculated by the formula: estimator $\pm 1.96 * (\text{square root of } (p * (1-p) / n))$, (confidence level of 0.95) using Excel in PC. (Daniel, 1999). The stratified incidence rate ratio (RR) between present estimated incidence in Hanoi City, Viet Nam and incidence of HCC among carriers of HBsAg (+) for males in previous results was also calculated, (Beasley et al., 1981), (STATA, 1997).

Results

The number of liver cancer cases was 496 and 137 in males and females, respectively for the three-year period from 1991-93. The annual incidence per 100,000 steadily increased with age in both males and females. Overall, the crude incidence of liver cancer was 15.91 and 4.24 per 100,000 in males and females, respectively, (Table 1). In males, the highest prevalence of HBV infection was 17.4%, 95% CI = 10.6-24.1 for the ages 20-29, then slightly diminished in the older ages. In females, the highest prevalence of HBV infection was 18.8%, 95% CI = 10.5-27.1 in ages 30-39, then sharply decreased in the older ages, (Table 1). Overall, the prevalence of HBV infection was 12.5%, 95% CI = 10.0-15.0 in males and 10.1%, 95% CI = 7.8-12.5 in females.

The estimated annual incidence of liver cancer sharply increased from 6 to 655 per 100,000 for persons aged 0-9

Table 1. Liver Cancer Registered and Prevalence of HBV Infection in the Population of Hanoi City

Age group	Estimated incidence of liver cancer in 1991-93*			Estimated infection with HBV in 1991-93**			95% CI
	Population at risk	Number of cases	Annual incidence per 100,000	Number of tested samples	Number of HBsAg(+)	Prevalence (%)	
Males							
0-9&&	232,530	4	0.57	84	7	8.3	2.4-14.2
10-19	224,737	9	1.33	151	18	11.9	6.8-17.1
20-29	170,377	16	3.13	121	21	17.4	10.6-24.1
30-39	161,989	60	12.35	92	14	15.2	7.9-22.6
40-49	97,079	86	29.53	56	9	16.1	6.5-25.7
50+	152,679	312	68.12	168	15	8.9	4.6-13.2
Total	1,039,391	496&	15.91	672	84	12.5	10.0-15.0
Females							
0-9&&	219,792	0	0.00	86	8	9.3	3.2-15.4
10-19	214,130	6	0.93	151	16	10.6	5.7-15.5
20-29	184,691	4	0.72	171	12	7.0	3.2-10.8
30-39	174,287	15	2.87	85	16	18.8	10.5-27.1
40-49	105,439	24	7.59	67	8	11.9	4.2-19.7
50+	177,943	88	16.48	72	4	5.6	0.3-10.8
Total	1,076,282	137	4.24	632	64	10.1	7.8-12.5

Adapted from * (Anh et al., 1997), ** (Tuan, 1986), &: Includes 9 cases of age unknown, &&: use of the estimated prevalence of HBV infection for age group 0-5 in 1986

and 50+, respectively, in males, and also sharply increased from 8 to 233 per 100,000 for the age groups 10-19 and 50+, respectively, in females. The annual incidence of HCC among carriers of HBsAg (+) was strongly correlated with increased age, and incidence markedly increased for persons over 50 in both males and females, (Fig. 1). Standardized incidence rate among carriers of HBsAg (+) was about 166

and 58 per 100,000 (ASR, world population) in males and females, respectively. Crude incidence rate was 114 per 100,000 in males and 37 per 100,000 in females, (Table 2). Crude annual incidence of liver cancer among the population of Hanoi City with chronic HBV infection-free was about 1.85 and 0.59 per 100,000 in males and females, respectively.

Table 2 also shows incidence of liver cancer among

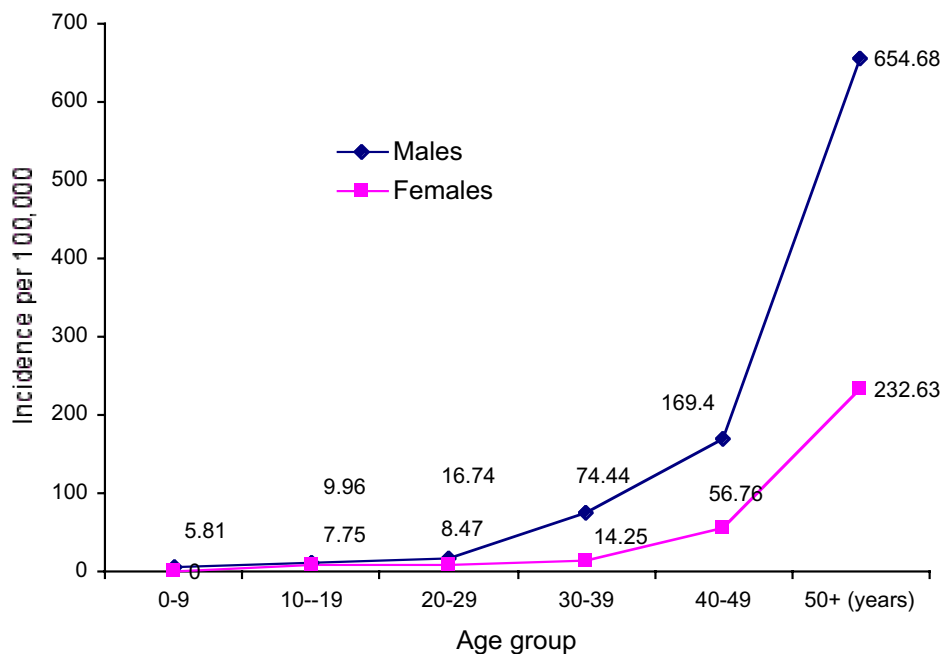


Figure 1. Estimates of Annual Incidences of HCC by Age Group Among Carriers of HBsAg (+) in the General Population of Hanoi City, Viet Nam, from 1991-93

Table 2. Incidence of Liver Cancer Among Selected Populations with Carriers of HBsAg (+): Time Study, Study Design, Ages of Carriers, Number of Liver Cancers Detected or Estimated, Crude and ASR Rate per 100,000 in Males and Females

Population, time and source	Study design, ages of carriers	Incidence per 100,000 in males			Incidence per 100,000 in females		
		Number of liver cancer	Crude rate	ASR	Number	Crude rate of HCC	ASR
Hanoi, Viet Nam, 1991-93, present analysis	Estimated for the general population, and all ages	496	114	166	137	37	58
Alaskan natives, 1972-83, (McMahon et al., 1990)	Prospective studies of general population for 5.6 years, and all ages at recruitment	18	387(1)	-	2	63(1)	-
Alaskan natives, Follow up for 12.3 years, (McMahon et al., 1999)	Prospective studies of general population for 12.3 years, all ages at recruitment	36\$	240(1)	-	36\$	130(1)	-
Blood donors in Fukuoka, Japan, 1977-83, (Tokudome et al., 1988), (Tokudome et al., 1987)	Prospective studies of blood donors for 5.86 and 5.05 years for males and females, respectively, 81.8% of donors under 40 years old,	15	99*(1)	-	4	21*(1)	-
Blood donors in Osaka, Japan, in 1972-80, (Oshima et al., 1984)	Prospective studies of blood donors for 6.2 years, ages 15-64	20	37*(1)	-	-	-	-

* Recalculated from original data, \$ Males and females combined, (1): Crude truncated incidence rates

carriers of HBsAg (+) in Hanoi City, Viet Nam together with that in Alaskan natives, and blood donors in Japan. Generally, the incidence of liver cancer in Hanoi City, Viet Nam was seen to be lower than that in Alaskan natives but higher than that in Japanese blood donors in both males and females. The stratified incidence rate ratio (Hanoi/Taiwan) was 1.14, 95% CI = 0.78-1.66, P = 0.47 (average 3.3 years follow-up in Taiwan) for the same age group 20-29, 30-39, 40-49 and 50-59 (Fig. 2).

Discussion

Our results for incidence of liver cancer among male carriers of HBsAg (+) in Hanoi City, Viet Nam are not significantly different from those in male Taiwan workers, RR = 1.14, 95% CI = 0.78-1.66, P = 0.47. The incidence of liver cancer was seen to be slightly higher in Hanoi for the age groups 20-29, 40-49, and 50-59 when compared to those in male Taiwanese (Fig. 2). The incidence of liver cancer among Japanese blood donors with carriers of HBsAg (+) was seen to be lower in comparison to those in Hanoi City, Viet Nam in both males and females, which was caused by “healthy donor effect” as previously mentioned, (Tokudome et al., 1988). The incidence among Alaskan natives was reported to be higher than that in Hanoi City, Viet Nam,

(Table 2). However, the incidence of liver cancer in Alaskan natives carriers decreased in males but increased in females between the average 5.6 and 12.3 years follow-up. This difference between the two periods among Alaskan natives carriers is due to the small number of liver cancer cases detected among carriers in Alaska, especially in the first follow up study, (Table 2). The higher incidence of liver cancer among Alaskan natives carriers for a median of 12 years follow-up in comparison with those in Hanoi (240 VS. 114 per 100,000 and 37 VS 130 per 100,000 in males and females, respectively) can, at least in part, be explained by three reasons. First, thirty-six patients with HCC were detected by screening twice a year, (McMahon et al., 2000; McMahon et al., 1999). If a patient’s disease was detected earlier than it would normally develop, then, the incidence rate in the study period would be higher than the normal condition. Second, carriers were aging for a median 12.3 years follow-up, therefore, there were very few or no study subjects younger than 12.3 years of age, (McMahon et al., 1999). In our analysis, more than 15% of carriers were younger than 10 years of age. Third, there are differences according to ethnic groups. The median age at the time HCC detected for Alaskan natives carriers was 24 years, ranking from 8 to 80 years old, (McMahon et al., 2000). However, there were no HCC cases detected among Asian carriers for

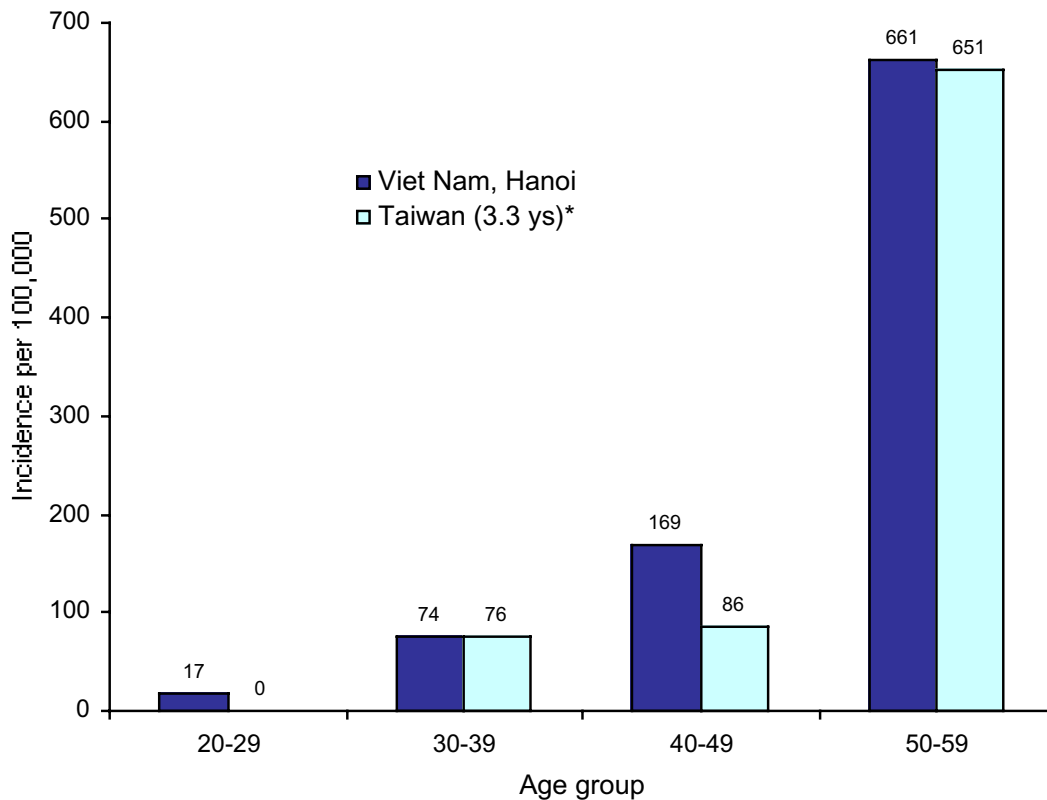


Figure 2. Estimates of Annual Incidences of HCC by Age Group Among Carriers of HBsAg (+) in the General Population of Hanoi City, Viet Nam, from 1991-93 and Taiwan Workers from 1975-86 for Males
 Source: *(Beasley et al., 1981), average 3.3 years follow-up

the age group 20-29 among 130 male patients for the average 8.9 years follow-up, (Beasley, 1988).

A strong correlation with ages for incidence of liver cancer among carriers of HBsAg (+) was observed in both males and females in the general population of Hanoi City, Viet Nam, (Fig. 1). A similar observation was also reported among carriers of HBsAg (+) in male workers in Taiwan. That is, for age at recruitment, the incidence of HCC was predominantly increased from 197, 302, 776, to 927 per 100,000 for ages from 30-39, 40-49, 50-59, to 60-69, respectively, (Beasley, 1988). Among carriers of HBsAg (+), the increased risk of developing HCC was correlated with increasing ages in Alaska, (McMahon et al., 1999). The higher incidence of liver cancer among carriers of HBsAg (+) in males than that in females was seen in the present results and also in Japanese blood donors and Alaskan natives, (McMahon et al., 1990; McMahon et al., 2000; Tokudome et al., 1987; Tokudome et al., 1988).

The incidence of liver cancer in the present study was taken from the results of the population-based cancer registry in Hanoi City. Liver cancer was the third common cancer in males and fifth common in females. This incidence rate was seen to be stable between 1991-93 and 1994-96 in the population of Hanoi City for both males and females, (Duc, 1998). Therefore, incidence of liver cancer in 1991-93 was

a real problem in the population of Hanoi City.

The prevalence of HBV infection in the general population in 1986 was 12.5%, 95% CI = 10.0-15.0 and 10.1%, 95% CI = 7.8-12.5 in males and females, respectively. The prevalence of HBV infection in the 1990s ranked from 13.4% to 14.9% for the general population and 16% for pregnant women and patients without liver diseases in Hanoi City, (Cuong & Thien, 1996; Nakata et al., 1994). These prevalence rates were ranked within a 95% confident interval in the most specific age groups in males and or in females in the present study, (Table 1). For example, the prevalence of HBV infection among female fertility ages was 18.8%, 95% CI = 10.5-27.1 and 11.9%, 95% CI = 4.2-19.7 in the age group 30-39 and 40-49, respectively, (Table 1). These facts confirm that the estimated prevalence of HBV infection in the present analysis represents the reasonable prevalence rate in the 1990s.

The present study does have some limitations. The odds ratio (OR = 61.7) of infection with HBV that was analyzed for HCC patients over 35 years of age was used to estimate the incidence of HCC for all age groups, (Cordier et al., 1993). The proportion of HCC was about 8.1% in males and 13% in females' age group 25-34 or younger in the population of Hanoi City. However, a previous report has confirmed that HCC of most young patients is caused by

HBV infection, that is, all nine HCC patients aged younger than 35 had HBsAg (+), (Lanier et al., 1987). And among 1,487 carriers of HBsAg (+), 19 of 32 HCC patients (59%) were under the age of 35, (McMahon et al., 2000). Another limitation is that we applied the prevalence of HBV infection in 1986 to estimate its prevalence in 1991-93. The annual loss of HBsAg was about 1% in Taiwan male workers, (Beasley, 1988). Therefore, there is a decline in prevalence of HBV infection between 1986 and 1991-93 especially for male patients over 30 years of age and female patients over 40 years of age, (after a peak age group of prevalence). Therefore, our estimation of incidence of liver cancer among carriers of HBsAg (+) for the older age groups may be underestimated.

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