Impact of Gender, Viral Transmission and Aging in the Prevalence of Hepatitis B Surface Antigen

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Background: Age, gender, and perinatal infection are associated with hepatocarcinogenesis. The influence of perinatal transmission in chronic hepatitis B virus infection between genders at different ages is not well documented.

Methods: A consecutive series of individuals who had general check-ups and three groups of relatives of patients with hepatocellular carcinoma were analyzed. Siblings of index cases and children of female index cases represented groups with high perinatal transmission, while children of male index cases represented a low perinatal transmission group.

Results: A total of 45,035 individuals who had general check-ups and 14,513 first degree relatives of patients with hepatocellular carcinoma were included. The families of patients with hepatocellular carcinoma included 4,455 siblings of index cases, 7,111 children of male index cases, and 2,947 children of female index cases. The prevalence of hepatitis B surface antigen (HBsAg) was high in groups with high perinatal infection and in men. Gender differences in the prevalence of HBsAg diminished in children of female index cases and siblings of index cases, and in all groups after the age of 60 years. The prevalence of HBsAg declined with increasing age in all groups, with the highest decline in male siblings of index cases (1.37% per year) and the lowest in female children of male index cases (0.05% per year) in the 35-59 year-old period. Hepatitis C antibody was higher in women (5.7%) than in men (4.0%) in the general check-up group.

Conclusions: Females were less susceptible to become HBsAg carriers if HBV was not transmitted during the perinatal period. The prevalence of HBsAg declined significantly in high perinatal infection groups, implying that neonatal tolerance does not endure. *(Chang Gung Med J 2009;32:155-64)*

Key words: perinatal transmission, neonatal tolerance, gender, family, HBsAg clearance, prevalence

Hepatitis B virus (HBV) infection in the perinatal period induces neonatal tolerance to hepatitis B surface antigen (HBsAg) and the newborn becomes a chronic HBsAg carrier.[1,2] This type of viral trans-

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mission is important because it increases the risk of hepatocellular carcinoma (HCC).[3-5] Complications of HBV infection usually occur five to seven decades after infection. Thus, it is difficult to know the route of transmission.

A nationwide prospective survey of first-degree relatives of patients with HCC was performed in Taiwan[6-10] and showed that families had different viral transmission routes. It was reported that about 70% patients with HCC were infected with HBV perinatally.[3-5,10] Siblings of HCC patients with the same mother as the indexed case have similar rate of perinatal HBV infection. Children of female index cases also had a high perinatal transmission rate, because about 41-50% of females with HCC are HBsAg carriers.[10-12] On the other hand, children of male index cases were generally infected horizontally because prevalence of HBsAg in their wives was considered similar to that in the general population (15-20%).[10]

Based on the reported maternal HBsAg prevalence in different groups of HCC families and female HCC patients,[10-12] the risks of perinatal infection in siblings of index cases, children of female index cases, and children of male index cases were approximately 60~70%, 41~50%, and 15~20%, respectively.

Men were more likely to develop severe complications of HBV infection than women.[12] The influence of perinatal transmission of HBV in different genders is not well documented. This study examined the pattern of HBsAg prevalence in three groups of HCC families and a control group that received general check-ups.

METHODS

General check-up group

Between January 2000 and December 2004, consecutive patients voluntarily visiting Chang Gung Memorial Hospital for a paid physical check-up were included. All received a complete examination, including hemogram, serum biochemistry, viral hepatitis markers, and abdominal ultrasonography. HBsAg and anti-HCV were analyzed by enzyme-linked immunosorbent assay (Abbott Ausria-II and Abbott HCV-ELISA III, Abbott Laboratories). Detailed information can be seen in our previous reports.[13]

Relatives of patients with hepatocellular carcinoma

A nationwide prospective survey of first-degree relatives of patients with HCC was done between 1992 and 1998. The study subjects included generations of parents, siblings, children, and grandchildren older than 15 years of age. Eleven major teaching hospitals in Taiwan participated in the survey. The siblings' and children's generations were included in this analysis. This study was approved by the Ethics Committee of each hospital and by the Department of Health, Taiwan.

Serum HBsAg (radioimmunoassay or enzyme-linked immunosorbent assay; Abbott Laboratories, Abbott Park, IL, U.S.A. or General Biologicals Corp, Science Based Industrial Park, Hsin Chu, Taiwan) and hepatitis C virus antibodies (Abbott HCV EIA II; Abbott Laboratories) studies were performed. Detailed information can be found in our previous reports.[9,10]

Only generations of children and siblings were included in this retrospective analysis. Because hepatitis C virus infection might induce a delayed clearance of HBsAg;[14] patients with anti-HCV were excluded. After excluding patients with chronic HCV infection, the gender ratio of HBsAg prevalence was compared between different viral transmission groups.

Statistical analysis

Continuous data were reported as mean and standard deviation. A one-way ANOVA test was used to test age differences in the different study groups. Categorical data were reported as frequencies and percentages. The chi-square test was used to analyze differences between categorical variables, while the sharpened Bonferroni procedure was used to adjust for individual alpha levels, thus keeping the overall alpha level at 0.05 when performing multiple tests. The association between gender and generation after controlling for age groups was examined by fitting logistic models. All statistical analyses were carried out using SPSS (version 11.5; SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

Patient data

Among the four study groups, the mean age was

highest in the general check-up group, followed by siblings of index cases and the lowest mean ages were seen in the children of index cases (Table 1; $p < 0.001$). The percentages of males were similar among the groups (range: 51-54.5%). The prevalence of HBsAg was highest in siblings of index cases, followed by children of female index cases, and children of male index cases, and lowest in the general check-up group ($p < 0.001$). The prevalence of anti-HCV was highest in the siblings of index cases, followed by the general check-up group, and lowest in the children of index cases ($p < 0.001$).

Prevalence of HBsAg and anti-HCV in the general check-up group

Among the 45,035 individuals who received a general check-up, 24,523 were male and 20,512 were female. The overall HBsAg prevalence was 15.5% and was higher in males (17.8% vs. 13.2%, $p < 0.001$). But the difference was not significant in those over 60 years of age (Fig. 1, Table 2). The peak prevalence of HBsAg was 21.7% for males 35-39 years old and 17.2% for females 30-34 years old. The prevalence decreased to 10.3% and 9.0% in males and females, respectively, at 70-74 years. The drop in HBsAg prevalence from age 30-60 years was 0.24% per year in males and 0.13% per year in females ($p < 0.001$). The difference was not significant after 60 years of age.

The prevalence of anti-HCV was around 1.5-1.6% at age 30-34 years, and increased to 10.3-11.4% at age 70-74 years. The rise in anti-HCV prevalence was 0.22% per year for males and 0.24% per year for females. A higher anti-HCV prevalence was found in females (5.7% vs. 4.0%, $p < 0.001$). Gender differences in anti-HCV prevalence were mainly seen in those from 35 to 69 years old ($p < 0.001$).

Relatives of patients with HCC

A total of 14,513 siblings and children of patients with HCC participated in a nationwide prospective survey between 1992 to 1997. The subject data is shown in Table 1. After excluding 837 (5.8%) relatives with anti-HCV sero-positivity, 4181 siblings of index cases, 6730 children of male index cases, and 2765 children of female index cases were included for further analysis. The prevalence of HBsAg in each five-year age interval is shown in Fig. 2. Patients with higher risk of perinatal transmission showed a higher HBsAg prevalence and greater decline in HBsAg prevalence during aging.

Siblings of index cases

In the 4181 siblings seronegative for anti-HCV, 2190 were male and 1991 were female. The prevalence of HBsAg was higher in males (54.8% vs. 49.9%, $p = 0.001$). Differences were mainly observed at ages 30-34 and 40-49 years (Table 3), but after correction of alpha using the sharpened

Table 1. Patient Data

Category	General checkup N = 45035	Siblings of indexed cases N = 4455	Children of male index cases N = 7111	Children of female index case N = 2947
Age	a	b	c	c
(year mean±SD)	50.36±11.90	43.3±13.4	39.2±10.6	40.4±10.2
Gender	a	b	a	b
Male	24523 (54.45)	2288 (51.36)	3863 (54.32)	1502 (50.97)
Female	20512 (45.55)	2167 (48.64)	3248 (45.68)	1445 (49.03)
HBsAg	a	b	c	d
Positive	6989 (15.52)	2298 (51.58)	2277 (32.02)	1174 (39.84)
Anti-HCV	a	b	c	d
Positive	2072 (4.60)	274 (6.15)	381 (5.36)	182 (6.18)
Estimated risk of perinatal transmission	15~20%[17-19]	60~70%[3-5,10]	15~20%[10,17-19]	41~50%[10-12]

Numbers in parentheses are percentages in each category.

Different letters (a,b,c, and d) indicate statistically significant differences between groups in each category (ANOVA test was used for continuous data and the chi-square test was used for categorical data. The sharpened Bonferroni procedure was used in multiple tests).

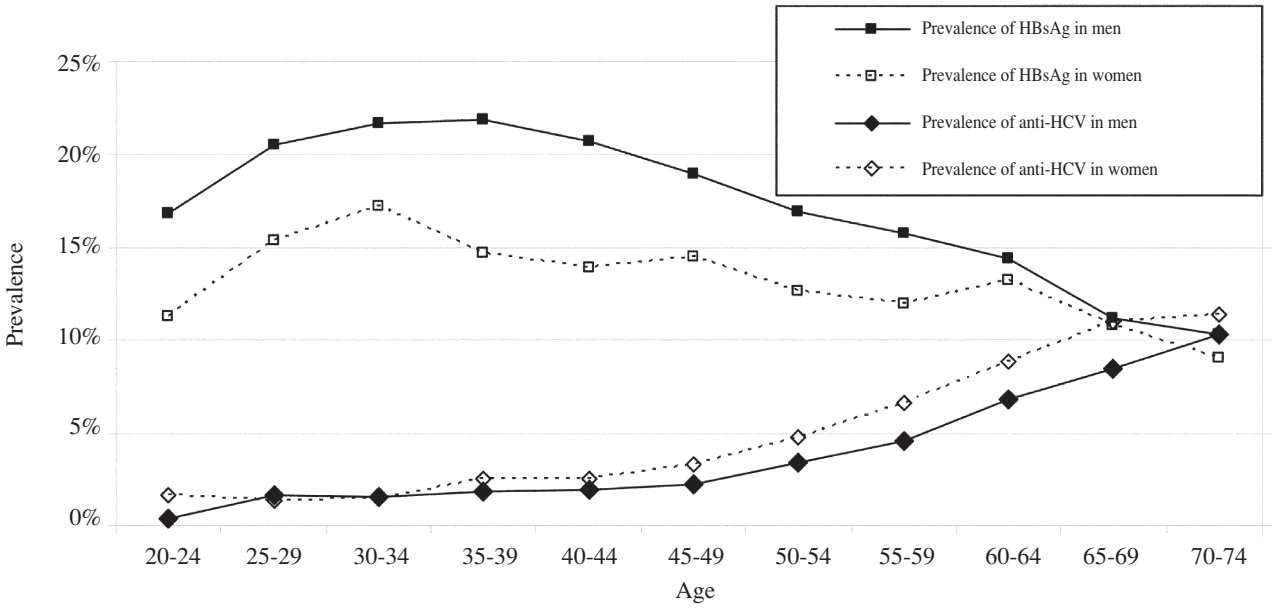

Fig. 1 Gender differences in prevalence of HBsAg and anti-HCV in 45,035 in the general checkup group. The prevalence of HBsAg was higher in men than in women ($p < 0.001$), especially for those younger than 60 years. The prevalence of anti-HCV was low in both genders before age 35. It rose progressively with increasing age. A significantly higher prevalence of anti-HCV was found in women than in men in those older than 35 years ($p < 0.001$).

Table 2. Prevalence of HBsAg and Anti-HCV in the General Check-up Group Stratified by Gender and Age Range

Gender	Age Range										
	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Prevalence of HBsAg											
Male %/Total No	16.8/232	20.5/755	21.7/1612	21.9/2407	20.7/3579	19.0/3769	16.9/3824	15.8/2689	14.4/2484	11.2/1872	10.3/1300
Female %/Total No	11.3/239	15.4/739	17.2/1131	14.7/1512	13.9/2281	14.5/2758	12.6/3725	12.0/2632	13.2/2457	10.8/1852	9.0/1186
Prevalence ratio*	1.49	1.33	1.26	1.49	1.49	1.31	1.34	1.32	1.09	1.04	1.14
Total %/Total No	14.0/471	18.0/1494	19.8/2743	19.1/3919	18.0/5860	17.1/6527	14.8/7549	13.9/5321	13.8/4941	11.0/3724	9.7/2486
Prevalence of anti-HCV											
Male %/Total No	0.4/231	1.7/751	1.6/1601	1.8/2400	1.9/3572	2.2/3760	3.4/3818	4.6/2685	6.8/2479	8.5/1870	10.3/1300
Female %/Total No	1.7/239	1.4/735	1.5/1127	2.4/1506	2.5/2276	3.3/2754	4.8/3717	6.6/2629	8.9/2454	11.0/1848	11.4/1185
Prevalence ratio*	0.24	1.21	1.07	0.75	0.76	0.67	0.71	0.70	0.76	0.77	0.90
Total %/Total No	1.1/470	1.5/1486	1.6/2728	2.0/3906	2.1/5848	2.7/6514	4.0/7535	5.6/5314	7.9/4933	9.8/3718	10.8/2485

*: A higher prevalence of HBsAg was found in males than in females; whereas the prevalence of anti-HCV was higher in females than in males (logistic model; $p < 0.001$).

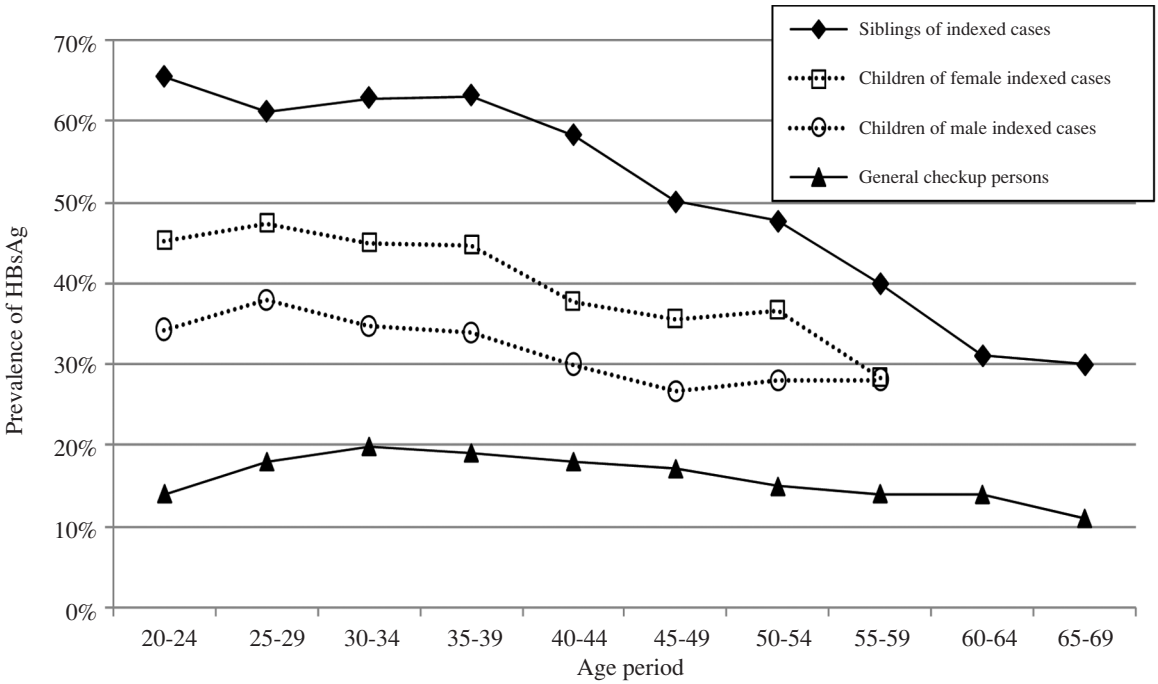

Fig. 2 Prevalence of HBsAg stratified by age in the general check up group and three groups of HCC relatives. The prevalence of HBsAg was higher in groups with higher perinatal transmission rates and declined progressively with increasing age in all groups. The rates of decline were positively correlated with the risk of perinatal transmission.

Table 3. Prevalence of HBsAg in the General Check-up Group* and Siblings of HCC Patients Stratified by Gender and Age Range

Gender	Age range									
	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
General Checkup group										
Male %/Total No	17.0/230	20.3/736	21.6/1575	21.8/2357	20.6/3504	19.0/3679	17.0/3690	15.8/2562	14.4/2310	10.6/1711
Female %/Total No	11.1/235	15.6/725	17.4/1110	14.7/1469	13.8/2219	14.6/2662	12.7/3539	12.0/2455	13.4/2235	11.1/1644
Odd ratio†	1.641	1.382	1.308	1.622	1.619	1.368	1.415	1.379	1.086	0.950
95% Confidence interval										
Upper	0.963	1.056	1.075	1.362	1.400	1.195	1.241	1.173	0.918	0.765
Lower	2.799	1.808	1.592	1.931	1.873	1.567	1.613	1.022	1.285	1.181
p value	NS	0.022	0.007	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	NS	NS
Total %/Total No	14.0/465	18.0/1463	19.9/2685	19.1/3826	18.0/5723	17.1/6341	14.9/7229	14.0/5017	13.9/4545	10.9/3355
Siblings of HCC										
Male %/Total No	66.7/54	62.5/128	67.7/235	65.7/344	62.8/400	55.3/246	48.8/248	38.3/214	32.0/128	28.8/73
Female %/Total No	64.3/56	59.6/109	57.5/212	60.6/320	53.4/367	45.3/274	46.5/254	41.6/202	29.9/117	31.3/64
Odd ratio†	1.111	1.128	1.543	1.244	1.470	1.496	1.098	0.873	1.104	0.888
95% Confidence interval										
Upper	0.506	0.668	1.049	0.907	1.102	1.058	0.733	0.589	0.642	0.427
Lower	2.440	1.905	2.270	1.706	1.961	2.114	1.559	1.292	1.900	1.848
p value	NS	NS	0.027	NS	0.009	0.022	NS	NS	NS	NS
Total %/Total No	65.5/110	61.2/237	62.9/447	63.2/664	58.3/767	50.0/520	47.6/502	39.9/416	31.0/245	29.9/137

*: Exclude anti-HCV (+) cases; †: The male/female prevalence odd ratios were significantly different between the general check-up group and HCC siblings after adjusting for the age range (logistic model; $p < 0.001$).

Bonferroni procedure, none of the differences were significant in those age groups. The peak prevalence of HBsAg was 67.7% for males aged 30-34 years and 64.3% for females aged 20-24 years. The prevalence decreased to around 30% at age 65-69 years in both genders.

The HBsAg prevalence declined at a rate of 1.37% per year in males and 0.95% per year in females between ages 35 to 59 years ($p < 0.001$).

Children of male index cases

In the 6730 anti-HCV negative children of male index cases, 3,652 were male and 3,078 were female, with a higher prevalence in males (37.6% vs. 26.6%, $p < 0.001$). The differences were detected among those 24 to 54 years of age (Table 4), and were statistically significant even after Bonferroni adjustment. The peak prevalence of HBsAg was 47.0% for males aged 25-29 years and 31.4% for females aged 20-24 years, which decreased to 29.7% and 26.0% for males and females, respectively, at 55-59 years of age. The rate of decline in HBsAg prevalence between 35 to 59 years of age was 0.51% per year in males and 0.05% per year in females.

Prevalence of HBsAg in children of female index cases

In the 2765 anti-HCV negative children of female index cases, 1362 were male and 1403 were female, with a higher HBsAg prevalence in males (44.1% vs. 38.1%, $p = 0.001$). After stratification by age group and correction of alpha using the sharpened Bonferroni procedure, the differences became non-significant in all age periods except for the 30-34 year age group ($p = 0.032$). The peak prevalence of HBsAg was 51.7% (age 30-34 years) in males and 45.8% (age 25-29 years, Table 4) in females, which decreased to 29.8% in males and 26.7% in females at age 55-59 years. The rate of decline in HBsAg prevalence from 35 to 59 years of age was 0.90% per year ($p < 0.001$) and 0.77% per year ($p < 0.001$) in males and females, respectively.

Table 4. Prevalence of HBsAg in Children of Male and Female HCC Patients Stratified by Gender and Age Range

Gender	Age range							
	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59
Children of male HCC								
Male %/Total No	37.4/243	47.0/336	39.2/622	39.9/1056	33.3/742	32.6/328	35.1/154	29.7/74
Female %/Total No	31.4/236	27.5/287	29.7/535	27.0/846	26.3/616	20.2/287	20.1/134	26.0/50
Odd ratio*	1.311	2.337	1.526	1.797	1.398	1.912	2.140	1.204
95% Confidence interval								
Upper	0.898	1.670	1.194	1.478	1.105	1.322	1.252	0.538
Lower	1.913	3.271	1.951	2.185	1.770	2.765	3.695	2.693
p value	NS	< 0.001	0.001	< 0.001	0.005	0.001	0.005	NS
Total %/Total No	34.4/479	38.0/623	34.8/1157	34.1/1902	30.1/1358	26.8/615	28.1/288	28.2/124
Children of female HCC								
Male %/Total No	50.0/34	48.8/82	51.7/201	47.7/405	38.8/327	40.1/147	35.2/88	29.8/47
Female %/Total No	41.0/39	45.8/72	37.8/185	42.0/414	36.9/331	32.1/184	38.0/108	26.7/45
Odd ratio*	1.438	1.129	1.761	1.256	1.098	1.420	0.889	1.167
95% Confidence interval								
Upper	0.569	0.579	1.174	0.953	0.794	0.904	0.495	0.470
Lower	3.632	2.123	2.643	1.655	1.491	2.233	1.595	2.897
p value	NS	NS	0.004	NS	NS	NS	NS	NS
Total %/Total No	45.2/73	47.4/154	45.1/386	44.8/819	37.8/658	35.6/331	36.7/196	28.3/92

*: The male/female prevalence odd ratios were significantly different between children of male and female index cases after adjusting for the age range (logistic model; $p < 0.001$).

Gender ratio in different groups of HBsAg carriers

HBsAg carrier gender ratios in each 5-year age period were compared between siblings and general check-up subjects, as well as between children of male and female index cases, by fitting a series of logistic models. We found that gender odds ratios were significantly different between groups with different HBV transmission routes. To be specific, the male to female odds ratio of HBsAg prevalence was significantly different between the general check-up group and siblings of patients with HCC after adjusting for age periods. The odds ratio was also significantly different between children of male and female index cases ($p < 0.001$).

DISCUSSION

Two recent large series from Greece and New Zealand showed a higher prevalence of HBsAg in males than females.[15,16] However, the HBsAg prevalence between genders was not significantly different in epidemiologic studies in Taiwan.[17-19] The case numbers in these studies were relatively small. In this study, a group of subjects who received a self-paid general physical check-up was included. They were not randomly selected persons but the large number of subjects can provide representative information in this area. The prevalence of HBsAg in the whole general check-up group and in each age period were similar to that in Taiwanese epidemiologic studies.[17-19] A significant difference in HBsAg prevalence between males and females was clearly shown in the 20-59 year age group. In contrast to HBV, the prevalence of anti-HCV was higher in females, which confirms the difference in gender preference between HBV and HCV infection.[15]

The gender difference in the prevalence of HBsAg was also found in siblings and children of HCC patients. However, the difference was smaller in siblings of HCC patients than in the general check-up group (Table 3; $p < 0.001$). Similar findings were found in children of male index cases and children of female index cases. These groups with higher risks of perinatal transmission showed a lower difference in HBsAg prevalence between genders. The prevalence ratio between males and females was 1.20 to 2.34 in children of male HCC patients in the 20 to 54 year age groups. The ratio decreased to 0.89 to 1.76 in children of female HCC patients (Table 4; $p < 0.001$). The prevalence of HBsAg was similar in both genders after age 60 in all groups. Since most women have reached menopause by 60 years of age,[20] it is possible that the difference in HBsAg prevalence is associated with sex hormones. Most HBV infection occurs before adolescence when the level of sex hormones is still low. Other factors, such as higher immunity in females than males may also contribute to HBsAg clearance. A gender difference in the prevalence of anti-HCV was found after 35 years of age, and may be due to gender-associated behavior rather than a hormonal effect.

The HBsAg prevalence was positively correlated with the risk of perinatal transmission (Fig. 2), which peaked at age 25 to 35 years and declined progressively thereafter in all groups. The rate of decline was also related to the risk of perinatal transmission. Siblings of index cases and children of female index cases showed high rates of decline, while children of male index cases showed the lowest rates of decline.

The declining prevalence of HBsAg was mainly due to the high spontaneous clearance of HBsAg,[10,21] and high mortality in HBsAg carriers.[9,22] The annual mortality rates (usually less than 1 %/year) were lower than the annual HBsAg clearance rates (around 1.5 %/year). Therefore, spontaneous HBsAg clearance is the main reason for the decline in HBsAg with increasing age. A longitudinal study will be done to evaluate the ratio between mortality and spontaneous HBsAg clearance by periodically following asymptomatic carriers.

In perinatal transmission, most children become chronic HBsAg carriers when the maternal HBV DNA level is higher than 30 pg/ml ($1.7*10^6$ IU/ml).[23] This was the reason that the gender difference in HBsAg prevalence was low in patients with high perinatal infection. The life expectancy in Taiwan is 73.5 years in males and 79.7 in females (Health and Vital Statistics 2004, Republic of China). The shorter life expectancy in men may contribute to the decreased gender difference in HBsAg prevalence for patients older than 60 years. Most offspring become chronic HBsAg carriers when maternal HBV DNA is high. In this situation, the role of genetic polymorphism in HBsAg clearance at initial exposure is low. In contrast, the prevalence of HBsAg in children of male index cases was relatively low.[10] The low prevalence of HBsAg is not due to a lack of

infection. Most adult Taiwanese are seropositive for hepatitis B core protein antibody.[17-19] The timing of infection is important. The HBsAg carrier rate was 23% for children infected before entering elementary school,[24] and dropped to 2.7% for college level students.[25] When only a small proportion of HBV infected patients become HBsAg carriers, genetic selection of patients who are less able to clear the virus will be unavoidable. This genetic selection may also be the reason for the low rate of decline in HBsAg with increasing age in children of male index cases.

In summary, this study confirmed that males are more likely to become chronic HBsAg carriers. The difference diminished in patients with perinatal infection. The declining prevalence of HBsAg in the aging process was found in groups with high perinatal infection which suggests neonatal tolerance to HBsAg does not endure.

Acknowledgements

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性別、病毒感染途徑及年齡增長對 B 型肝炎表面抗原盛行率的影響

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背 景： 年齡、性別及生產期間感染 B 型肝炎病毒均與肝癌發生有關。B 型肝炎病毒感染途徑對不同性別之影響，以及隨年齡增長後 B 型肝炎表面抗原 (HBsAg) 帶原比例之變化並無文獻記錄，因此進行本分析。

方 法： 分析對象包括連續性之自費健康檢查個體以及參與前瞻性肝病篩檢之肝癌家屬。肝癌家屬再區分爲肝癌手足、男性肝癌子女與女性肝癌子女三群。肝癌手足與女性肝癌子女爲多數於出生前後感染 B 型肝炎病毒組。男性肝癌子女爲少數於出生前後感染 B 型肝炎病毒組。

結 果： 總共有 45,035 位自費健康檢查個體及 14,573 位肝癌患者之一等親屬資料進入本分析。肝癌親屬包括 4,455 位肝癌手足，7,111 位男性肝癌子女及 2,947 位女性肝癌子女。在多數於出生前後感染 B 型肝炎病毒組及男性患者 HBsAg 盛行率較高。男女間 HBsAg 盛行率之差異在多數於出生前後感染 B 型肝炎病毒組及 60 歲以上之族群有減少之現象。所有各組 HBsAg 盛行率皆隨年齡增加而減少。於 35 到 59 歲間，HBsAg 盛行率減少最多者爲男性肝癌手足 (每年 1.37%)；減少最不明顯者爲男性肝癌之女兒 (每年 0.05%)。健康檢查個體中，C 型肝炎盛行率則女性 (5.7%) 高於男性 (4.0%)。

結 論： 一般而言，HBsAg 盛行率男性高於女性，然而對於生產期間感染 B 型肝炎病毒之患者男女之差異減少。生產期間感染 B 型肝炎病毒之患者 HBsAg 盛行率皆隨年齡增加而顯著減少。意謂著生產期間感染之帶原者、特別是男性、有較高之死亡率及或延遲性 HBsAg 清除率。也顯示新生兒對 HBsAg 的免疫耐性可隨年齡增加而衰微。
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關鍵詞： 生產期間感染，新生兒的免疫耐性，性別，家族，B 型肝炎表面抗原，盛行率

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