Modelling death rates for carriers of hepatitis B

J. A. DICKINSON*, Y. T. WUN AND S. L. WONG

Department of Community and Family Medicine, The Chinese University of Hong Kong, 4/F School of Public Health, Prince of Wales Hospital, Health Centre, Shatin, N.T., Hong Kong

SUMMARY

Hepatitis B carriers who acquired the infection perinatally die from hepatocellular carcinoma (HCC) and cirrhosis at high rates. Published cohort studies are largely limited to males and are too small to estimate the age-specific risk of death. We therefore used routinely collected Hong Kong data to estimate the risks. Deaths were partitioned between carriers and non-carriers, then current life table calculations determined life expectancy and probability of dying from HCC or cirrhosis. HCC is the dominant cause of death for male carriers in middle adulthood with a lifetime risk of 27% for HCC compared to 4% for females. Predicted life expectancy is 72 years for male carriers, compared to 79 years for non-carriers. Female carriers have a life expectancy of 81 years and non-carriers 83 years. This model probably applies to all southern Chinese populations and emigrants with similar life history, and other populations that acquired infection early in life.

INTRODUCTION

Hepatitis B (HBV) carriage is common in many parts of the world, especially East Asia and Sub-Saharan Africa, and many carriers die prematurely of complications, mainly hepatocellular carcinoma (HCC) and cirrhosis [1, 2]. Asian, Alaskan and African carriers have much higher complication rates than Europeans, probably due to predominant perinatal or infant acquisition, rather than sexual or parenteral transmission later in life [3]. This early acquisition by the vast majority of carriers leads to long-term carriage with loss of circulating antigen in less than 1% per year [4].

While vaccine now protects the generations born since its widespread use, carriers in previous cohorts will be at risk of developing complications for the rest of their lives. Such carriers in high-prevalence coun-tries are aware of the complications, so many of them ask their doctors about their risk and what will happen to them. However, epidemiological studies of the association between HBV and these complications have been done mainly for study of causation rather than estimation of risk, and are not helpful for this purpose. In a systematic review we found 12 population-based cohort studies. They are mostly small, and only three provide age-specific data: only one of these examined both sexes. On the basis of one study in Taiwan [5], different authorities calculate that 25–50% of the (male) carriers will die as a result [1, 6]. Obtaining this information through cohort studies is difficult, and since the widespread use of antiviral treatments, may be impossible. Consequently, we developed an epidemiological model from basic health statistics to estimate the effect of this excess mortality for HBV carriers.

* Author for correspondence.

METHODS

The mathematical model is based on the concept that in a population with high prevalence of carriers most of the hepatocellular cancer and cirrhosis occurs among the carriers. This effect is measured in case-control studies, which show high relative risks. Thus, the number of deaths from these diseases can be partitioned according to such relative risk estimates between the small group of carriers and the rest of the population. This calculation can be undertaken to estimate the death rates from each disease for the carriers and the rest of the population among each age and sex group. We assume that the baseline death rate from all other causes is the same for carriers as for other members of the population, and therefore add these three rates to obtain the total death rate, for both the carrier group and the non-carriers. Therefore, we can estimate the age and sex-specific death rates from specific diseases and overall, as they would be observed in a cohort study.

We then used a standard epidemiological approach, the life-table, to calculate the effect on four cohorts of people: carriers and non-carriers of both genders.

Variables used

HCC in Hepatitis B carriers is associated with several factors: cirrhosis, smoking, alcohol and hepatitis C [7, 8], but the most important are gender and age [9]. The role of alcohol in the carcinogenesis of HCC is disputed [10], and is not a major aetiological factor in Hong Kong [11]. Association with cigarette smoking is equivocal [8]. There are studies suggesting aflatoxins as an aetiological factor for HCC [8, 12], but direct proof is lacking [10], and this is unlikely to be a major factor in Hong Kong where food quality is good. In Hong Kong only 7·3% of liver cancer patients have circulating hepatitis C antigen [13–15] and its prevalence in the general community is very low, of the order of 0·4–0·5% [16]. Thus, the initial model can be simplified to include only gender and age as the predictive variables.

Population and mortality data

Hong Kong is now a developed, westernized city, whose population is over 95% Chinese in ethnic origin. There are regular formal censuses. Births and deaths are registered with a high degree of accuracy, and most deaths occur in well-run government or private hospitals where illnesses are investigated using the full array of diagnostic tests and imaging. A cancer registry obtains and cross-correlates data from hospitals and pathology laboratories, making use of the unique identity card number. Thus routine data are as good as in any other developed country, and are of sufficient quality for estimation purposes.

To smooth annual variations we used the most recent 5 years of published data from the cancer registry [17] from 1990 to 1994. For the same years we obtained population data by sex and in 5-year age groups from tables produced by the Census and Statistics Department of Hong Kong [18].

Prevalence of hepatitis B carriers

The prevalence of HBV carriers in Hong Kong adults has been estimated from a variety of opportunistic serological studies on blood donors, antenatal women and hospital patients, as about 10% for all ages and both sexes [19]. We used this figure for the model.

Complications of hepatitis B

HCC

The Hong Kong Cancer Registry measured the mortality from HCC as being about 60% of the incidence [17]. This is likely to be an underestimate; mortality from this disease was nearly 100% before 1995 as HCC were seldom detected when still small and surgically treatable [20]. In Hong Kong, the median survival of untreated patients was 8 weeks from symptomatic presentation [11]. Around the world, survival for over a year after onset of HCC symptoms is unusual [20]. Some HCC patients would have been certified as dying from other causes, such as surgery complications, or other organ failure. Consequently, we chose to use the incidence rate to represent the best available measurement of deaths resulting from HCC, and presumed that the lag between incidence and death is not long enough to require adjustment.

Detailed analyses reported by the Cancer Registry [17] in the years 1992, 1993 and 1994 show that, where a histological diagnosis was available, 81% of the liver cancers in males and 51·3% in females were HCC. We assumed that the same fractions applied to those where histology was not available. One analysis of HCC patients showed that 313 among 381 males (82·2%) and 28 among 43 females (65·1%) were HBV

carriers [13].Between 1996 and 1998, the database of the joint Hepatoma Clinic in the Prince of Wales Hospital found that 687 of 861 males (79·8 %) and 124 of 177 females (70·1 %) were carriers (P Johnson, A Tang, personal communication). Another study in Hong Kong showed that about 85 % of HCC tissue samples had clear evidence of the viral genome in the cells [11]. Therefore we have used the baseline values of 80 % for males and 70 % for females.

Cirrhosis

In Hong Kong about 80 % of all hospital clinic cases of cirrhosis occur among HBV carriers [13]. Defining cirrhosis is difficult and subject to substantial clinical measurement variation, however, since better data are not available, we chose to use reported 1990–4 death rates from cirrhosis (#571, ICD9) [21].

Death rate and life table calculations

For each 5-year age and sex group the deaths from HCC and cirrhosis were partitioned between carriers and non-carriers according to the assumptions made. A 'basal' death rate for all other causes was obtained by subtraction of HCC and cirrhosis deaths from the total. Then the partitioned disease-specific rates for male and female, carriers and non-carriers, were added to the basal rate to produce age and sex-specific mortality rates for each group (Appendix 1).

We estimated the cumulative effect of death rates on a cohort of people over their lifetime by the abridged life-table method [22] in which a hypothetical population of 100 000 is assumed to experience the current mortality rates, and the survivors of each 5 years experience the mortality rate for the next, in sequence (Appendix 1). This simulates what would happen to populations of carriers and non-carriers with the characteristics of Hong Kong, presuming that they were exposed to current rates over their whole life. The life-table approach also provides estimates of likely survival for a person of any given age.

Proportion dying from complications

We calculated the number of HCC and cirrhosis cases dying in each year of the life table cohorts, and summed them across age groups to estimate how many carriers would die from these two or all other causes of death (by age 50 and throughout lifetime respectively).

Sensitivity analysis

To determine the effects of error in the estimates, we conducted sensitivity analysis for the major assumptions, by substituting alternative values as follows:
A. We simulated the effect of varying the proportions of carriers in the population. We chose rates of 6 % and 14 %.
B. We simulated the effect of the percentage of HCC among liver cancers at 90, 80, 70 or 50 % for both men and women.
C. We tested the effect of different percentages of HCC due to hepatitis B carriers. We chose rates of 90 or 70 % for men, and 80 or 60 % for women.
D. We tested the effect of assuming that excess deaths among carriers caused by liver diseases other than cancer are equal to the deaths certified as due to cirrhosis, or 60 % of this number.

All other factors were held constant at the original value while each assumption was tested. For each of these variations, we show, the effect on survival to age 50, 60 and 70 and on average life expectancy for HBV carriers of both genders.

RESULTS

The calculated mortality rate for HCC among carriers is compared with mortality rates for HCC among non-carriers and overall population mortality rates in Figure 1. To allow comparisons of ratios across all age groups they are displayed in logarithmic scale. Thus, in the graph, two lines will be the same distance apart if their ratios are equal. The HCC rate for male carriers rises faster than the population death rate from the age of 20 years and peaks at 70 years. Indeed for HBV carrier men between 35 and 50 years, HCC death rate is higher than the general population death rate for all other causes combined. The death rate from HCC for female carriers is much lower and never rises above the total death rate for females. The values selected produce a relative risk for male carriers to develop HCC about 50 times that of non-carriers through all age groups; the corresponding relative risk for females is about 17.

Figure 2 shows the total (baseline + HCC + cirrhosis) mortality rates for carriers and non-carriers. For those aged 35–60 years the rate for male carriers is two to four times higher than that for non-carriers (which almost coincides with the baseline mortality rate for males (not shown). Above 60 years, the annual carrier
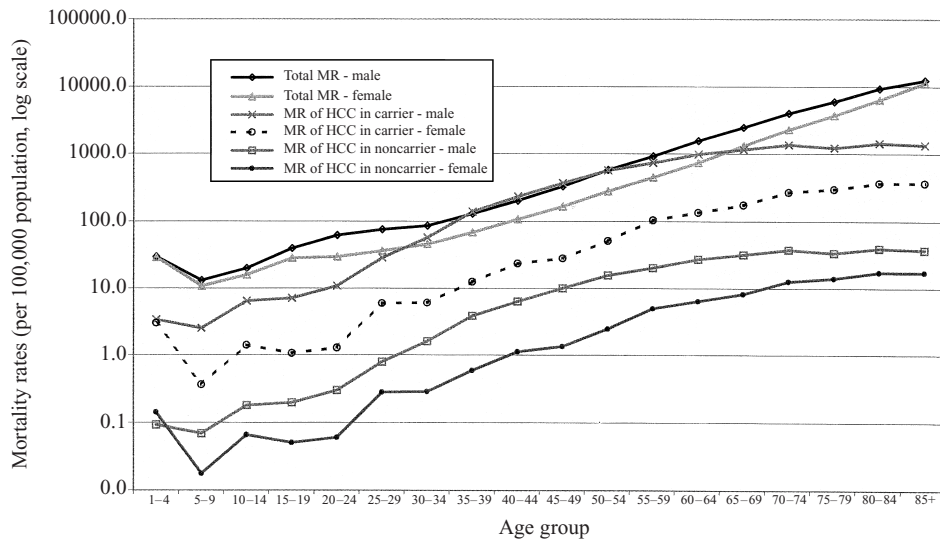
Fig. 1. Mortality rates for HCC in carriers and non-carriers, compared to total population mortality rate (log scale).
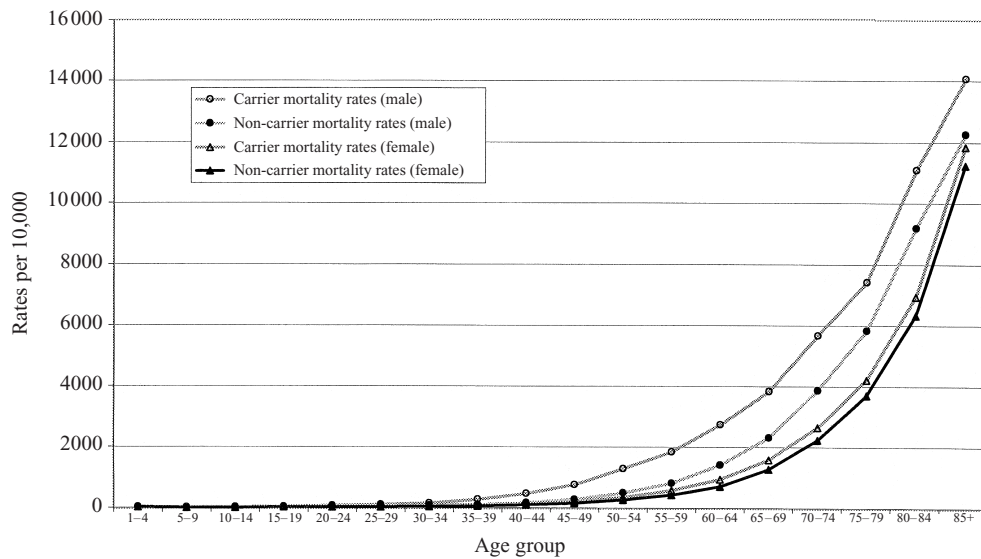

Fig. 2. Total mortality rates for hepatitis B carriers and non-carriers.

death rate is persistently more than 1000 per 10^5 higher than that for the non-carriers. For female carriers, the death rate is raised but never more than 1·4 times greater than the non-carriers, and the difference is always less than 700 per 10^5.

The life table analysis (Fig. 3) shows the expected effects of these death rates on a cohort affected by current death rates over the whole of their lives. Female non-carriers have the lowest death rates and therefore the greatest survival: 82·3 years. Female carriers die earlier with an average life expectancy about 80·4 years but they are still better off than male non-carriers, whose expectancy is 76·9 years. Male carriers have substantially lower survival from the fourth decade. The total effect is that they are 20 %

less likely to survive through the seventh and eighth decades, with life expectancy of 70·5 years.

Figure 4 shows the expectations of life at a given age for Hong Kong people, according to their carrier status. The lines converge very slowly until age 40 then more rapidly. Table 1 shows our estimates of cause-specific deaths among carriers and non-carriers expressed as a percentage of total deaths, to compare with other authors. Over half of male deaths up to age 50 are hepatitis B related, but over a lifetime, the fraction is smaller, since other causes become more common at late age. Female rates are much lower.

Sensitivity analyses of the carrier death rates show that the greatest effect comes from variations in estimates of the prevalence of carriage (Table 2). In
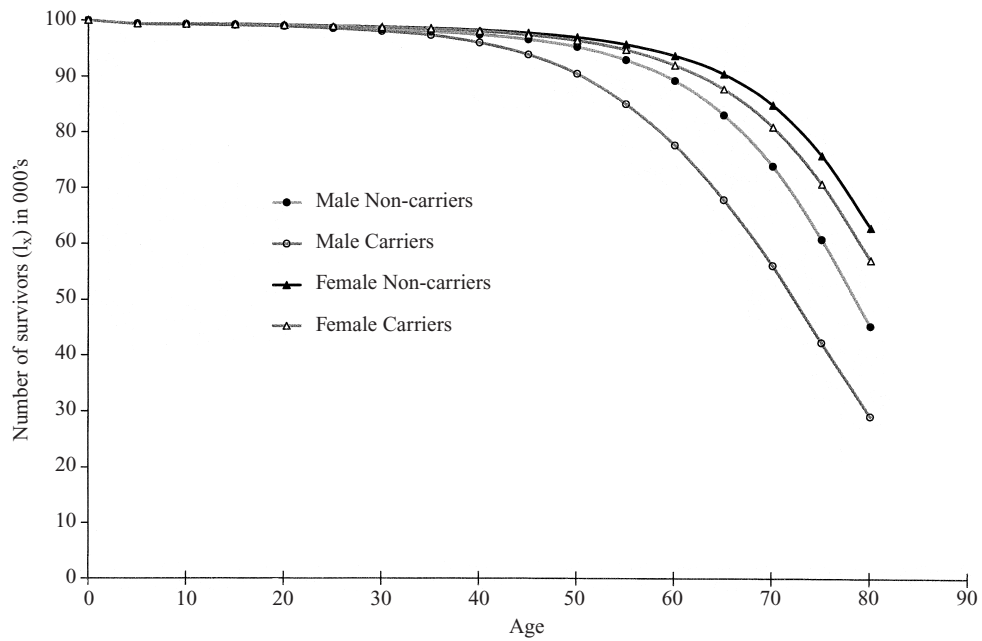
Fig. 3. Current life-table analysis of number of survivors (l_x) out of 100000 live births, using 1990–4 mortality rates.
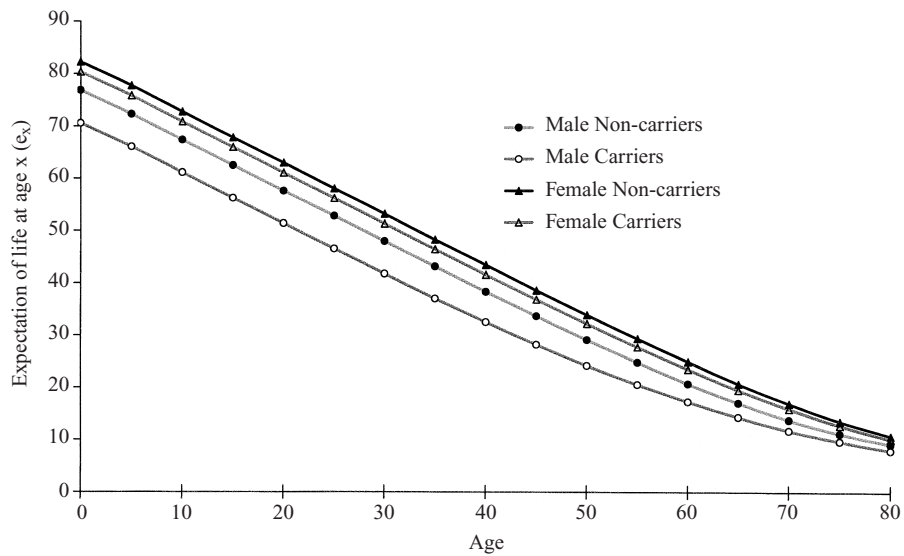

Fig. 4. Expectation of life at age x, 1990–4 Hong Kong current life-table.

Table 1. *Percentage of deaths due to HCC and cirrhosis cumulated to age 50 and over whole of lifetime among HBV carriers and non-carriers*

	Male				Female			
	By age 50		Lifetime		By age 50		Lifetime	
	Carriers	Non-carriers	Carriers	Non-carriers	Carriers	Non-carriers	Carriers	Non-carriers
HCC	44·1*	2·4	26·9	0·8	11·2	4·0	4·0	0·9
Cirrhosis	12·9	0·8	8·2	0·3	6·5	0·2	3·4	0·1
Total HB-related	57·0	3·2	35·1	1·1	17·7	4·2	7·5	1·0
Other causes	43·0	96·8	64·9	98·9	82·3	95·8	92·5	98·9

* Some figures do not add up due to rounding.

Table 2. *Sensitivity analyses of carrier survival rates for differing assumptions in the model*

	Male					Female			
	% Carriers surviving at age					% Carriers surviving at age			
	40	50	60	70		40	50	60	70
(A) Sensitivity analysis for varying carrier rates									
Carrier rates (%)					Carrier rates (%)				
6	95·1	87·3	70·6	43·4	6	97·9	96·0	90·8	78·3
10	**96·0***	**90·4**	**77·6**	**56·1**	10	**98·1**	**96·4**	**92·0**	**80·9**
14	96·4	91·8	80·9	60·8	14	98·1	96·6	92·5	82·0
(B) Sensitivity analysis for differing estimates of percentage of hepatocellular cancers (HCC) among all liver cancers									
% of HCC					% of HCC				
90	95·9	90·1	76·8	54·9	90	98·0	96·1	91·2	79·4
80	**96·0**	**90·4**	**77·6**	**56·1**	80	98·0	96·2	91·4	79·8
70	96·2	90·9	78·6	57·5	70	98·0	96·3	91·6	80·2
50	96·4	91·7	80·5	60·3	50	**98·1**	**96·4**	**92·0**	**80·9**
(C) Sensitivity analysis for varying percentage of HCC caused by HBV									
% of HCC					% of HCC				
90	95·9	90·0	76·6	54·6	80	98·0	96·3	91·8	80·6
80	**96·0**	**90·4**	**77·6**	**56·1**	70	**98·1**	**96·4**	**92·0**	**80·9**
70	96·2	90·9	78·7	57·6	60	98·1	96·5	92·1	81·2
(D) Sensitivity analysis of varying percentage of liver cirrhosis deaths caused by HBV									
% Cirrhosis deaths					% Cirrhosis deaths				
100	96·0	90·2	76·9	55·1	100	98·1	96·4	91·8	80·5
80	**96·0**	**90·4**	**77·6**	**56·1**	80	**98·1**	**96·4**	**92·0**	**80·9**
60	96·1	90·7	78·3	57·1	60	98·1	96·4	92·1	81·3

* **Bold** figures indicate baseline assumptions.
† All other factors held constant at baseline level for each univariate sensitivity analysis.

particular, if the true population prevalence is lower than 10% the deaths are concentrated among fewer people, so the predicted survival of these men at age 60 drops by about 1·5% for each 1% reduction in prevalence and by about 2% at age 70. Assuming that all liver cancers are HCC reduces the carrier survival rate by only 3% at age 70. Changing the estimate of the proportion of liver cancer caused by HBV from 80% to 100% reduces the death rate by only 4%. Changed estimates of the proportion of mortality due to liver cirrhosis change the mortality estimates at age 70 by less than 1%. Effects for females are proportionately less.

DISCUSSION

This modelling approach using population data allows estimation of the effects that might be observed in a large cohort study of carriers. We have used local data and demonstrated that being an HBV carrier in Hong Kong causes vastly increased mortality for males, but very little for females. For male carriers the mortality from HCC is higher than the average population mortality during young adult life, and its effect is only relatively reduced when other competing causes of death become dominant after the age of 65. Adding the effect of cirrhosis deaths increases the HBV effect further. The current life table demonstrates the effect of disease on a cohort of people subject to current rates over their lifetime. It shows that at the worst, at age 75, there would be a 33% difference in mortality between male carriers and non-carriers (Figs 2, 3). For women, the difference is always less than 10%.

Overall life expectancy in Hong Kong is among the highest in the world, but liver cancer is a major cause of death. For those who are not carriers of HBV, life expectancy is even higher. Such data may not apply in other third world countries with high carriage rates, but may well do so in those which have also undergone such rapid epidemiological transition. The lifetime HCC risk of 27% for carrier men is comparable to estimates of 25–40% derived from the Taiwan cohort [1, 6] and so is the additional risk of death from liver

cirrhosis of one quarter to one third, though this later effect was not observed in Alaska [23]. The expectation of life is useful for doctors explaining HBV sequelae for people in the community, since it shows the effect for the age the patient has reached. While individuals vary, this graph gives much more relevant information than the blank statement that a certain proportion of carriers will die as a result, since it tells when the risk occurs. The effects of being a HBV carrier are substantial, but few men die of these causes in young adult years, and most carriers will live past middle age, while women have much lower death rates overall and from HBV complications. Though survival rates after the development of liver cancer appear similar for males and females [24], age and sex differences in incidence rates are so great that studies which mix males and females, or do not analyse for age, are difficult to interpret properly. Data on the outcomes of the HBV carrier state should always be analysed separately by sex, and with age standardization.

Limitations

The results we obtained are dependent upon the assumptions we made and the quality of the data we used. The assumptions are: that incidence as measured by the cancer registry is a better measure of deaths caused by HCC than the mortality data, the prevalence of HBV carriage is 10%, the proportion of HCC among liver cancers, the proportions of HCC and of cirrhosis death caused by HBV. Sensitivity analysis shows that the dominant factor in our results is the carrier prevalence. Varying the other assumptions within credible values had smaller effects. Therefore we did not go on to examine the effect of simultaneous change in more than one variable.

The discrepancy between incidence and death data in the registry may be due to differences in certification practice, which systematically omit some deaths from liver cancer. If the true mortality rates were lower than we assumed, then the effects observed would be proportionally less.

The prevalence of HBV is based on a series of specific surveys predominantly on young adults. The data currently available for the older population are limited, and it is possible that the prevalence among women is lower than men [19]. If so, the true mortality rates for carrier women may be higher than our model indicates. However, most studies of carrier mortality [10, 23] show lower death rates for women as we found. Universal HBV vaccination for newborns started in Hong Kong in 1988, so nearly all infants and some older children were immune at the time the data we use were collected. Since the introduction of immunization, there would be fewer carriers and deaths from complications among the young, but these would be so few as not to affect the overall results.

Mortality from cirrhosis is harder to measure than for HCC, and many deaths of patients with this disease may be ascribed to other causes. Because of the different epidemiology of cirrhosis among men and women, the contribution from HBV may be less for women, but we have no good local data to provide better estimates. A lower proportion of HBV cirrhosis among women would reduce the calculated carrier mortality and slightly increase non-carrier mortality, minimizing the difference between the groups. All the estimates for women have a greater potential for variation, since the studies used [11, 13] include smaller numbers of women, and therefore the estimates of proportions are less certain for them.

The model also depends on the assumption that adding causes of death will approximate the total death rate for each group. However, dying from hepatitis complications may be related to other health habits and may partly substitute for other causes of death so the total death rate among carriers may be somewhat less than implied by this method. In Alaska, the non-liver deaths for carriers were somewhat lower than for the rest of the population, mainly due to fewer violent deaths: a problem in that society [23]. Since violent deaths are rare in Hong Kong, it is difficult to know what correction to make. Any effect would reduce the differences between carriers and non-carriers.

In a real cohort that started with 10% prevalence from infancy, this rate would reduce with age because of spontaneous sero-conversions and the higher attrition by death of HBV carriers, so the proportion of carriers among older people would be much lower. Current sero-prevalence data are based on people who come from a series of cohorts, which may have had very different original carrier rates. The spreadsheet can be set to contain varied prevalence rates by age, and could be corrected for attrition from death and sero-conversion within the mathematical model, but we have chosen not to do so because it would be better to obtain more accurate empirical prevalence rates.

We have not calculated confidence intervals, because the results are based on very large numbers, and therefore stochastic errors are small. Larger errors are

likely to have arisen because of bias in the initial figures used, and the problems noted above. The sensitivity analyses indicate the effects produced by varying the assumptions.

It appears that continuing presence of HBV envelope antigen (HBeAg) may be better than surface antigen alone as a predictor of continuing replication and liver damage [25, 26]. However, understanding is complicated by the presence of pre-core mutants in some patients who no longer have circulating e antigen but still appear to have viral replication. Few serologic prevalence data are currently available about HBeAg, nor the proportions of cancer or cirrhosis patients with this finding. It is not yet clear how much changed HBeAg status affects risk for hepatocellular carcinoma. Thus at present the model cannot take this factor into account.

The rates of HCC and cirrhosis among non-carriers are lower than for carriers, but the HCC rates are well above those observed in most societies without endemic HBV. This incidence may be due to misclassification of carriage state in the studies we have used for estimates, and in addition to the presence of hepatitis C in about 0·3–0·5 % of the population, since hepatitis C also causes such liver complications.

Comparisons with other data

These calculations depend on the observed epidemiology and therefore are applicable to Hong Kong people. The relative risks are comparable to those reported in Taiwan [21, 27–29] but larger than a previous report from Hong Kong in 1982 [30] and the estimates of the proportion of male carriers who will die from complications are in the same order of magnitude as other calculations based on the Taiwan cohort study [1, 6]. The figures are likely to be similar throughout South East Asia and southern China where the epidemiology of HBV and overall life expectancy is similar. We will attempt to repeat this calculation using data outside Hong Kong, e.g. Taiwan, where the model can be compared with a cohort study to provide an external validation of the method. However, Hong Kong is unusual in having a high prevalence of HBV, but very low hepatitis C rates, so replication may be difficult.

Use of the model

Our pseudo-cohort model was initially established for clinical prediction, to produce helpful estimates that would assist clinicians and their patients. While clearly being a carrier is a major health problem, most patients still survive to a considerable age, unlike the impression among many of our population, that carriers will inevitably die young. While immunization will protect those who are currently children and adolescents, clinical presentation of HBV-related complications will continue for the next 50 years. New anti-viral drugs suppress hepatitis viral DNA but they have side effects and are expensive, and may need to be taken for long periods, possibly for life. This model may help providers and patients to make decisions about whether and at what age to use these drugs for the greatest chance of benefit.

This method may also have other uses. Since the outcomes can be calculated from routinely collected data, which are available in many countries, the approach may prove valuable for understanding the effects of HBV in other populations where cohort studies are not available. It may help to understand causation by comparing the extent to which different populations, racial or other social groups suffer badly from HBV, and which are much less affected. The model could be valuable for planning intervention studies, since it provides a way to predict the expected outcomes for a patient cohort with mixed age and sex. This would form a basis for calculating sample size for trials of screening or the new treatments that are being developed.

The model needs refinement through further studies giving better estimates of the various probabilities included, and would need recalculation in other locations where the values are different and the effects of other associated factors are greater. In regions where hepatitis C and alcohol intake play greater roles in aetiology a more complex adaptation is needed. Even in Hong Kong HBV carriers are not a homogeneous population, and progression of disease depends on individual factors, including HBeAg status. When empirical studies provide better evidence for subgroups, the model can be developed accordingly.

APPENDIX 1

Mathematical method

Box 1 shows how the spreadsheet was used to partition the mortality from HCC and cirrhosis between the carriers and the non-carriers. The source of data is indicated and the calculation steps are shown. The age-specific death rates resulting were then used in life table calculations, as follows:

Constructing an Abridged Life Table. (From Chiang [22] 140–1)

1. Compute the probability, $\hat{q}_i$, of dying in the interval (x_i, x_{i+1})

$$\hat{q} = \frac{n_i M_i}{1 + (1 - a_i) n_i M_i},$$

where M_i is the age-specific death rate, n_i is the length of the age interval, which is 1 for the first year, 4 for the second interval, and 5 thereafter. a_i is the fraction lived of the last age interval of life (using the Japan 1975 data)

2. Compute the number of death in the interval, d_i If l_o is the number of the population at the beginning and l_i is the number alive at age x_i, then

$$d_i = l_i \hat{q}_i \quad i = 0, 1, \ldots, w - 1$$

(where w is the final interval of life)

$$l_{i+1} = l_i - d_i \quad \text{(Fig. 3)}$$

3. Compute L_i which is the number of years lived in the interval $(x_i, x_i + n_i)$ by the l_i survivors at age x_i

$$L_i = n_i(l_i - d_i) + a_i n_i d_i.$$

The final interval is open, and l_w, M_w and L_w represent the l, M, and L in the age L_w and over,

$$L_w = l_w / M_w$$

4. Compute the total number of years, T, to be lived by those individuals attaining age x_i

$$T_i = L_i + L_{i+n_i} + \ldots + L_w \quad i = 0, 1, \ldots, w$$

5. The expectation of life at age x_i is the ratio

$$\hat{e}_i = \frac{T_i}{l_i} \quad i = 0, 1, \ldots, w \quad \text{(Fig. 4)}$$

These calculations were conducted in the same spreadsheet, which then allows observation of the resulting effect after changing any of the input data or assumptions.

Box 1. *Calculation of HBV risks for HBV surface antigen carriers*

A.	Population (data)	a	
B.	Prevalence of carriers (estimate see text)	b	
C.	Population of carriers	$c = a \times b$	
D.	Population of non-carriers	$d = a \times (1 - b)$	
E.	Total deaths from HCC in the period (Cancer registry incidence data)	e	
F.	Proportion of HCC in carriers (estimate see text)	f	
G.	Proportion of HCC in non-carriers	$g = 1 - f$	
H.	Death from HCC in carriers	$h = e \times f$	
J.	Mortality rate of HCC in carriers	$j = h/c$	(Fig. 1)
K.	Death from HCC in non-carriers	$k = e \times g$	
L.	Mortality rate from HCC in non-carriers	$l = k/d$	(Fig. 1)
M.	Total deaths from cirrhosis (death certificate data)	m	
N.	Proportion of cirrhosis due to hepatitis B (estimate see text)	n	
O.	Proportion of cirrhosis in non-carriers	$o = 1 - n$	
P.	Death from cirrhosis in carriers	$p = m \times n$	
Q.	Mortality rate from cirrhosis in carriers	$q = p/c$	
R.	Deaths from cirrhosis in non-carriers	$r = m \times o$	
S.	Mortality rate from cirrhosis in non-carriers	$s = r/d$	
T.	Total deaths (death registry)	t	(Fig. 1)
U.	Non-liver deaths = total deaths – (HCC deaths + cirrhosis deaths)	$u = t - (e + m)$	
V.	Non-liver mortality rate	$v = u/a$	
W.	Carrier total mortality rate (m_x)	$w = v + j + q$	(Fig. 2)
Y.	Non-carrier total mortality rate (m_x)	$y = v + l + s$	(Fig. 2)
Z.	Difference in mortality rates	$z = w - y$	

Performed in spreadsheet for each age group and sex separately.

REFERENCES

1. Zuckerman A. More than third of world's population has been infected with Hepatitis B virus. BMJ 1999; **318**: 1213.

2. O'Carroll FA, Oberle NR, Teutsch S, et al. CDC Prevention guidelines: a guide for action. Baltimore MD: Williams & Wilkins, 1997.

3. Parkin D, Muir C. Cancer incidence in five continents Lyon 1992; **120**: 45–173.

4. Alward W, McMahon B, Hall D, Heyward W, Francis D, Bender T. The long-term serological course of symptomatic hepatitis B virus carriers and the development of primary hepatocellular carcinoma. J Infect Dis 1985; **151**: 605–9.

5. Beasley R, Hwang L, Lin C, Chien C. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan. Lancet 1981; **ii**: 1129–33.

6. Ince N, Wands J. The increasing incidence of hepatocellular carcinoma. New Engl J Med 1999; **340**: 798–9.

7. Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano O, Tanaka M. Follow-up study of HBsAg-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. Int J. Cancer 1984; **34**: 775–9.

8. Chen C, Yu M, Liaw Y. Epidemiological characteristics and risk factors of hepatocellular carcinoma. J Gastroenterol Hepatol 1997; **12** (Suppl.): S294–S308.

9. Johnson P. The epidemiology of hepatocellular carcinoma. Europ J Gastroenterol Hepatol 1996; **8**: 845–9.

10. Okuda K. Hepatocellular carcinoma: recent progress. Hepatol 1992; **15**: 948–63.

11. Shiu W, Dewar G, Leung N, et al. Hepatocellular carcinoma in Hong Kong: clinical study on 340 cases. Oncology 1990; **47**: 241–5.

12. Lau J, Lai C. Hepatocarcinogenesis. Trop Gastroenterol 1990; **11**: 9–24.

13. Leung NW, Tam JS, Lai J, Leung TW, Lau W, Shiu W, Li AK. Does hepatitis C virus infection contribute to hepatocellular carcinoma in Hong Kong? Cancer 1992; **70**: 40–4.

14. Lam K, Lai C, Wu P, Todd D. Etiological spectrum of liver cirrhosis in the Chinese. J Chronic Dis 1980; **33**: 375–81.

15. Lai C, Lau J, Wu P, et al. Subclinical hepatocellular carcinoma in Hong Kong Chinese. Oncology Switzerland 1992; **49**: 347–53.

16. Department of Health Hong Kong. Public Health Report No. 3. Viral hepatitis and liver cancer and unintentional injuries in children. Hong Kong: Department of Health Hong Kong. 1998.

17. Hong Kong Cancer Registry. Cancer incidence and mortality in Hong Kong 1993–1994. Hong Kong Hospital Authority, 1998.

18. Census and Statistics Department HK. Hong Kong 1991 Population Census. Hong Kong: Hong Kong Government, 1991.

19. The Scientific Working Group on Viral Hepatitis Prevention. Surveillance of viral hepatitis in Hong Kong: 1997 update report. Hong Kong: Department of Health, 1997.

20. Johnson P. Why can't we cure primary liver cancer? Europ Cancer 1995; **31A**: 1562–4.

21. Chen C, Liang K, Chang A, et al. Effects of hepatitis B virus, alcohol drinking, cigarette smoking and familial tendency on hepatocellular carcinoma. Hepatol 1991; **13**: 398–406.

22. Chiang CL. The life table and its applications. Florida: Robert E Krieger Publishing Company, 1984.

23. McMahon B, Alberts S, Wainwright R, Bulkow L, Lanier A. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. Arch Intern Med 1990; **150**: 1051–4.

24. Lai C, Gregory P, Wu P, Lok A, Wong K, Ng M. Hepatocellular carcinoma in Chinese males and females. Possible causes for the male predominance. Cancer 1987; **60**: 1107–10.

25. Wong J, Koff R, Tine F, Pauker S. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. Ann Intern Med 1995; **122**: 664–75.

26. Tsai J, Jeng J, Ho M, Chang W, Hsieh M, Lin Z, Tsai J. Additive effect modification of hepatitis B surface antigen and e antigen on the development of hepatocellular carcinoma. Br J Cancer 1996; **73**: 1498–502.

27. Beasley R. Hepatitis B virus: The major etiology of hepatocellular carcinoma. Cancer 1885; **61**: 1942–56.

28. Chen C, Yu M, Wang C, Huang H, Lin W. Multiple risk factors of hepatocellular carcinoma: A cohort study of 13 737 male adults in Taiwan. J Gastroenterol Hepatol 1993; **8**: S83–7.

29. Lu S, Lin T, Chen C, et al. A case-control study of primary hepatocellular carcinoma in Taiwan. Cancer 1988; **62**: 2051–5.

30. Lam K, Yu M, Leung J, Henderson B. Hepatitis B Virus and cigarette smoking: risk factors for hepatocellular carcinoma in Hong Kong. Cancer Res 1982; **42**: 5246–8.