Lecturer

Should we screen hepatitis B carriers?

James Arthur DICKINSON[1] and Yuk Tsan WUN[2]

[1]University of Calgary, Canada, formerly from Chinese University of Hong Kong and [2]Research Committee, Hong Kong College of Family Physicians, Hong Kong

Abstract

Chronic Hepatitis B is a common problem, especially in Asian countries. This disease causes complications of cirrhosis and liver cancer. Therefore doctors and patients are concerned whether to treat or screen for these complications. We searched the literature for evidence to determine the risk for people with chronic hepatitis B, the evidence that treating patients changes their outcome, and the effect of screening on death rates. We found little evidence from high quality cohort studies to demonstrate the outcome of chronic hepatitis B infection. Consequently, we constructed a mathematical model to demonstrate outcome for them. The model showed that as a result of having chronic hepatitis B, men lose a mean of 7 years of life, whereas women lose only 2 years. While antiviral treatments change the serological status and reduce liver inflammation, there is insufficient information about their effect on cancer reduction. Our Cochrane review of screening for liver cancer in chronic infection shows no high quality randomised controlled trials and poor non-trial evidence. It appears unlikely that screening programs are effective in reducing mortality for this disease, a conclusion shared by other groups. Therefore, at present, doctors are limited in what we can do to change the outcome for this group of patients.

Key words: carriers, cirrhosis, hepatitis B, liver cancer, screening

Introduction

Outside the developed countries, a large proportion of the world's population have chronic hepatitis B infection. Although many doctors still use the term 'carriers' because most appear to suffer no harm, modern terminology generally prefers 'chronic hepatitis B' because nearly all have some degree of liver damage. In this article we use the terms interchangeably. Some of these people develop liver cancer. Because of the lack of health infrastructure in most developing countries, data are limited. However, liver cancer is probably one of the commonest cancers in the world.

Hong Kong has a high quality cancer registry, which is uncommon among countries with high prevalence of hepatitis B. In 1994, liver cancer was the second commonest cause of cancer deaths among men, with 914 cases compared to 1882 cases of lung cancer.[1] It was the fourth commonest female cancer with 254 cases. As for lung cancer, most patients who develop liver cancer die as a result, 80% within 1 year. Figure 1 shows the number of new cases and incidence rates for men and women. The incidence rates rise steadily throughout life, but the greatest number of cases is among people in their 60s, since there are fewer old people. These cancers mostly arise from among the 10% of the population who are carriers.[2] In many other countries, hepatitis C also contributes to a substantial number of advanced liver cirrhosis and liver cancer, though in Hong Kong this disease is relatively rare.[3] It is also notable that although hepatitis C studies from liver clinics demonstrate high rates of progression, studies in newly infected cohorts show much lower rates in the community.[4] It is possible that similar situations arise for hepatitis B.

Most carriers are aware that they are at risk of developing liver cancer and may ask their doctors:

1. What is my risk of getting cancer or complications?
2. How will this affect my life?
3. What is my chance of dying young?
4. What can I do to change it?

How should doctors respond?

Many hepatologists and oncologists recommend screening with ultrasound, alpha-fetoprotein (AFP) or both, at varying intervals based on their experience of seeing many cases of cirrhosis and liver cancer. Most hospital-based specialty clinic studies include a population with more severe diseases, often with cirrhosis or even symptomatic liver disease; thus, it is not surprising that such patients

Correspondence: Professor James Dickinson, Department of Family Medicine, University of Calgary, Canada.
Email: dickinsj@ucalgary.CA
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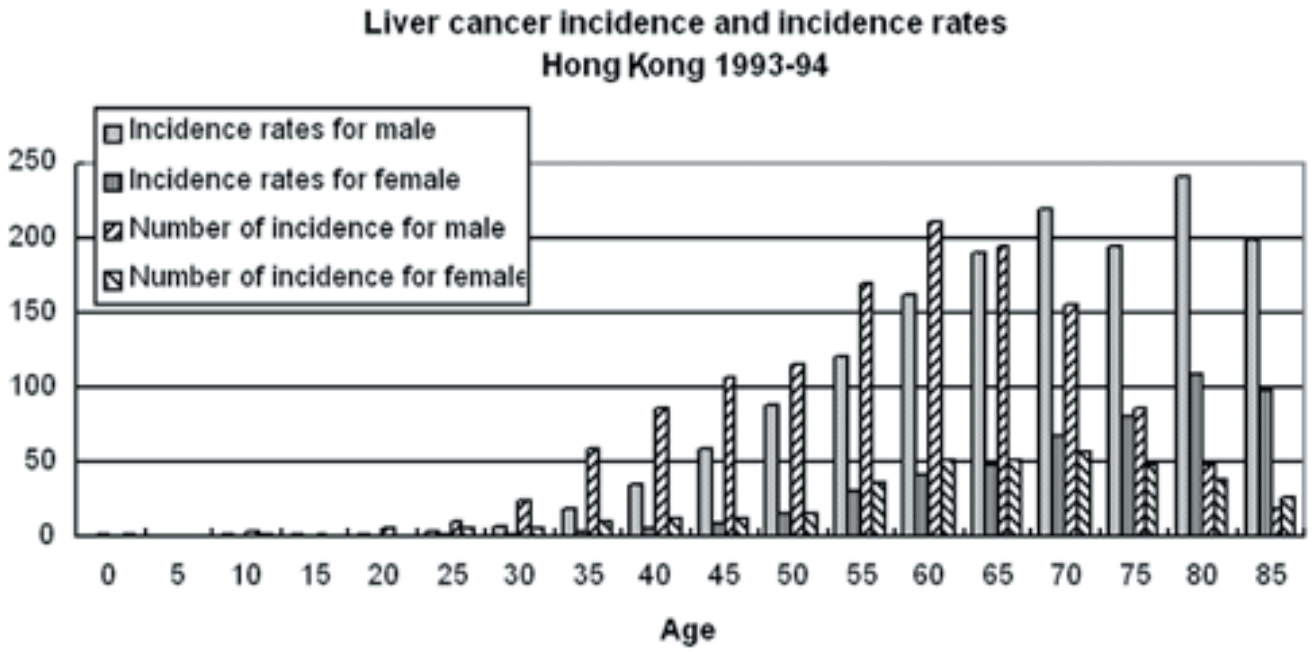

Fig. 1 Number of new cases of hepatocellular cancer and incidence rates by age for men and women, Hong Kong, 1994

have high rates of complications or death. We cannot extrapolate their results to the type of patients we see in primary care clinics. Therefore, we must ask what should primary care doctors advise their patients? We searched the literature to find the answers to these important clinical questions.

What is the risk of developing cancer or complications?

We sought evidence for the risk from complications of hepatitis B infection among patients in the community. Our systematic review searched all the major databases for cohort studies based on symptomatic subjects in the general population. Eleven studies were found but only one study from Alaska[5] described patients from the general population. Occupational cohorts in Taiwan[6] and Japan[7] demonstrated rates for middle-aged men only. Studies of blood donors of both sexes in Japan,[8,9] Canada[10] and Italy[11] were mostly on young patients. Only three studies could be stratified by age to demonstrate liver cancer incidence rates among carriers by age and sex. These results are shown in **Table 1**. Incidence rises with age and it appears that rates in Alaska are higher in young people than in Taiwan and Japan, but the sample sizes within these age groups are small, so confidence intervals are wide. The data on risk of cirrhosis are even less satisfactory.

We conclude there are insufficient quality studies on this topic to provide adequate information on age and sex groups and for the possibility that risks are different according to racial groups or social development.

As a consequence of the limited data, we developed a mathematical model to predict risk using Hong Kong data. In this model we presume that nearly all of the liver cancer and cirrhosis occurs among the proportion of the population who are hepatitis B carriers. Full details of this work are described in our paper[12] but in brief, we found that among male carriers, the risk of developing liver cancer (hepatocellular carcinoma [HCC]) is so high that between the ages of 35 and 55 mortality from HCC among male carriers is higher than for all other causes of death combined. For women, mortality rates of carriers are raised but the additional risk never exceeds the normal mortality rate. When we add the mortality rates for cirrhosis, liver cancer and deaths from other causes to estimate total mortality among male carriers, it starts to rise noticeably from about the age of 35 to be twice the total mortality for non-carriers, while for women the difference is always quite small (**Fig. 2**). We then used a life-table approach that takes a hypothetical newborn population of 100 000 people and assumes they would have the current death rates from all causes over their whole lifetime. This produces curves that show that survival for male carriers begins to drop noticeably from

Table 1 Incidence rate or mortality rates of hepatocellular cancer among hepatitis B carriers by age and sex, obtained from population cohort studies

Age	Alaska (IR)		Taiwan (IR)†	Japan(IR)
	Female	Male	Males	Males
0–9	0.0	0.1	NA / NA / NA	NA
10–19	0.1	0.4	NA / NA / NA	NA
20–29	0.1	0.3	0.0 / 0.0 / 0.0	NA
30–39	0.1	0.3	0.2 / 0.2 / 0.2	0.04
40–49	0.1	0.3	0.3 / 0.3 / 0.6	0.2
50–59	0.0	1.2	0.8 / 0.8 / 0.6	0.7
60–69	0.0	1.2	0.9 / 0.8 / 0.6	NA
70–79	0.0	1.2	0.0 / 0.8 / 0.6	NA
>80	0.0	1.2	0.0 / 0.8 / 0.6	NA

†Different rates in Taiwan come from three different reports of the same study.

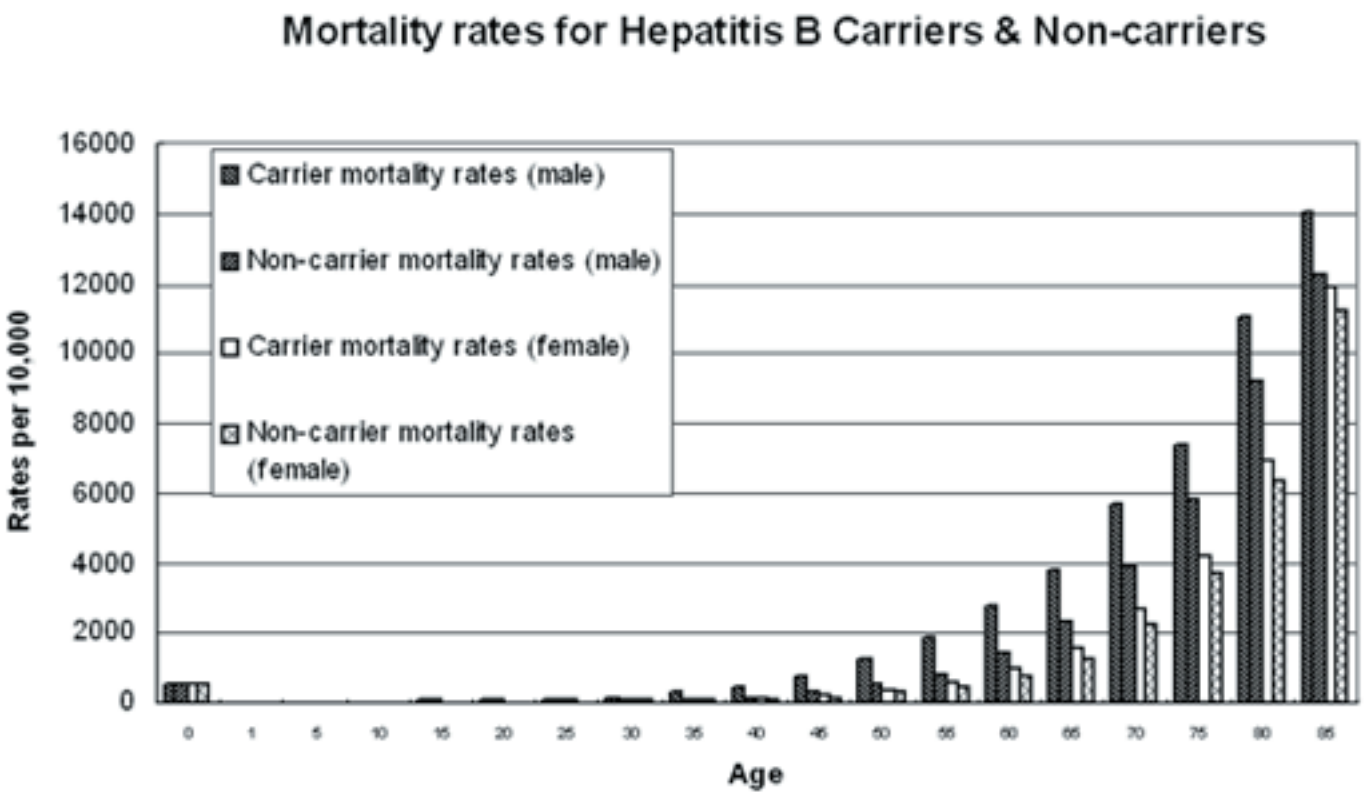

Fig. 2 Calculated mortality rates for hepatitis B carriers and non-carriers

the age of 35–40, and leads to about 10% mortality by age 50 and 20% by age 60. Their average life expectancy is about 72 years, whereas non-carriers in Hong Kong would live 7 years longer, approximately 79 years. For female carriers the survival rate is always better than for male non-carriers, beginning to drop from about the age of 60 so that mortality reaches 10% by age 70. Half the female carriers live to around 80, whereas female non-carriers on average live to approximately 82[12].

Thus we have shown that the risk is high, especially for men, probably at about the same risk as cigarette smokers, half of whom will die in middle age as a result of smoking.[13]

What can we do for these patients? Treatment or screening?

The current pathogenetic concept for these diseases is that patients who acquire the infection either at birth or in the first few years of life have a high risk of becoming chronic hepatitis B patients with circulating surface antigen, which indicates persistent replication of the virus in liver cells. The circulating antigen may be lost by about 1% per year, but these patients never lose the virus genome in their liver cells. Liver serum enzyme levels measure the waxing and waning of these infections. We can also measure the e-antigen (envelope antigen), which indicates infectivity. Patients with this may also sero-convert and e-antigen-negative patients are at lower risk for developing complications.[14] However, some e-antigen-negative patients still develop liver cancer and it is not clear exactly how much lower their risk is. Some precore mutants are not detectable with current tests.

Two treatments are now available for hepatitis B: interferon and lamivudine. Interferon is effective in reducing liver inflammation but has substantial side-effects for a considerable period. A much better tolerated drug with very few side-effects is lamivudine, which reduces hepatic inflammation and the changes of cirrhosis. If continued for more than a year, a substantial rate of sero-conversion to e-antigen-negative does occur but over time there is an increasing number of drug-resistant mutations which escape suppression, so that liver damage continues.[15] Both of these drugs are expensive, especially for people in less developed countries and since these approaches are still new, the long-term outcome for reduction of liver cancer is still unclear. Many hepatologists recommend chronic long-term lamivudine, but at the moment this is hopeful rather than based on data, since this drug has not been available long enough to produce the necessary supportive evidence.

Clearly it would be desirable to prevent liver cancer from occurring, but if we cannot, is screening effective? Potential screening tools are AFP and/or ultrasound. A variety of recommendations are made on who to screen, how often to screen and effectiveness of these programs. Therefore, we undertook a Cochrane systematic review of screening.[20] The data are thus very limited and not encouraging. the value of screening people with chronic hepatitis B infection for liver cancer.[16] One trial in China directly addressed the question.[17] These researchers detected many more tumors in the screened group and these cancer patients had a longer survival rate post-diagnosis than the patients who presented clinically in the unscreened group.[17] This trial is sometimes quoted as proving the value of screening, but when we reanalyzed to compare the overall liver cancer death rates, they were not significantly different.[16] Thus they produced one of the

classic biases of screening: the lead-time bias.[18] One other randomised controlled trial fulfilled the quality criteria, but compared AFP against AFP and ultrasound[19] without comparison to controls. One trial in Alaska compared AFP against an historical control group without screening.[20] The data are thus very limited and not encouraging.

While these studies detected liver cancer at the preclinical stage, and also detected a number of small liver cancers at a stage when surgical resection could potentially make a difference, the effort and cost of screening is high. The Chinese trial required 1006 AFP, 329 ultrasounds or 403 AFP plus ultrasounds to detect one liver cancer smaller than 5 cm diameter. The researchers' optimistic estimate of delaying 10 deaths would require screening 937 patients annually for 5 years. Sherman's group performed nearly 800 AFP tests to find one small liver cancer[19] and in Alaska McMahon's group undertook 800 AFP to find one liver cancer or 2000 to find one small liver cancer.[20] Across 4159 patients in this study, sensitivity of AFP appears to be about 72.5%, and specificity 93.7%. Given the model described above[12] and assuming the prevalence of liver cancer is twice the calculated incidence, the positive predictive value would be approximately 6% in men aged 40–49, 12% in those aged 50–59, and 24% in those aged 60–69. Further investigation is then needed to demonstrate that most patients with positive AFP tests do not have a liver cancer.

Thus we conclude that while AFP conducted annually or twice yearly can detect more small and even operable liver cancers with a longer survival rate than those unscreened, this is likely due to lead-time bias. There is no trial evidence that screening postpones or decreases the death rates of carriers or improves their quality of life.

If empiric evidence for a screening test is not available, we use a set of standard criteria for screening tests. When we compare liver cancer against these (**Table 2**) we conclude that screening fails. While this is an important disease, this cancer grows relatively rapidly and screening tests only work effectively for chronic, slowly developing disease. At the moment we are unclear on the value of the two potential screening tests, and even worse, it is not yet clear that early treatment for this cancer is truly effective, especially as these cancers tend to be multifocal, rising at many points in a damaged liver, so that many patients are inoperable because of severe underlying liver disease, while there is a high operative mortality and postoperative recurrence rate, even for those previously operated upon. Liver transplant might be a potential solution, but in many countries where this disease is a major problem, donation of organs is not socially acceptable, while the operation is complex and extremely costly. Even where it is performed, there will never be sufficient donor livers available.

Performing a screening program would cause substantial harm because of the high rate of false positives, with the resultant anxiety, worry and high cost for these people. We must recognize the aphorism of Muir Gray: 'All screening programs do harm; some can do good as well. The harm from a screening program starts immediately; the good takes longer to appear. Therefore the first effect of any program, even an effective one, is to impair the health of the population.'[20]

Table 2 Matching screening chronic hepatitis B paitients for liver cancer against criteria for screening

A. Experimental criterion: randomixed controlled trial of screening, with mortality as endpoint
• One trial, reported sketchily; outcome: no difference[16]
B. non-experimental WHO criteria (amended)
(Since the non-experimental criteria are sequential, failure in any one prevents an effective program).
Properties of disease (hepatocellular carcinoma):
• important health problem: yes
• recognizable latent stage: not certain
• natural history of development understood: not clear
Properties of test (AFP, ultrasound):
• test properties suitable for use as screening test: yes
• test acceptable to population: yes
• case finding should be continuing process: yes
Properties of treatment (segmental resection, liver transplantation):
• accepted treatments for early disease: yes, but unclear how effective
• facilities for diagnosis and treatment should be available: very limited except in developed countries
• treatment of early disease should be more effective than for late disease: possibly, but most cancer detected by screening is beyond the threshold for treatment

Criteria adapted from Muir Gray[20]

Conclusion

Therefore, our answers to patients' requests are:

1 Having chronic hepatitis B is a severe problem for men, but much less for women.
2 Carriers can get liver cancer, while chronic liver disease occurs at about one-third of the rate, but most of these presentations occur over the age of 60.
3 Treatment with interferon or lamivudine is possible and may reduce cirrhosis progression but we do not know the effect on liver cancer.
4 Screening is unlikely to be beneficial but will be costly, cause worry and excess investigation.

The Malaysian Consensus Committee on screening for hepatocellular cancer[21] agrees with our assessment that there is no evidence of value and there are poor data for improving survival, probably due to length bias, but they still recommended screening. It is common for authoritative committees to make recommendations that do not follow from the evidence, since all of us at the emotional level want to do something for patients facing this unpleasant disease. However, our assessment of the evidence is that screening chronic hepatitis B patients for liver cancer would provide minimal benefit, while being burdensome and costly, so it should not be offered or recommended.

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