Screening for hepatocellular carcinoma (HCC): Is it cost-effective?*

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Summary

Hepatocellular carcinoma (HCC) killed 1286 people in 1996 in Hong Kong. It is the second most common cancer death for men and the fourth for women. Over 90% of HCC occur after the age of 40 and 84% are in chronic hepatitis B carriers. The only cure for HCC is surgical resection when it is small. This article applies current evidence to our local epidemiological data to estimate the cost-effectiveness of different HCC screening programmes for hepatitis B carriers aged 40 to 69. The estimated number of persons needed to screen (NNT) for 30 years is 16 for men and 44 for women and the cost is HK$1.30 million for men and HK$3.56 million for women per life saved by four-monthly ultrasonography and serum alpha foetal protein (α-FP) screening. The cost per life saved is lower for the less intensive screening programmes but some potentially preventable HCC deaths may be missed. HCC screening for chronic hepatitis B carriers is more cost-effective than mammogram screening and is comparable to cervical cancer screening. Screening for HCC satisfies nearly all the principles for screening, but its effectiveness and feasibility have to be proven by further clinical trials.

摘要

肝細胞癌是香港男性第二位，女性第四位的癌症殺手，1996年有1286人因此病而死亡。肝細胞癌發病九成以上年齡超過40歲，84%發生於慢性乙型肝炎的帶菌者。目前唯一的治療方法是早期切除腫瘤。本文根據現有資料，對年齡介於40歲至69歲乙型肝炎帶菌者進行了篩選成本效益評估。以每4個月超聲波檢查和甲胎蛋白質(α-FP)測試作為篩選方法，30年NNT男性為16，女性為44，估計男性需要花費一百三十萬，而女性則需要用三百五十六萬來預防一人死亡。以成本效益相比，與子宮頸癌相約，比乳房造影更經濟。現用肝細胞癌的篩選方法差不多完全符合篩選原則，但其效益和可行性則有待實際驗證。

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Introduction

Hepatocellular carcinoma (HCC) is a common cancer affecting half a million of people each year worldwide, and 60% of cases occurring in China.[1] In Hong Kong, there were 1738 new cases of and 1286 deaths from liver cancer in 1996 and nearly all of them were HCC.[2] HCC is the second most common cancer death for men and the fourth for women.[2] The life-time risk of HCC is 1 in 24 for men and 1 in 91 for women.

Hepatitis B (HB) carriers have extremely high risk for HCC. Their estimated relative risk is 100 times higher than non-HB carriers.[3] Eighty-four percent of HCC patients were HB carriers (Cheng C C *et al*, personal communication), which was similar to the 85% found earlier by Shiu *et al*.[4] Surveillance studies have shown that 11% of adult males and 6% of adult females in Hong Kong are chronic HB carriers.[1] The majority of HCC occur after the age of 40 years. The cumulative HCC mortality rate for people aged 40 to 69 is 2239/100,000 for men and 437/100,000 for women in 1996 in Hong Kong.[2] This translates to an estimated cumulative mortality rates of 17098/100,000 (2239 × 84%/ 100,000 × 11%) for men and 6118/100,000 (437 × 84%/ 100,000 × 6%) for women, who are hepatitis B carriers aged 40 to 69.

Family doctors are often asked by their HB carrier patients whether they need regular screening for HCC. Since screening is costly and stressful to the patient, we have to provide our patients with the current evidence to help them make an informed decision.

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Effectiveness of screening

Can screening prevent HCC deaths? The prognosis of symptomatic HCC is poor with a median survival of only two to four months.[3,4] The only hope for long-term survival is successful surgical resection.[3-5] Tumour size and liver function status are important determinants of success in surgical resection.[4,5] Studies have shown that HCC less than 3 cm in diameter have a 5-year survival rate of 50% after successful resection.[3] Advances in techniques have enabled larger tumours to be resectable but there is little data on their long-term survival.[3-5] The liver reserve must be adequate for the patient to survive after the resection.[4,5]

Most HCC less than 3 cm in diameter are asymptomatic and can only be detected by regular screening. Screening is often targeted to HB carriers with cirrhosis or chronic active hepatitis because these patients are at higher risk of developing HCC.[3] However, early detection of small HCC in them may not improve their survival because they are often not fit for surgery. Screening may be more cost-effective if it is directed to HB carriers with normal liver function, who will have a better chance for survival after curative resection.

Ultrasonography (USS) and serum alpha foetal protein (AFP) can detect asymptomatic HCC, but there is no consensus on the optimal screening programme.[3,6-10] An important determinant of the effectiveness of a screening programme is its sensitivity in detecting HCC of less than 3 cm in diameter. The minimal size of detectable HCC is 1 cm in diameter.[3,7] The sensitivity of the screening programme depends on the growth rate of the cancer and the frequency of the test. Kang *et al* reviewed the natural history of 65 HCC and estimated that the median time for it to grow from 1 to 3 cm is 1.63 years (range 0.38-8.96 years). **Table 1** shows the specificity and sensitivity of detecting HCC of 1 to 3 cm in diameter by different methods and intervals for screening.[6-8]

Case controlled studies by Tang *et al* in China showed that the 5-year survival of HCC patients detected by screening was 50% and that of patients with symptomatic HCC was 20%, the relative risk reduction in mortality by screening was 37%.[9] A study in Japan by Mima *et al* showed that HCC detected by community based screening had a 7-year survival of 15.4% but the study did not have a control population.[10] The results of other studies did not have information on long-term outcomes.[8,11]

Cost-effectiveness of screening

The cost-effectiveness of a cancer screening programme can be measured by the cost of screening per life saved, which is the product of the number needed to screen (NNT) for each cancer death reduced and the cost of screening for each person. The NNT can be calculated from the absolute mortality rate of the at-risk population, the relative mortality reduction (RRR) by screening and the sensitivity of the screening programme by the following formula:-

$$NNT = 1/(\text{absolute mortality rate} \times RRR \times \text{sensitivity of screening})$$

The cost of a liver USS is HK$600 and that of AFP is HK$300.[12] If we screen the HB carriers between the age of 40 and 69 years, screening will be done for 30 years. The costs of the different screening programmes per person are shown in **Table 2**.

The estimated cumulative mortality risk from the age of 40 to 69 years for HB carriers are 17098/100,000 for men and 6118/100,000 for women as shown above. If a screening programme can detect 100% HCC and if HCC

Table 1: Sensitivity of screening for small HCC by method and frequency of tests

Screening test	Specificity	Sensitivity by screening interval		
		4 monthly	6 monthly	Yearly
AFP (>20mcg/L)	90%	80%	75%	68%
USS of liver	98%	98%	95%	88%
USS + AFP	98%	100%	98%	90%

Table 2: Cost of HCC screening programmes per person screened from 40 to 69 years old

Programme	Cost in Hong Kong dollars
4 monthly USS + AFP	$900 × 3 × 30 = $81,000
6 monthly USS + AFP	$900 × 2 × 30 = $54,000
6 monthly USS	$600 × 2 × 30 = $36,000
Yearly USS + AFP	$900 × 30 = $27,000
6 monthly AFP	$300 × 2 × 30 = $18,000
Yearly USS	$600 × 30 = $18,000
Yearly AFP	$300 × 30 = $9,000

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detected by screening has a reduction in relative mortality of 37% as shown by Tang *et al*,[9] the number of deaths that screening can prevent is 6326/100,000 men and 2264/100,000 women screened for 30 years. The NNT per HCC death prevented is 16 (100,000/6326) for men and 44 (100,000/2264) for women. Regular AFP and USS screening at 4-monthly interval can potentially achieve this and the cost per life saved is HK$1.30 million for men and HK$3.56 million for women. The cost-effectiveness of different screening programmes is summarised in **Table 3**. Yearly AFP is the cheapest but it also misses many potentially curable HCC, especially for male HB carriers. Six-monthly AFP is actually less cost-effective than yearly USS although the screening cost is the same. Its NNT is higher because it misses more small HCC. For simplicity sake, the cost associated with further investigations for positive and false positive cases have not been included in the cost-effectiveness analysis.

The cost per life saved has to be balanced against the number of preventable HCC deaths missed. **Figures 1** and **2** show the relative operation curves (ROC) of the cost per HCC death prevented against the number of cases of preventable HCC deaths missed of the different screening programmes for men and women respectively. The optimal (first upward-turning) point is six-monthly USS and the second upward-turning point is yearly USS, for both men and women.

It is difficult to judge the worth of a screening programme in absolute terms. It depends on the availability of resources and the competition from other health care needs.[13] **Table 4** compares the cost-effectiveness of HCC screening to mammography screening and cervical cancer screening.[14,15] HCC screening is more cost-effective than mammography screening and comparable to that of cervical cancer screening.

Conclusions

HCC satisfies the principles of screening advocated by Wilson and Jungner.[13] It is a serious and prevalent disease. Its epidemiology and natural history are known. There is a latent asymptomatic stage. Acceptable, accurate and safe screening methods are available. There is an effective treatment and an agreed policy on who should be treated. An ongoing programme is feasible; and the cost is comparable to other screening programmes. However, the effectiveness of screening has only been

Table 3: Cost-effectiveness by method and frequency HCC screening

Screening programme (sensitivity and cost)	Sex	NNT	Cost* per life saved	Missed preventable deaths per 100,000 HB carriers[a]
4/12 USS + AFP	M	16	$1.30 million	0
(100%, $81,000)	F	44	$3.56 million	0
6/12 USS + AFP	M	16.3	$880,200	127 (6326 x 2%)
(98%, $54,000)	F	44.9	$2.42 million	45 (2264 x 2%)
6/12 USS	M	16.8	$604,800	316 (6326 x 5%)
(95%, $36,000)	F	46.3	$1.67 million	113 (2264 x 5%)
Yearly USS +AFP	M	17.8	$480,600	633 (6326 x 10%)
(90%, $27,000)	F	48.9	$1.32 million	226 (2264x 10%)
Yearly USS	M	18.2	$327,600	759 (6326 x 12%)
(88%, $ 18,000)	F	50.0	$900,000	272 (2264 x 12%)
6/12 AFP	M	21.3	$383,400	1582 (6326 x 25%)
(75%, $18,000)	F	58.6	$1.05 million	566 (2264 x 25%)
Yearly AFP	M	23.5	$211,500	2024 (6326 x 32%)
(68%, $9,000)	F	64.7	$582,300	724 (2264 x 32%)

a. The expected number of HCC deaths that can be prevented by screening 100,000 hepatitis B carriers if the sensitivity is 100% = 17098 × 37% = 6326 for men and 6118 × 37% = 2264 for females

* *Cost in Hong Kong dollars*

Figure 1: Relative operation curve of the cost per HCC death prevented against the number of cases of preventable HCC deaths missed for male HB carriers

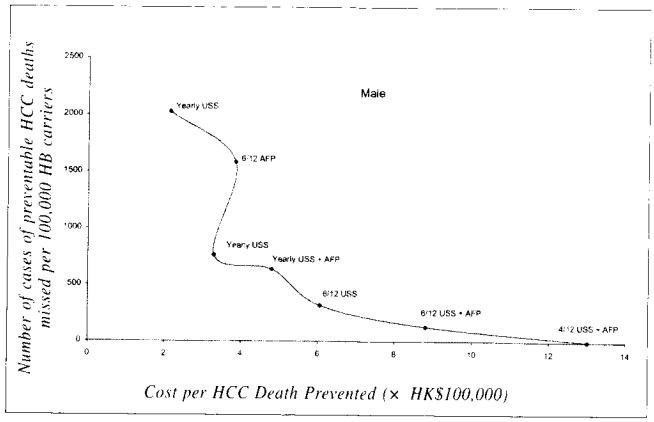

Figure 2: Relative operation curve of the cost per HCC death prevented against the number of cases of preventable HCC deaths missed for female HB carriers

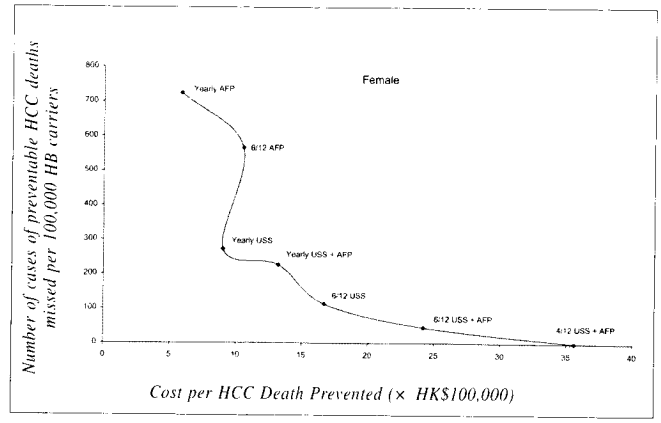

Table 4: Cost-effectiveness comparison between cancer screening programmes

Screening programme	Sex	Cumulative mortality[a]	NNT	Cost* per life saved
4/12 USS + AFP for HCC in HB Carriers 40-69	M	17098/100,000	16	$1.30 million
	F	6118/100,000	44	$3.56 million
6/12 USS for HCC in HB Carriers 40-69	M	17098/100,000	16.8	$604,800
	F	6118/100,000	46.3	$1.67 million
Yearly USS for HCC in HB Carriers 40-69	M	17098/100,000	18.2	$327,000
	F	6118/100,000	50.0	$900,000
Mammography[b] for breast cancer in women 50-69		627/100,000	568	$5.68 million
Cervical Smear[c] for cervical cancer in women 30-64		368/100,000	543	$1.52 million

Note:
a. *Cancer incidence and mortality in Hong Kong 1995-1996, Cancer Registry, 1999.*
b. *The expected relative mortality reduction by biannual mammography screening is 28%.*[14] *A total of 10 bi-annual screenings are required form the age 50 to 69. The cost per mammography is $1000.*
c. *The estimated relative mortality reduction by cervical cancer screening is 50%.*[15] *A total of 14 cervical smears are required from age 30 to 64 if it is done annually for three years and then three-yearly. The benefit of screening is expected to last for 10 years until the age of 74. The cost per cervical smear is $200.*
* *Cost in Hong Kong dollars*

shown in one study in China. Its effectiveness on our population needs to be confirmed.

This paper has applied the current evidence on the effectiveness and accuracy of screening programmes to our local epidemiological data to estimate the cost-effectiveness of different HCC screening programmes for HB carriers. Screening is more cost-effective for men than women because HCC is three times more prevalent in the males than females. The cost and effectiveness vary with the sensitivity of the different screening protocols. Six monthly USS may be the most appropriate

Key messages

1. Hepatocellular carcinoma (HCC) is the second most common cause of cancer death for men and the fourth for women in Hong Kong.
2. HCC satisfies nearly all the principles of screening advocated by Wilson and Jungner.
3. One case-controlled study showed that the 5-year relative mortality of HCC detected by screening was 37% less than that of symptomatic HCC.
4. The estimated number needed to screen and cost per life saved by four-monthly liver ultrasonography and alpha foetal protein screening for 30 years is 16 and HK$1.30 million for men; they are 44 and HK$3.60 million for women.
5. The optimal balance between the cost per life saved and the number of HCC missed is six-monthly ultrasonography, for both men and women.

for male HB carriers, while yearly USS may be adequate for female HB carriers. Annual AFP is cheap but it misses nearly one third of small HCC. There is little justification for choosing six-monthly AFP screening since it is more expensive but less effective than yearly USS, unless ultrasonography is not available.

So, what should we tell our patients who are chronic HB carriers? I will tell them HCC screening before the age of 40 is probably not fruitful because it is rare. There is evidence to show that screening might reduce their chance of dying from HCC but I must admit that we are not absolutely sure. It has to be made clear that screening does not prevent HCC. It only detects it earlier so that treatment can be given earlier and it does not always make a difference to the final outcome. If the patient wishes and resources are available, I will advise my male and female HB carrier patients from the age of 40 onwards to have six-monthly USS and yearly USS, respectively. ■

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