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Alpha-foetoprotein and/or liver ultrasonography for screening of hepatocellular carcinoma in patients with chronic hepatitis B (Review)

Aghoram R, Cai P, Dickinson JA

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Alpha-foetoprotein and/or liver ultrasonography for screening of hepatocellular carcinoma in patients with chronic hepatitis B.
Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD002799.
DOI: 10.1002/14651858.CD002799.pub2.

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[Intervention Review]

Alpha-foetoprotein and/or liver ultrasonography for screening of hepatocellular carcinoma in patients with chronic hepatitis B

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Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2012.

Citation: Aghoram R, Cai P, Dickinson JA. Alpha-foetoprotein and/or liver ultrasonography for screening of hepatocellular carcinoma in patients with chronic hepatitis B. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD002799. DOI: 10.1002/14651858.CD002799.pub2.

ABSTRACT

Background

Chronic hepatitis B virus infection is a risk factor for development of hepatocellular carcinoma. Alpha-foetoprotein and liver ultrasonography are used to screen patients with chronic hepatitis B for hepatocellular carcinoma. It is uncertain whether screening is worthwhile.

Objectives

To determine the beneficial and harmful effects of alpha-foetoprotein or ultrasound, or both, for screening of hepatocellular carcinoma in patients with chronic hepatitis B virus infection.

Search methods

Electronic searches were performed until December 2011 in the Cochrane Hepato-Biliary Group Controlled Trials Register (December 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 4) in *The Cochrane Library*, MEDLINE (1948 to 2011), EMBASE (1980 to 2011), Science Citation Index Expanded (1900 to 2011), Chinese Medical Literature Electronic Database (WanFang Data 1998 to 2011), and Chinese Knowledge Resource Integrated Database (1994 to 2011).

Selection criteria

All published reports of randomised trials on screening for liver cancer were eligible for inclusion, irrespective of language of publication. Studies were excluded when the hepatitis B status was uncertain, the screening tests were not sensitive or widely-used, or when the test was used for diagnosis of hepatocellular carcinoma rather than screening.

Data collection and analysis

We independently analysed all the trials considered for inclusion. We wrote to the authors of one of the trials to obtain further information.

Main results

Three randomised clinical trials were included in this review. All of them had a high risk of bias. One trial was conducted in Shanghai, China. There are several published reports on this trial, in which data were presented differently. According to the 2004 trial report, participants were randomised to screening every six months with alpha-foetoprotein and ultrasonography (n = 9373) versus no screening (n = 9443). We could not draw any definite conclusions from it. A second trial was conducted in Toronto, Canada. In this trial, there were 1069 participants with chronic hepatitis B. The trial compared screening every six months with alpha-foetoprotein alone (n = 532) versus alpha-foetoprotein

and ultrasound (n = 538) over a period of five years. This trial was designed as a pilot trial; the small number of participants and the rare events did not allow an effective comparison between the two modes of screening that were studied. The remaining trial, conducted in Taiwan and published as an abstract, was designed as a cluster randomised trial to determine the optimal interval for screening using alpha foetoprotein and ultrasound. Screening intervals of four months and 12 months were compared in the two groups. Further details about the screening strategy were not available. The trial reported on cumulative four-year survival, cumulative three-year incidence of hepatocellular carcinoma, and mean tumour size. The cumulative four-year survival was not significantly different between the two screening intervals. The incidence of hepatocellular cancer was higher in the four-monthly screening group. The included trials did not report on adverse events. It appears that the sensitivity and specificity of the screening modes were poor, accounting for a substantial number of false-positive and false-negative screening results.

Authors' conclusions

There is not enough evidence to support or refute the value of alpha-foetoprotein or ultrasound screening, or both, of hepatitis B surface antigen (HBsAg) positive patients for hepatocellular carcinoma. More and better designed randomised trials are required to compare screening against no screening.

PLAIN LANGUAGE SUMMARY

Alpha-foetoprotein or liver ultrasonography, or both, for liver cancer screening in patients with chronic hepatitis B

Liver cancer is a leading cause of death among people with chronic hepatitis B infection. Screening such patients with ultrasound of the liver or alpha-foetoprotein in the blood, or both, is widely performed to detect liver cancer at an early stage. The hope is that early stages of liver cancer can be treated by resection or transplantation, or both, with improved outcomes. Only three trials could be included in this review. One of these trials was conducted in Shanghai, China. It compared screening twice yearly with ultrasound and alpha-foetoprotein against no screening. The trial has a high risk of systematic errors (bias) and several published reports of the trial provide different results. Another trial was conducted in Toronto, Canada. It compared screening with alpha-foetoprotein and ultrasound versus screening with alpha-foetoprotein alone. This trial had too few participants. As there were no participants who were not screened, we cannot assess whether screening is effective in reducing mortality. The remaining trial was published as an abstract only. It was designed to determine the optimal time interval for screening using alpha fetoprotein and ultrasound. The cumulative four-year survival was not significantly different between the two studied screening intervals of four months and 12 months. Thus, to date, there is insufficient evidence regarding screening for liver cancer among patients with chronic hepatitis B infection.

BACKGROUND

Description of the condition

Hepatocellular carcinoma is the third leading cause of cancer deaths worldwide, accounting for approximately 600,000 deaths annually. The incidence of liver cancer is two to four times higher in men than women (Bosch 2004). Geographic differences also exist and can be largely attributed to the differences in the distribution of risk factors like hepatitis B virus, hepatitis C virus, and the toxin aflatoxin (Kumagi 2009). The number of liver cancers is increasing in some parts of the world, such as the United States, while a decreasing trend has been reported for some other areas like China. Immunisation against hepatitis B and migration from endemic areas contribute to these changing trends of hepatocellular carcinoma. Other factors implicated in the changing trends of hepatocellular carcinoma include an aging population, increasing survival in those with cirrhosis due to more effective treatment, and a changing epidemiology of hepatitis B and C virus (Llovet 2003).

Hepatitis B is a potent hepatocarcinogen (Tsai 2010). Patients with cirrhosis have a 3% to 5% annual risk of malignant transformation (Coon 2007) but when cirrhosis is secondary to chronic hepatitis B, the risk is as high as 8% (Tsai 2010). Hepatocellular carcinoma develops in patients with chronic hepatitis B without cirrhosis at a rate of 0.5% to 0.6% per year (Llovet 2003). A recent study in Australia showed that those with hepatitis B virus infection have a relative risk of dying from hepatocellular carcinoma of 34.9 (95% confidence interval (CI) 30.4 to 40.2) compared to those without infection (Walter 2011). The risk of developing hepatocellular carcinoma among people with chronic hepatitis B varies. There is a higher risk among males, and for those who are older, have a family history of hepatocellular carcinoma, consume alcohol regularly, have elevated serum alanine aminotransferase (ALT) levels, have positive hepatitis B e antigen (HBeAg) status, with high hepatitis B viral loads, and have specific genotypes of hepatitis B virus. These have been formulated into a nomogram and validated on a Taiwanese population (Yang 2010). Even in the presence of low viral load, the risk of hepatocellular carcinoma among hepatitis B infected people is 4.4 times the risk of those who are not infected (Iloeje 2007). Worldwide, hepatitis B is estimated to account for 80% of patients with hepatocellular carcinoma (Llovet 2003).

Chronic hepatitis B affects around 400 million people worldwide, with prevalence in some areas like China and sub-Saharan Africa approaching 15% of the general population (WHO 2002). Hepatitis B acquired in childhood has a different natural history compared to that acquired in adulthood (Pungpapong 2007). Being a DNA virus, hepatitis B virus integrates with the host genome, and the possibility of reactivation exists even after clearance of circulating hepatitis B surface antigen (HBsAg) (Pungpapong 2007). Hepatitis B infection during childhood becomes chronic in up to 90% of individuals, who pass into an immune tolerant phase where high levels of hepatitis B virus (HBV) replication occurs with little or no liver inflammation (Pungpapong 2007). This may persist for years or decades and often changes into an immune active phase with active liver inflammation. The severity and duration of this inflammation determines the progression to cirrhosis (Thomas 2010). Seroconversion with amelioration of liver inflammation passing into a low replicative phase or 'inactive carrier' phase occurs at a rate of less than 10% per year (Chu 2000). During these phases reactivation can occur at any time resulting in a return of inflammation even though HBeAg may be negative and anti-HBeAg may be positive. When HBV infection is acquired in adulthood, less than 5% develop chronic infection (Pungpapong 2007). This type of infection is characterised by an absence of the immune-tolerant phase, with persistence of active inflammation ending either in resolution of the infection or the occurrence of complications.

While histology remains the gold standard for making a diagnosis of hepatocellular carcinoma and differentiating it from other types of liver cancer, it cannot always be performed. Concerns about the underlying liver condition, bleeding risks, the risk of tumour seeding of the biopsy tract, the impact of the diagnosis, and patient refusal all affect the decision to biopsy (Coon 2007; Burak 2010). Furthermore, in the presence of cirrhosis a negative biopsy of a suspicious nodule does not rule out hepatocellular carcinoma (Kumagi 2009). This has resulted in the development of diagnostic criteria by various professional organizations such as European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) (Bruix 2010; Jelic 2010). The EASL diagnostic criteria include cyto-histological criteria and non-invasive criteria (restricted to cirrhotic patients). The non-invasive criteria are radiological criteria, with two coincidence imaging techniques showing a focal lesion larger than 2 cm with arterial hypervascularity; or combined criteria, with one imaging technique showing focal lesion larger than 2 cm with arterial hypervascularity plus alpha-foetoprotein levels greater than 400 ng/mL. Using these criteria, lesions larger than 2 cm can be identified as hepatocellular carcinoma with more than 95% certainty (Kumagi 2009). However, for a lesion of 1 cm to 2 cm the sensitivity of these criteria is only 33% (Forner 2008). Many studies, especially older ones, do not use these criteria and often diagnosis is established by a 'long-term follow-up'.

Many prognostic indicators have been postulated for hepatocellular carcinoma, but the two most important ones are the stage of the cancer and the underlying liver disease (Coon 2007). There are various staging systems available, like the tumour node metastases (TNM) staging system and the Barcelona staging system. In many hepatitis B endemic countries, like China, locally developed staging systems are used. The Barcelona staging system has been widely used in trials of the treatment of hepatocellular carcinoma (Bruix 2010). Studies using different staging systems are poorly comparable.

Symptomatic hepatocellular carcinoma usually presents at an advanced stage (Kumagi 2009). Treatment options for late stage hepatocellular carcinoma are few and often restricted to palliative measures (Oliveri 2011). Furthermore, patients with hepatocellular carcinoma invariably have advanced liver disease. Hepatocellular carcinoma can cause decompensation in previously compensated cirrhosis. In the event of death, it is often difficult to discriminate between being secondary to the cancer or the underlying liver disease as the cause of death (Llovet 2008). Survival at this stage, with only supportive measures, is between three months and seven months (Coon 2007).

For early stage disease, resection or transplantation is thought to be effective. However, only 20% to 25% of hepatocellular carcinoma can be managed with a curative intent (Yeung 2005). Other treatment methods like transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), or radiofrequency ablation (RFA) have been used, but the trials in this area are few and often of poor quality (Kumagi 2009; Oliveri 2011).

Description of the intervention

Screening is accomplished by ultrasound or biomarkers, such as alpha-foetoprotein, alpha-foetoprotein-L3, protein induced by vitamin K absence II (PIVKA-II), or glypican-3 (Bruix 2010).

Ultrasound has been widely used for liver imaging. It is increasingly believed to be the method of choice for screening. Although it is highly observer dependent, the pooled sensitivity for hepatocellular carcinoma is estimated at 94%, with a lower sensitivity of 63% for early disease with smaller tumours (Coon 2007). Specificity is estimated at between 92% and 98% (Coon 2007). Newer techniques such as microbubble contrast enhancement and harmonic imaging techniques may significantly improve detection rates by demonstrating the arterialization of hepatocellular carcinoma, allowing differentiation from other liver tumours that are fed by the portal vein. Since these are recent developments, only specialised centres offer these techniques, and their role in screening has not been studied in randomised clinical trials (Kudo 2010).

Serum biomarker estimation has also been used as a screening technique. Alpha-foetoprotein remains widely used although it has never been sufficiently studied as a single screening tool. Alpha-foetoprotein is secreted by immature hepatocytes. Apart from with pregnancy and some germ cell tumours, increased levels are seen in inflammation of the liver (such as in chronic hepatitis), regenerating nodule(s), and hepatocellular carcinoma. Around 20% of hepatocellular carcinomas do not secrete alpha-foetoprotein. At a cut-off of 20 ng/mL of alpha-foetoprotein, the sensitivity and specificity are estimated to be between 39% to 64% and 76% to 91%, respectively, with a positive predictive value of 9% to 32% (Coon 2007). The other biomarkers remain investigational. In one phase II study, PIVKA-II and alpha-foetoprotein L-3 were found to be less sensitive for the diagnosis of early hepatocellular carcinoma than alpha-foetoprotein at a cut-off of 10.9 ng/mL, though this cut-off needs further evaluation (Kudo 2010).

How the intervention might work

With newer diagnostic methods, it is now possible to detect hepatocellular carcinoma much earlier. Around 55% to 65% of tumours detected by screening among high risk groups in Japan are at an early stage (Kudo 2010). Potentially effective treatment modes, such as hepatic resection and liver transplantation, are now available to well-selected patients in the early stages of the disease. Resection is advised for a single tumour nodule that is peripheral in location with no vascular invasion together with good liver function (Child-Pugh A) and functional status, and normal portal pressure (Bruix 2010). Treatment with hepatic resection results in a five-year survival of 50%, with a 70% risk of recurrence or multi-focal development over the same time period. Transplantation is recommended in Child-Pugh stages A-B with one tumour nodule less than 5 cm or three tumour nodules that are each less than 3 cm. This tumour size definition (Milan criteria) has been expanded by the University of California, San Francisco protocol to include a single nodule less than 6.5 cm or three nodules each less than 4.5 cm with similar results. Transplantation is associated with a five-year survival of 60%, with less than 25% recurrence over that time period (Coon 2007). Since liver transplantation treats hepatocellular carcinoma as well as liver failure, some centres also offer it to patients with Child-Pugh stage C cirrhosis and tumours within the Milan criteria, with five-year survival of 73.5% and tumour recurrence of less than 15% (Burak 2010).

This improved prognosis of early hepatocellular carcinoma, which is often asymptomatic, has led to the belief that early detection of tumours will reduce the mortality from hepatocellular carcinoma. Thus, many expert professional organisations recommend screening (Bruix 2010; Jelic 2010). However, even in the best circumstances, only 50% of hepatocellular carcinomas from any screened cohort are at an early enough stage to be eligible for effective therapy.

Why it is important to do this review

Hepatocellular carcinoma screening satisfies many of the criteria for a successful screening program in being fairly common in certain definable groups, causing substantial mortality, and with fairly simple screening tools. However, it is a fast growing tumour, and treatment with curative intent is available only to a highly selected group (Yeung 2005). Many hepatologists recommend screening (Bruix 2010; Jelic 2010), and its performance is widespread (Chalasani 1999). Many non-randomised studies support this stand. However, even in the best of circumstances non-randomised studies often use voluntary participants (selection bias), tend to detect slower growing tumours (length time bias), and assume that all of the increase in survival is due to early detection (lead time bias). Thus, we undertook this review of randomised clinical trials to examine the evidence for the efficacy of screening programs for hepatocellular carcinomas.

OBJECTIVES

To determine the beneficial and harmful effects of screening patients with chronic hepatitis B for hepatocellular carcinoma using alpha-foetoprotein or ultrasound, or both.

METHODS

Criteria for considering studies for this review

Types of studies

All reports in the form of abstracts or full text articles of randomised clinical trials of screening, irrespective of publication language, were eligible. Any method of randomisation was acceptable, including those trials in which individuals, locations, or practices had been randomised.

Types of participants

Trials including people with chronic hepatitis B virus, defined by persistence of hepatitis B surface antigen (HBsAg) for more than six months, whether symptomatic or not were eligible for this review. Trials could be with any population. Trials including either sex or both sexes were eligible.

Types of interventions

Trials using alpha-foetoprotein or ultrasound, or both, for screening for hepatocellular carcinoma were eligible.

Alpha-foetoprotein should have been measured by either an enzyme-linked immunoassay (EIA) or radioimmunoassay (RIA) method. The threshold abnormal level for alpha-foetoprotein is usually taken as 20 µg/L.

Only trials using high resolution, real-time ultrasound machines with transducers working at 3.5 MHz or above were eligible.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Disease-specific mortality: controversy exists regarding the use of this outcome to estimate the efficacy of a screening programme. Cause of death is often difficult to determine, and deaths due to the screening process per se or its complications are often not included under disease-specific mortality. Thus, this is an inadequate surrogate to all-cause mortality, but it is often the only available outcome measure (Black 2002).
3. Adverse events. Proportion of patients with serious adverse events and proportion of patients with non-serious adverse events. Serious adverse events are defined according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event that may have jeopardised the patient or requires intervention to prevent it. All other adverse events are considered non-serious.
4. Quality of life.

Secondary outcomes

5. Number of patients with hepatocellular carcinoma detected per 1000 patients with chronic hepatitis B virus infection screened.
6. Number of patients with early stage of hepatocellular carcinoma detected per 1000 patients with chronic hepatitis B virus infection screened per year.
7. Differences, if any, in survival of patients with hepatocellular carcinoma: survival is measured using the denominator 'all those with the disease'; the screening group will have artificially increased survival proportions due to lead and length-time bias. Thus, it is not an inverse of mortality, which uses as its denominator 'all those at risk for the disease' (Kramer 2009).

All these secondary outcomes, though consistently reported in the screening trials, are inherently biased (Croswel 2010). We merely noted these as they are popularly quoted. Although criteria exist for diagnosing hepatocellular carcinoma even in the absence of histology, both trials included in this review were performed before these became available. We noted how the diagnosis of hepatocellular carcinoma was confirmed but we did not exclude studies based on this.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index Expanded (Royle 2003), Chinese Medical Literature Electronic Database (WanFang Data), and Chinese Knowledge Resource Integrated Database until December 2011. The search strategies with the time span of the searches are given in Appendix 1.

Data collection and analysis

We performed the review following the recommendations of The Cochrane Collaboration (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2012). The analyses were performed using Review Manager 5 (RevMan 2011).

Selection of studies

The title and abstract of the citations were screened independently by two review authors to identify potential trials for inclusion (O'Connor 2011). The review authors were not blinded to the authors of the publications or journals. In the case of disagreement, consensus was reached by discussion. If consensus was not reached, the senior author would review the paper also, but this was not needed. All studies that were excluded during the citation and full-article screening processes were recorded along with the reasons for exclusion.

Data extraction and management

Data from the studies were extracted independently by both review authors. A standardised data extraction form was used. Where multiple reports of the same trial were available, data were collated from all the reports and entered in the data extraction form. Disagreements were resolved by discussion and, where necessary, relevant authors were contacted for further information to clarify details for appraisal or data for analysis.

Assessment of risk of bias in included studies

The risk of bias was assessed using the Cochrane Collaboration's recommended domain-based evaluation by the two review authors (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Higgins 2011). Other biases, at both the study level and outcome level, were noted (Moher 2009).

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice were adequate if performed by an independent adjudicator.
- Uncertain risk of bias: the trial is described as randomised, but the method of sequence generation was not specified.
- High risk of bias: the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients, are inadequate and will be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Low risk of bias: allocation was controlled by a central and independent randomisation unit, sequentially numbered, opaque and sealed envelopes, or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Uncertain risk of bias: the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants or if the study was

quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

Blinding

- Low risk of bias: the trial was described as blinded. The parties that were blinded and the method of blinding were described, so that knowledge of allocation was adequately prevented during the trial.
- Uncertain risk of bias: the trial was described as blinded but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias: the trial was not blinded, so that the allocation was known during the trial.

Incomplete outcome data

- Low risk of bias: the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Uncertain risk of bias: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- High risk of bias: the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Low risk of bias: all primary outcomes as defined for this review were reported on in the included trials.
- Uncertain risk of bias: not all outcomes were reported on or were not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more outcomes were not reported on; data on these outcomes were likely to have been recorded.

Other bias

- Low risk of bias: the trial appears to be free of other components (measurement bias and confounding) that could put it at risk of bias.
- Uncertain risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias, e.g., for-profit involvement, authors have conducted other trials on the same topic etc.

We assessed the overall risk of bias for each included trial according to all bias domains. Trials with any high risk of bias component or at least one unclear component were considered as trials with high risk of bias. In all other cases, we considered the trials as having low risk of bias.

Dealing with missing data

We planned to perform all analyses using the intention-to-treat method. In the case of missing data, the last reported or observed response ('carry forward') was to be used including all participants irrespective of compliance or follow-up. We recorded how the authors performed the analyses and how missing data were handled.

RESULTS

Description of studies

Results of the search

The search resulted in 1437 citations. After reviewing title and abstract of all of them, 72 were selected for full-text review. Of these, there were 14 reports of studies with cohort or cross-sectional study design, 47 were reviews, and the remaining 11 publications were trial reports on four randomised trials identified for the review.

The reasons for inclusion and exclusion of the identified trials are listed under 'Characteristics of included studies' and 'Characteristics of excluded studies', respectively.

Included studies

Three of the four trials fulfilled our inclusion criteria. The included randomised trials were conducted in: Toronto, Canada, between 1989 and 1994 (Sherman 1995); in Taiwan (Wang 2011); and in Shanghai, China, between 1992 and 1997 (Zhang 2004). The trial by Zhang et al (Zhang 2004) was reported in seven publications that we found in English and Chinese language journals, while the trial by Sherman et al (Sherman 1995) was reported in one publication and the trial by Wang et al was available only as an abstract (Wang 2011).

Patients

The Sherman et al trial involved 1069 participants from a multi-ethnic background (71% of 1037 participants whose ethnic origin was recorded were classified as Asian) (Sherman 1995). All participants were HBsAg positive. This population was the result of a mixture of referrals from family physicians, gastroenterologists, and general public responding to advertisements in the popular media. A total of 538 participants were individually randomised to screening with alpha-fetoprotein and ultrasound versus 531 randomised to screening with alpha-fetoprotein alone. The mean age of the trial population was 39 years (SD 12). About 2.4% of this population had evidence of cirrhosis, and 40% had abnormal liver enzymes at recruitment.

The trial by Wang et al was conducted in an endemic area covering 10 townships. Participants were randomly allocated to a four-month screening group or an annual screening group (Wang 2011). Within the 10 townships, the trialists identified patients with a platelet count less than 150 x 10^9, or positive for HBsAg, or positive for HCV antibody, and invited them for screening. In the four-month screening group there were 387 participants, while in the 12-month screening group there were 357 participants.

Factories, schools, or enterprises were used as the units of randomisation in the Zhang et al trial (Zhang 2004). Each unit became a cluster of patients. General practitioners serving these institutions recruited patients for the intervention site of the trial. According to the 2004 report, the trial involved 18,816 participants; 9373 were randomised to the screening group and 9343 to the no screening group (Zhang 2004). The mean age of the participants was 41.5 years (range 35 to 59), and 63% were males. The participants were presumably ethnically homogenous. No information was given regarding the initial liver functions of the participants.They were either participants with HBsAg positive (91.6%) or HBsAg negative (8.4%) chronic hepatitis. The small proportion of participants with other chronic hepatitis infections

included in the trial does not in our opinion significantly affect the results.

Interventions

Sherman et al used real-time ultrasound and radioimmunoassay for alpha-foetoprotein as the screening tools (Sherman 1995). They followed all participants at six-monthly intervals (Sherman 1995). If a participant missed a screening appointment, he or she was contacted to confirm withdrawal from the trial or to confirm occurrence of outcome measures, hepatocellular carcinoma or death specifically. The diagnosis was confirmed by biopsy, surgical resection, or by a combination of elevated alpha-foetoprotein and typical features on ultrasound or computed tomography. There was a high attrition rate of 254 people (23.7%) dropping out before completion of the trial.

In the trial by Sherman et al (Sherman 1995), resection was the only treatment option.

The trial by Wang et al was designed to determine the optimal interval for screening using alpha-fetoprotein and ultrasound (Wang 2011). Screening in the two groups was offered at a four-monthly and annual intervals. Further details about the screening strategy were not available.

The two groups in the Zhang trial were similar with respect to age, sex, HBsAg positivity and HBsAg negativity (Zhang 2004). Screening was carried out at six-monthly intervals using alpha-foetoprotein estimation by enzyme-linked immunosorbent assay and real-time ultrasound. Confirmation of diagnosis was done with ultrasound examination by a senior physician or computed tomography or, if required, magnetic resonance imaging of the lesion. Further confirmation was achieved by long-term follow-up or biopsy.

The screened participants in the Zhang et al trial were followed at six-monthly intervals, while the controls were not actively followed (Zhang 2004). Information regarding hepatocellular carcinoma occurrence and deaths were collected from their general practitioners or from the Shanghai cancer registry, or both (Zhang 2004). Interval cancers and cancers among those not compliant with screening were also identified by this method. Most participants in the screened group received between one and 10 screens (median five). Participation was 58.2% initially, but it dropped to around 30% by the eighth screening. Resection, transarterial chemoembolization, or percutaneous ethanol injections were offered, as appropriate, for treatment of hepatocellular carcinoma.

The trials by Sherman 1995 and Zhang 2004 used alpha-foetoprotein levels greater than 20 µg/L as the cut-off for abnormal.

Outcomes

Suspected hepatocellular carcinomas were confirmed by ultrasonography in most participants. Studies have shown that even in the absence of liver biopsy, diagnosis can be made with fair certainty (Kumagi 2009) using imaging techniques like computer tomography with contrast or magnetic resonance imaging, where the vascular pattern of the tumour can be demonstrated (Forner 2008). Ultasound alone is inadequate for this purpose.

Staging of hepatocellular carcinoma was done by a local system where stage I is hepatocellular carcinoma with no signs or symptoms; stage III is hepatocellular carcinoma with decompensated liver disease; and stage II is everything in between. This system of staging does not allow inference regarding the size of the tumour or its extent. This method is not validated and is not comparable with other accepted methods (Bruix 2010).

The Sherman et al trial was designed as a pilot feasibility trial prior to a planned randomised clinical trial to study the efficacy of screening for hepatocellular carcinoma (Sherman 1995). Thus, the outcomes studied in the trial were prevalence and incidence of hepatocellular carcinoma and mortality in a cohort of participants, as well as sensitivity, specificity, and positive predictive values of alpha-foetoprotein levels and ultrasound for hepatocellular carcinoma.

The trial abstract for the study by Wang et al does not clearly identify the primary outcomes (Wang 2011). The trial reports on cumulative three-year incidence of hepatocellular carcinoma, mean tumour size, and cumulative four-year survival.

The outcomes used by Zhang et al were mortality due to hepatocellular carcinoma, stage and resectability of hepatocellular carcinoma, and survival after diagnosis of hepatocellular carcinoma (Zhang 2004).

Excluded studies

One trial was excluded (Chen 2003). This trial was conducted in the Qidong county of China between 1989 and 1995 (Chen 2003). Two reports found in one Chinese and one English language journals were identified (Chen 2003). This trial was excluded as screening of participants was performed using a reverse passive hemagglutination method for estimation of alpha-foetoprotein. This method is about half as sensitive as the enzyme-linked immunoassay. This introduces bias and reduces our ability to assess the benefits and harms of the intervention. This trial involved 5581 HBsAg positive participants between the age of 35 and 69 years. The participants were randomised after stratifying at township level to yield a screening group (n = 3702) and no screening group (n = 1809). Screening was carried out by a six-month estimation of alpha-foetoprotein by the reverse passive hemagglutination method, with a cut-off of 100 µg/L. Confirmation of diagnosis was done by ultrasonography in most participants, with addition of a computer tomography scan in about 4.3%. Autopsy and biopsy confirmed the diagnosis in a few patients. Outcome measures studied were death and incidence of hepatocellular carcinoma. The outcome measures in the control group were assessed through a population-based cancer registry. The trial found 257 participants with hepatocellular carcinoma among the participants in the screened group and 117 in the control group. More cancers were at stage I among the screened participants (29.6%) compared with the control group (6%). A local system of staging was used, where stage I refers to hepatocellular carcinoma with no symptoms or signs. There was no significant difference in either hepatocellular carcinoma mortality specifically (1132/100,000 versus 1113/100,000) or all-cause mortality (1842/100,000 versus 1788/100,000).

Risk of bias in included studies

The trial by Sherman et al used simple random sampling (Sherman 1995). It was designed as a pilot trial and aimed at describing the prevalence and incidence of hepatocellular carcinoma and mortality in this cohort, and the test characteristics

of alpha-foetoprotein estimation and ultrasound for diagnosis of hepatocellular carcinoma. It did not allow for any inference regarding the efficacy of screening compared with no screening. Furthermore, the small number of participants (n = 1069) and the small number of events (n = 14 hepatocellular carcinomas detected) also precluded any comparison of the two methods of screening. No sample size calculation was mentioned. Intention-to-treat analysis was used.

The trial by Wang et al was a cluster randomised trial using townships as the units for allocation (Wang 2011). Details about the randomisation were not available. Similarly sample size calculations were not provided, and it is unclear if intention-to-treat analysis was used. Also, this trial was designed to determine the optimal interval for screening and thus did not include a group that was not screened.

The randomised trial by Zhang et al was a cluster randomised trial (Zhang 2004). The 2004 report says "...simple cluster sampling was carried out.", while the 1997 report states it as "Regarding 'factory', 'enterprise', or 'school' as a unit, we then drew a simple random sample from these units...". The number of controls was 9711 in two reports, in 1996 and 1997; and this dropped to 9443 in all subsequent reports. A sample size calculation was not given. Intention-to-treat analysis was used in the final report of the trial.

Allocation

The generation of the allocation sequence and its concealment were not reported in any of the trials.

Blinding

The Sherman et al trial does not mention blinding at all (Sherman 1995). The Wang trial gives no indication of whether blinding was used (Wang 2011). In the Zhang et al (Zhang 2004) trial, the physicians who performed the staging were blinded to the screening status. However, blinding of the participants, care-givers, or those assessing other outcomes was not reported. Probably, these groups were not blinded.

Incomplete outcome data

In the Sherman et al trial, 23.8% of the participants withdrew from the trial and were not further followed-up (Sherman 1995). Mean follow-up was 26 months. Confirmation was done by histology of a resected specimen in at least 50% of the resected group; however, the details regarding how the diagnosis was confirmed were inadequate. Staging of the disease was not mentioned.

No primary outcome was identified, and no information regarding completeness of follow-up is presented in the abstract of the trial by Wang et al (Wang 2011).

No dropouts were specified and number of participants at follow-up was not mentioned in the trial by Zhang et al (Zhang 2004). Different methods were used to ascertain outcomes in the two arms of the trial: reports from general practitioners and a cancer registry for the control group, and through active follow-up for the screening group.

Selective reporting

The trial by Wang et al did not report any mortality, but only follow-up for up to four-year survival was mentioned in the results (Wang 2011). Zhang et al did not report all-cause mortality, only mortality due to hepatocellular carcinoma (Zhang 2004).

There was no mention of adverse events in any of the trials.

Other potential sources of bias

The Sherman et al trial recruited both a hospital population and volunteers, thus it was at risk of selection bias (Sherman 1995). The percentage of the trial population derived from each group was not specified. The trial had a high dropout proportion (23.8%), but the reasons were not given. Only resection was available as a treatment option. Though the trial stated that only 2.4% of its participants had cirrhosis and 40% had elevated liver enzymes at recruitment, the status of liver function on follow-up, particularly for those with hepatocellular carcinoma, were not mentioned.

It is not possible to assess other sources of bias from the information available in the abstract for the trial by Wang et al (Wang 2011).

In the trial by Zhang et al, informed consent was obtained from the intervention group (Zhang 2004). The number of participants who refused to sign informed consent was 384 (4.1%). The reasons for this were not given. It is unclear if the identified controls were followed-up in any way.

Furthermore, all the three trials, being screening trials, suffer the possibility of 'over-diagnosis bias'.

Effects of interventions

The Sherman et al trial reported 14 hepatocellular carcinomas detected during the trial period (2340 person years of observation); the incidence of hepatocellular carcinoma being 470/100,000 person years (Sherman 1995). No information regarding the stage of the disease was given nor whether there was any clear indication of which screening group the people with hepatocellular carcinomas belonged to. Only half of the patients had liver resection. There were 11 deaths in total, accounting for an all-cause mortality of 470/100,000 person years; and five deaths due to hepatocellular carcinoma, resulting in a disease-specific mortality of 213.7/100,000 person years in the entire cohort of 1069 patients. The sensitivity, specificity, and positive predictive values of alpha-foetoprotein estimation were 64.3%, 91.4%, and 9% respectively. For ultrasound, the values were 71.4%, 93.8%, and 15.1%, respectively. No adverse events were reported.The authors conceded that the events were too few to enable comparison of the two screening modes, so no such information was provided in the trial report.

Multiple reports of the Zhang et al trial presented different results (Zhang 2004). The number of controls and total number of participants dropped from 9771 and 19,144 in the 1997 report, before completion, to 9443 and 18,816 in the reports published at the end of the trial. For the sake of simplicity, discrepancies noted in two reports that were both published after the end of the trial, one in a Chinese language journal and the other in an English language journal, are presented in the tables below. The reasons for these differences are not given in any of the two publications, and while we did make contact with one of the authors he did not give answers to our questions.

Table 1: Discrepancies in results of the Shangai trial in two reports, both published after the end of the trial.

Study author, year, and Journal	Person years follow-up of controls	Person years follow-up of those screened	Number of cancers those screened	Number of cancers in controls	Number of deaths due to hepatocellular carcinoma among screened versus controls
Zhang B et al 2004 in J Cancer Clin Res Oncol	41,077	38,444	86 (71 detected at screening)	67	32 versus 54.
Yang B et al 1999 in Natl Med J China	32,944	22,631.5	86 (59 detected at screening)	51	Not given.

Table 2: Discrepancies in results of the Shangai trial in two reports, both published at the end of the trial, continued.

Study author, year and Journal	Number(%) of cancers resected in screened versus control	Survival of those with hepatocellular carcinoma in percent at years 1, 2, 3, 4, and 5 among screened					Survival of those with hepatocellular carcinoma in percent at years 1, 2, 3, 4, and 5 among controls				
		1	2	3	4	5	1	2	3	4	5
Zhang B et al 2004 in J Cancer Clin Res Oncol	40 (46.5%) versus 5 (7.5%)	65.9	59.9	52.6	52.6	46.4	31.2	7.2	7.2	0	0
Yang B et al in 1999 in Natl Med J China	40 (46.5%) versus 4 (7.8%)	65	65	52.7	52.7	52.7	30	6.5	0.0	0.0	0.0

Wang et al did not report on any of the primary outcomes identified in this review (Wang 2011). The cumulative four-year survival was reported as insignificantly different between the groups: 45.3% in the four-monthly group and 42.7% in the annual group. The cumulative three-year incidence of hepatocellular carcinoma was also reported as not significantly different:: 11.7% in the four-monthly screening group and 9.7% in the annual screening group. In the four-monthly screening group more patients were detected with tumour size of 2 cm or less and at a very early Barcelona-Clinic Liver Cancer (BCLC) stage, fit for curative treatment.

DISCUSSION

Summary of main results

This systematic review is an update of a previous systematic review and meta-analysis published in 2003 (Wun 2003). Since then, only one new trial of screening for hepatocellular carcinoma among people with chronic hepatitis B could be found (Wang 2011). However, three new reports of older trials, two from the trial by Zhang et al (Zhang 2004) and one by Chen et al (Chen 2003), were identified and more data included in this review.

The Sherman et al trial was not designed to test the efficacy of screening (Sherman 1995). The small number of participants and the small number of events preclude any inference regarding the benefit or harm of screening with alpha-fetoprotein alone, or with alpha-foetoprotein and ultrasound. This trial only reported all-cause mortality for the entire cohort and not for any of the individual groups (Sherman 1995).

The trial by Wang et al, published in abstract format only, did report on survival and occurrence of hepatocellular carcinoma (Wang 2011). The trials by Sherman et al (Sherman 1995) and Zhang et al (Zhang 2004) reported disease-specific mortality. None of the trials reported adverse events or quality of life outcomes.

The trial by Chen was excluded as the method of estimation of alpha-foetoprotein was insensitive (Chen 2003). This trial did not demonstrate a difference in all-cause mortality between the two trial intervention groups. The trial by Zhang et al had many methodological flaws, and the multiple reports of the trial presented conflicting evidence (Zhang 2004). This made the results of the trial difficult to evaluate. The inclusion of the two latest reports of the trial by Zhang et al did not clarify any of the issues (Zhang 2004).

In the trial by Wang et al, the incidence of hepatocellular cancer was higher in the four-monthly screening group (Wang 2011). In the two other trials, hepatocellular cancer incidence was higher in the screened group, though the absolute magnitude varied widely for both the control and intervention groups in both trials. This may be the result of inherent differences in the populations studied. In the Sherman and Zhang trials, around 50% of the detected cancers were treatable (Sherman 1995; Zhang 2004). Such information is not available for the Wang et al trial.

In the Wang et al trial, cumulative four-year survival was not significantly different when the two screening intervals were compared (Wang 2011). Survival was evaluated in the trial by Zhang et al, though various reports present it differently (Zhang 2004).

Overall completeness and applicability of evidence

Many cohort studies support screening of patients with chronic hepatitis B using ultrasonography or alpha-foetoprotein, or both. Two community-based studies in the United States, a retrospective cohort (Wong 2009) and a case-control study (Tong 2010), concluded that screening improved survival among patients at risk of hepatocellular carcinoma. Hepatitis B virus infection is endemic among Alaskan indigenous groups in the United States. MacMohan et al reported on regular screening for hepatocellular carcinoma in this population. The authors concluded that compared to historical controls, the cohort in whom regular screening with alpha-foetoprotein was carried out every six months had better survival (McMahon 2000). In an Italian cohort study of patients admitted with hepatocellular carcinoma, screen detected cancers appeared to have better outcomes than incidentally detected cancers among those with cirrhosis (Farinati 2001; Santi 2010). All these studies, being non-randomised, have the same problem of having dissimilar comparison groups and of being subject to length bias and lead-time bias. Kunz et al demonstrated that estimates of effect in cohort studies differ widely from those of randomised trials, by -78% to 400% (Kunz 2007). Thus, results from non-randomised studies cannot be taken as proof of efficacy of screening.

Even among patients with chronic hepatitis B virus infection, the risk of hepatocellular carcinoma varies, and this is dependent on ethnicity (Bruix 2010). Asian males over the age of 40 years with or without active viral replication develop hepatocellular carcinoma at the rate of 0.2% per year, while Caucasians with no active viral replication are at no increased risk of hepatocellular carcinoma (Bruix 2010). Thus, evidence from one ethnic group may not be directly applicable to other groups. This highlights the need for using ethnicity as a stratification factor in randomised clinical trials.

Unfortunately, there is a paucity of randomised trials on screening for hepatocellular carcinoma in patients with chronic hepatitis B. This lack of trials is surprising considering the large numbers of people with chronic hepatitis B virus infection worldwide who are at risk of hepatocellular carcinoma and are being screened. This may in part reflect the distribution of chronic hepatitis B virus infection, which is common in developing and underdeveloped countries where resources required to conduct such a large scale trial may be hard to assemble. However, many experts have asserted that a screening program works (Bruix 2010; Jelic 2010) and have pre-empted the question of whether a randomised trial is needed.

Since the time of these studies, in the late 1990s, there have been many developments in the area of diagnosis and treatment of hepatocellular carcinoma (Coon 2007; Bruix 2010; Jelic 2010; Kudo 2010; Forner 2012). None of the trials in the review offered transplantation as a treatment for hepatocellular carcinoma. This may affect the outcome of the trials, though liver transplant is not available in many parts of the world nor is it likely that enough liver transplants will be available to treat all patients detected in a trial. The trial by Wang et al looks at screening people with chronic viral hepatitis for hepatocellular carcinoma at four-monthly versus yearly intervals using alpha-fetoprotein and ultrasound (Wang 2011). The published trial abstract indicates that there is no significant difference in survival between the two groups.

Quality of the evidence

Screening trials are fraught with many biases. Lead-time and length-time biases are well known and can be overcome by adequate randomisation (Croswel 2010). However, other forms of bias such as the healthy volunteer bias and overdiagnosis bias may still persist. The outcome measure often used is disease-specific mortality, and many screening trials are powered to detect changes in this quantity (Kramer 2009). However, the cause of mortality is difficult to determine even if there is blind third party adjudication and may result in sticky diagnosis bias or slippery-linkage bias (Black 2002). Furthermore, screening is a programme implementation rather than a one-at-a time project. Thus screening trials must be very carefully conducted and evaluated before conclusions can be drawn.

Overall, the quality of evidence in the trials included in this review was judged as at high risk of bias.

One of the two included trials presented conflicting results in its various reports. When we contacted the authors, they did not give any clear explanation for the noted discrepancies.

Potential biases in the review process

We cannot exclude the possibility that there may be unpublished trials that we did not identify. Such publication bias is more likely to affect trials with a neutral or negative result. Thus, even if such a publication bias does exist it would be unlikely to be in favour of screening for hepatocellular carcinoma.

Agreements and disagreements with other studies or reviews

Compared to the previous version of this review, we identified and added two new reports on the trials by Chen 2003 and Zhang 2004. The new reports did not change our initial opinion regarding inclusion or exclusion of the trials, nor our conclusions. In addition, we were able to identify one new trial whose results, when published fully, may shed additional light on the issue of screening for hepatocellular carcinoma.

Multiple professional organisations (Bruix 2010; Jelic 2010) recommend screening, based on poor quality evidence with high risk of bias (systematic errors) and high risk of play of chance (random errors) (Keus 2010). A recent review by the Health Technology Assesment, United Kingdom on screening for hepatocellular carcinoma among those with cirrhosis concluded that there was insufficient evidence to recommend screening (Coon 2007). Cirrhosis and hepatitis C are other risk factors for hepatocellular carcinoma and we could not identify any systematic reviews for screening in these groups either.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend for or against screening for hepatocellular carcinoma with alpha-foetoprotein and liver ultrasonography, or both, among patients with chronic hepatitis B virus infection.

Implications for research

There is an urgent need for well-designed randomised clinical trials in this area. Future research should compare screened individuals with a control group without screening. Such trials should include adequate sample size calculations and proper blinding processes. Diagnosis, staging, and therapy offered must be according to current recommendations. The primary outcomes should include all-cause mortality. The patients should be stratified according to liver function and ethnicity. Additionally, information about other significant outcomes, particularly anxiety, false positive proportions, and harms including extra operations and other treatments should also be reported. Finally, trials should follow the recommended guidelines for the reporting of clinical trials (Consolidated Standards of Reporting Trials (CONSORT): www.consort-statement.org).

ACKNOWLEDGEMENTS

To Yuk Tsan Wun, who was the author of the original protocol published in The Cochrane Library 2000, Issue 4 (Wun 2000) and the subsequent review published in *The Cochrane Library* 2003, Issue 2 with a similar title (Wun 2003), and also for help with searching the Chinese language databases.

To Kelly Burak for additional comments on our review.

To Dimitrinka Nikolova, Denmark, for comments and corrections and Sarah Klingenberg, Denmark, for literature searches.

To peer reviewers and editors of the Cochrane Editorial Team for their comments and corrections.

Review update

Peer reviewers: Fabio Farinati, Italy; Ronald L Koretz, USA.
Contact editor: Christian Gluud, Denmark.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Sherman 1995

Methods	Randomised clinical trial, designed as a pilot feasibility trial. The trial was conducted in Canada. Follow-up for 5 years (1989 to 1994). Intention-to-treat analysis used. Sample size calculation not mentioned.
Participants	1069 participants, recruited from clinic-based population and by following advertisement in popular media. Multi-ethnic population (71% Asian). Individually randomised 538 to alpha-fetoprotein and ultrasound, and 531 to alpha-fetoprotein alone. 40% had elevated liver enzymes and 2% had evidence of cirrhosis.

Sherman 1995 *(Continued)*

	23.8% dropouts.
Interventions	AFP alone (n = 531) versus AFP and US (n = 538) every 6 months. Those with elevated serum AFP or US suggestive of mass had additional investigations. • Repeat AFP in one month in all with elevated AFP. • If AFP > 20 µg/L and no pregnancy or reactivation of chronic hepatitis, US exam was done. Participants missing screening appointment were contacted for withdrawal from the trial or occurrence of outcome measures, namely, hepatocellular carcinoma and/or death.
Outcomes	The trial was designed as a feasibility trial. The authors do not present the data in comparative groups only as an entire cohort. Mortality due to hepatocellular carcinoma: 213.7/100,000 person-years. All-cause mortality: 470/100,000 person-years. No information regarding adverse events or quality of life. Incidence of hepatocellular carcinoma was 470/100,000 person years in the entire cohort. 50% of the participants with detected hepatocellular carcinomas underwent resection.
Notes	The trial was not designed to study efficacy of screening for hepatocellular carcinoma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information regarding allocations sequence generation.
Allocation concealment (selection bias)	Unclear risk	No information regarding allocations sequence concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information regarding blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	- The trial had a high per cent of dropouts, ie, 23.8%. - Although 14 participants with hepatocellular carcinoma had been diagnosed in the population, details are given only for 13.
Selective reporting (reporting bias)	Low risk	The trial was designed as a feasibility trial and the authors presented their results as such.
Other bias	Unclear risk	- Contained a mixture of hospital-based and volunteer population (proportions not clear). - Staging of liver cancer has not been mentioned. - Small study population with low number of events. - Not designed to study the efficacy of screening.

Wang 2011

Methods	A community trial. The trial was conducted in Taiwan.

Wang 2011 *(Continued)*

	Ten townships were randomly assigned to 4-month and 12-month surveillance. Participants, invited to participate in the trial, were selected on the basis of platelet count ≤ 150 (x 109)/L, positive hepatitis B-surface antigen or antibody to hepatitis C virus. 785 participants in the 4-month group and 796 in the 12-month group were invited of whom 398 in the 4-month group and 439 in the 12-month group declined to participate.
Participants	387 remained in the 4-month group and 357 in 12-month group.
Interventions	Liver ultrasound (US) and alpha-foetoprotein were used for hepatocellular carcinoma surveillance. Residents with hepatic nodules suspicious for hepatocellular carcinoma were referred to medical centre for further evaluation and management.
Outcomes	No difference in cumulative four-year survival (4-month: 45.3%; 12-month: 42.7%; P = 0.38). Disease-specific mortality/adverse events/quality of life were not mentioned in the abstract. Incidence of hepatocellular carcinoma was similar (4-month: 11.7%; 12-month: 9.7%; P = 0.2) A greater number of early stage cancers was detected (P = 0.057), and curative treatment was given to patients in the 4-months group (P = 0.049).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not given in the abstract.
Allocation concealment (selection bias)	Unclear risk	Not available from the abstract.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention in the abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No follow-up data given.
Selective reporting (reporting bias)	High risk	Did not report on any of the primary outcomes identified in this trial, including all-cause and disease-specific mortality.
Other bias	Unclear risk	No judgements can be made from the limited information in the abstract.

Zhang 2004

Methods	Cluster randomised trial using 300 factories, enterprises, or schools as units were listed. The trial was conducted in China between 1992 and 1997. No information regarding allocation sequence generation or concealment. Not blinded. Follow-up for 5 years; number of patients with follow-up is not mentioned. Intention-to-treat analysis: used in the final report.

Zhang 2004 *(Continued)*

	Sample size calculation: not mentioned.
Participants	18,816 Shanghai urban residents with positive HBsAg for more than six months (92%) or chronic hepatitis (8%). 9373 participant randomised to the screening group. Number of patients in the trial and in the control group in the 1997 report is 19,144 and 9771 respectively, but in all subsequent reports, the number of patients are given as 18,816 and 9443. Informed consent taken in the screened group, with 384 (4.1%) refusing consent. Informed consent for the control group is not mentioned.
Interventions	AFP + US every six months (n = 9343) versus no screening. If AFP is greater than 20µg/ml and US negative, AFP was repeated in one month. If persistently positive, US repeated by more experienced sonographer or CT/MRI performed. Diagnosis confirmed by US, CT, MRI, long-term follow-up, or biopsy. Control events obtained at the end of the trial from General Practitioners or Shanghai Cancer Registry. Treatment (resection, percutaneous ethanol injection, or transarterial chemoembolization) provided for most at the Fudan University Hospital.
Outcomes	All cause mortality: not reported. Disease-specific mortality: 32 deaths due to hepatocellular carcinoma in the screened group with a mortality proportion of 83.2/100,000 person years, and 54 deaths in the control group with a mortality proportion of 131.5/100,00 person years. Adverse events and quality of life not reported. Number of participants with hepatocellular carcinoma detected by screening. - 86 detected in screened group (39 tumours less than 5cm). - There is a difference in the number of cancers in the control group; 51 cancers in the control group were reported in 1999 report and 67 in 2004 report, though both publications were published after the completion of the trial. - 40 participants with hepatocellular carcinoma in the screened group and 5 in the control group were resected. - Patient years of follow-up given as 32,944 for the control group and 22,631 in the 1997 report; while in the 2004 report, it is 41,077 and 38,444, respectively; again the reasons for this discrepancy are not provided. Survival among those participants with hepatocellular carcinoma appears to be better in the screened group; the exact number is difficult to estimate due to the discrepancies. This may, however, reflect lead-time bias.
Notes	Lead time bias estimated in the trial was 5.4 months. Many discrepancies in data in various reports of the same trial. Details were sought by contacting the authors between January and February 2011. Contact was established with one, but he did not provide a clear response to our queries.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of how the sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Not described in any of the reports.
Blinding (performance bias and detection bias)	Unclear risk	Not clearly described. Participants not blinded. Blinding of outcome assessors or blinding of sonographers not stated.

Zhang 2004 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information of completeness of follow-up or dropouts mentioned. Different methods to measure outcomes makes bias likely.
Selective reporting (reporting bias)	High risk	All-cause mortality not reported. Only disease-specific mortality was reported.
Other bias	High risk	Multiple discrepancies in the various reports. Different methods for follow-up of control and screened groups. Underlying liver function has not been documented. Staging of hepatocellular carcinoma done according to local system. Resection was the only effective treatment for hepatocellular carcinoma that was offered as part of the trial. Overdiagnosis bias is likely to have occurred.

M = male
F = female
{} = information compiled or comment by review author
AFP = alpha-foetoprotein
US = ultrasound

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chen 2003	AFP estimation done using RPHA method - the latter has poor sensitivity compared to enzyme immunoassay or radio-immunoassay, so hence poor ability to demonstrate effect of screening.

AFP = alpha-foetoprotein
RPHA = reverse passive haemagglutination

APPENDICES

Appendix 1. Search strategies

Database	Search date	Search methodology
Cochrane Hepato-Biliary Group Controlled Trials Register	December 2011.	(alpha-fetoprotein* OR alfa-fetoprotein* OR alpha-foetoprotein* OR alfa-foetoprotein* OR alpha-fetalprotein* OR alfa-fetalprotein* OR 'alpha fetoprotein*' OR 'alfa fetoprotein*' OR 'alpha foetoprotein*' OR 'alfa foetoprotein*' OR 'alpha fetalprotein*' OR 'alfa fetalprotein*' OR alphafetoprotein* OR alfafetoprotein* OR alphafoetoprotein* OR alfafoetoprotein* OR alphafetalprotein* OR alfafetalprotein*) OR (liver AND (ecograph* OR echograph* OR ultrasonograph*)) AND 'hepatitis b'
Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*	Issue 4, 2011.	#1 MeSH descriptor alpha-Fetoproteinsexplode all trees #2 (alpha-fetoprotein* OR alfa-fetoprotein* OR alpha-foetoprotein* OR alfa-foetoprotein* OR alpha-fetalprotein* OR alfa-fetalprotein* OR 'alpha fetoprotein*' OR 'alfa fetoprotein*' OR 'alpha foetoprotein*' OR 'alfa foetoprotein*' OR 'alpha fetalprotein*' OR 'alfa fetalprotein*' OR alphafetoprotein* OR alfafetoprotein* OR alphafoetoprotein* OR alfafoetoprotein* OR alphafetalprotein* OR alfafetalprotein*)

(Continued)

		#3 (#1 OR #2) #4 MeSH descriptor Ultrasonographyexplode all trees #5 ecograph* OR echograph* OR ultrasonograph* #6 (#4 OR #5) #7 MeSH descriptor Hepatitis B explode all trees #8 hepatitis b #9 (#7 OR #8) #10 ((#3 OR #6) AND #9)
MEDLINE (Ovid SP)	1948 to December 2011.	1. exp alpha-Fetoproteins/ 2. (alpha-fetoprotein* or alfa-fetoprotein* or alpha-foetoprotein* or alfa-foetoprotein* or alpha-fetalprotein* or alfa-fetalprotein* or alpha fetoprotein* or alfa fetoprotein* or alpha foetoprotein* or alfa foetoprotein* or alpha fetalprotein*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 3. 1 or 2 4. exp Ultrasonography/ 5. (ecograph* or echograph* or ultrasonograph*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 6. 4 or 5 7. exp Hepatitis B/ 8. hepatitis b.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 9. 8 or 7 10. 6 or 3 11. 10 and 9 12. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 13. 11 and 12
EMBASE (Ovid SP)	1980 to December 2011.	1. exp Alpha Fetoprotein/ 2. (alpha-fetoprotein* or alfa-fetoprotein* or alpha-foetoprotein* or alfa-foetoprotein* or alpha-fetalprotein* or alfa-fetalprotein* or alpha fetoprotein* or alfa fetoprotein* or alpha foetoprotein* or alfa foetoprotein* or alpha fetalprotein*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 3. 1 or 2 4. exp Echography/ 5. (ecograph* or echograph* or ultrasonograph*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 6. 4 or 5

(Continued)

		7. exp Hepatitis B/ 8. hepatitis B.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 9. 8 or 7 10. 6 or 3 11. 10 and 9 12. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 13. 11 and 12
Science Citation Index Expanded	1900 to December 2011.	# 6 #5 AND #4 # 5 TS=(random* or blind* or placebo* or meta-analysis) # 4 (#1 OR #2) AND #3 # 3 TS=(hepatitis b) # 2 TS=(ecograph* or echograph* or ultrasonograph*) # 1 TS=(alpha-fetoprotein* or alfa-fetoprotein* or alpha-foetoprotein* or alfa-foetoprotein* or alpha-fetalprotein* or alfa-fetalprotein* or alpha fetoprotein* or alfa fetoprotein* or alpha foetoprotein* or alfa foetoprotein* or alpha fetalprotein*)
Chinese Knowledge Resource Integrated Database	December 2011.	肝炎乙型 (hepatitis B) [title] 肝炎 (hepatitis) [subject heading (主題)] à 乙型 (B type) [title] à 篩查 (screening) [within searched results] 甲胎蛋白(alpha-foetal protein) [subject] à 肝炎 (hepatitis) [subject] à 超聲檢查 (ultrasound screening) [subject] 肝炎 超聲 (hepatitis AND ultrasound) [subject heading] à 肝癌 (liver cancer) [within searched result] 肝炎 甲胎蛋白 (hepatitis AND alpha-foetal protein) [subject] à肝癌 (liver cancer) [within searched result] à 乙型肝炎 (hepatitis B) [within searched result]
Wangfang Data (Chinese Medical Association Journals)	December 2011.	甲胎蛋白(alpha-foetal protein) AND 肝炎 AND 超聲檢查 (ultrasound screening) [titles] 肝炎 [title] à 甲胎蛋白 [title] 肝炎 [title] à 超聲 [title] 肝炎 [title] à 乙型 [title] à 甲胎蛋白 [keyword] 肝炎 [title] à 乙型 [title] à 超聲[keyword]

WHAT'S NEW

Date	Event	Description
24 February 2012	New citation required but conclusions have not changed	One new trial publication in the form of an abstract was identified. The review was updated following latest guidelines in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011).
22 February 2012	Amended	Title slightly amended. The previous published review version had the title: "Alpha-fetoprotein and/or liver ultrasonography for liver cancer screening in patients with chronic hepatitis B".
22 February 2012	New search has been performed	Searches performed 07 of December 2011.

CONTRIBUTIONS OF AUTHORS

RA prepared an update of the protocol, originally published in Issue 4, 2000 of *The Cochrane Library*. PC and JD revised the protocol. RA and PC independently selected trials, extracted outcome data, and assessed the quality of the studies. JD appraised the reports and validated these data. RA drafted the review. JD and PC edited the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Department of Family Medicine, University of Calgary, Calgary, Canada.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As acknowledged, this review is the product of a protocol originally prepared by Yuk Tsan Wun et al in 2000 (Wun 2000). Since then, while working on the review, several changes have been made and are explained in the following passage.

The original protocol was designed to include non-randomised studies. However, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the fact that estimates of benefit provided by non-randomised studies vary widely from those of randomised trials (Kunz 2007), we chose to include only randomised trials. We intended to include both published and unpublished trials on the topic. The original review used the Medcyber database as one of the sources for Chinese language literature. This portal has since become commercial and is used to promote products and to provide information to the general public. This database was therefore ignored and another database, the Chinese Knowledge Resource Integrated Database, was used instead. The outcome measures to be assessed in the original protocol and review included cost, sensitivity and specificity of alpha-foetoprotein and ultrasonography for screening. In this review, we chose to consider all-cause mortality, disease-specific mortality, adverse events, and quality of life indicators as the primary outcomes of interest, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We believe the effectiveness of the screening procedure is best defined by its effect on all-cause mortality, a more patient important outcome. We did not perform cost and economic analyses in this review. Data are too scarce and such analyses would require too many theoretical assumptions rendering such analysis useless for its readers.

We believe that these changes were within acceptable limits and helped us produce a better review.

INDEX TERMS

Medical Subject Headings (MeSH)

Biomarkers [blood]; Carcinoma, Hepatocellular [blood] [*diagnosis] [diagnostic imaging]; Hepatitis B Surface Antigens [blood]; Hepatitis B, Chronic [*complications]; Liver [*diagnostic imaging]; Liver Neoplasms [blood] [*diagnosis] [diagnostic imaging]; Randomized Controlled Trials as Topic; Ultrasonography; alpha-Fetoproteins [*analysis]

MeSH check words

Humans