

Cancer Expert Working Group on Cancer Prevention and Screening

Recommendations on Prevention and Screening for Liver Cancer For Health Professionals

Local epidemiology

1. In 2015, liver cancer was the fourth commonest cancer in men and the tenth commonest cancer in women. A total of 1,791 liver cancer cases were recorded, accounting for 5.9% of all newly diagnosed cancer cases. The age-standardised incidence rate (ASIR) was 22.7 for male and 6.2 for female per 100,000 standard population. The median age at diagnosis was 65 for males and 73 for females.¹

2. There were 1,540 deaths due to liver cancer in 2016, ranking third as leading cause and constituting 10.8% of all cancer deaths. The age-standardised mortality rates (ASMR) of liver cancer were 18.0 for male and 4.9 for female per 100,000 standard population. After adjusting for population ageing, both the ASIR and ASMR in males and females showed a consistently downward trend in the past two decades. 62% of its deaths were registered under hepatocellular carcinoma (HCC) in 2016.^{2,3} More information on liver cancer statistics can be found at the Centre for Health Protection (CHP) website: <http://www.chp.gov.hk/en/content/9/25/52.html>.

Risk factors

3. HCC is a complex disease entity with multiple possible etiologies, and associated with many risk factors and cofactors. The major risk factors for HCC include:

- (a) chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)^{4,5}
- (b) cirrhosis from all causes⁶
- (c) consumption of alcoholic drinks^{5,7,8}
- (d) ingestion of foods contaminated with aflatoxin (a toxin found in some food such as mouldy peanuts and grains).^{5,7}

Other risk factors include diabetes, obesity, smoking, and certain hereditary conditions such as haemochromatosis, glycogen storage disease and Wilson's disease.^{4,7,8,9}

Primary prevention

4. Some preventive measures can help reduce the risk of HCC which is the major type of liver cancer:

- (a) Vaccinate against HBV¹⁰
- (b) Do not drink
- (c) Do not smoke
- (d) Avoid unprotected sexual intercourse or sharing needles
- (e) Avoid food source of aflatoxins such as mouldy peanuts and grains
- (f) Maintain healthy diet and body weight

Early detection

5. Early stage liver cancer can be asymptomatic. Common signs and symptoms of liver cancer include unexplainable weight loss, jaundice, dark urine, pale stool, abdominal pain and swelling. Individuals with these signs and symptoms should be investigated for liver cancer.

Screening

6. There is a lack of strong randomized controlled trial evidence for the effectiveness of HCC screening by Alpha-fetoprotein (AFP) test and Ultrasonography (USG).

Screening tests

7. Alpha-fetoprotein (AFP) remains widely used for screening HCC although it has never been adequately studied as a single screening tool.^{8,11} Apart from HCC, increased levels of AFP are seen in some germ cell tumours and inflammation of the liver (such as in chronic hepatitis), regenerating nodules and pregnant women.^{10,12} Whereas around 20% of HCC do not secrete AFP, at a cut-off of 20 ng/mL, the sensitivity of AFP is about 39% to 64% and the specificity ranges from 76% to 91%.¹³

8. Ultrasonography (USG) has been used for clinical surveillance to patients with

chronic HBV for HCC. The pooled sensitivity for HCC is estimated at 94%, with a lower sensitivity of 63% for early disease with smaller tumours. Specificity is estimated at between 92% and 98%.¹⁴ USG is highly-observer dependent and is of limited value in patients with obesity and ascites. Interpretation can be difficult in patients with cirrhosis and regenerative nodules. USG can be used in conjunction with AFP.

9. Computed tomography (CT) and magnetic resonance imaging (MRI) have higher sensitivities and specificities, but the radiation exposure (for CT), high cost, and availability of machines preclude the use of these imaging techniques for regular surveillance. For patients with high-riding liver or obesity, where the whole liver cannot be reliably examined by USG, CT and MRI would have obvious benefits.¹⁵

10. Newer techniques such as microbubble contrast enhancement and harmonic imaging techniques may significantly improve detection rates by demonstrating the arterialization of HCC, allowing differentiation from other liver tumours that are fed by the portal vein. These emerging techniques are only available in specialized centres and their role in screening has not been studied in randomised clinical trials.¹⁶

Effectiveness of liver cancer screening for people at high risk

11. To date, studies on liver cancer screening on high risk groups are few. The two community trials on patients with chronic HBV infection conducted in Qidong¹⁷ and Shanghai¹⁸ did not show consistent effect of HCC screening by AFP and USG on mortality reduction and survival. A systematic review in 2014¹⁹ concluded that, due to methodological flaws in existing studies, there was only very-low-strength evidence from which to draw conclusions about the effectiveness of liver cancer screening in high-risk patients with chronic liver disease. A local retrospective cohort study²⁰ showed that HCC screening in chronic HBV patients by AFP and /or USG could identify tumours at an early stage, thereby increasing the chance of receiving curative treatment. A meta-analysis performed in 2014²¹ also showed that HCC screening in patients with cirrhosis was associated with improved early stage detection (OR 2.08, 95% CI 1.80-2.37) and curative treatment rates (OR 2.24, 95% CI 1.99-2.52).

12. After taking into consideration local epidemiology, emerging scientific evidence, local and overseas screening practices, the Cancer Expert Working Group on Cancer Prevention and Screening (CEWG) made the following recommendations on liver

cancer screening at its 27th meeting on 23 November 2017:

For persons at average risk	
1.	Routine screening with alpha-fetoprotein (AFP) or ultrasonography (USG) for asymptomatic persons at average risk is not recommended.
For persons at high risk	
2.	People with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or liver cirrhosis regardless of the cause are at increased risk of hepatocellular carcinoma (HCC). Depending on certain criteria such as age, family history, presence of cirrhosis and other clinical parameters, some subgroups are at higher risk and should consider receiving periodic cancer surveillance (e.g. every 6-12 months) with AFP and USG. People with chronic HBV or HCV infection, or liver cirrhosis should thus seek advice from doctors to determine their need for and approach of cancer surveillance.

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References

- ¹ Hong Kong Cancer Registry, Hospital Authority. Liver Cancer in 2015. Available at http://www3.ha.org.hk/cancereg/pdf/factsheet/2015/liver_2015.pdf.
- ² Department of Health and Census and Statistics Department, HKSAR. Mortality Statistics, 2016.
- ³ Yim HJ, Suh SJ, Um SH. Current management of hepatocellular carcinoma: an Eastern perspective. *World Journal of Gastroenterology*. 2015;21(13):3826-42.
- ⁴ Cheung TK, Lai CL, Wong BCY, et al. Clinical features, biochemical parameters, and virological profiles of patients with hepatocellular carcinoma in Hong Kong. *Aliment Pharmacol Ther*. 2006;24:573-583.
- ⁵ List of Classifications by cancer sites with sufficient or limited evidence in humans Vol 1 to 117, International Agency for Research on Cancer. Available at <http://monographs.iarc.fr/ENG/Classification/Table4.pdf>.
- ⁶ Forner A, Llovet JM, and Bruix J. Hepatocellular carcinoma. *The Lancet*. 2012;379:1245-55.
- ⁷ Gomaa AI, Khan SA, Toledano MB, et al. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. *World J Gastroenterol*. 2008;14:4300-4308.
- ⁸ Chuang SC, La Vecchia C, and Boffetta P. Liver cancer: descriptive epidemiology and risk factors other than HBV and HCV infection. *Cancer Lett*. 2009;286:9-14.
- ⁹ El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;132:2557-76.
- ¹⁰ Surveillance of Viral Hepatitis in Hong Kong 2015 Update Report. Viral Hepatitis Preventive Service. Department of Health. December 2016.
- ¹¹ Aghoram R, Cai P, Dickinson JA. Alpha-fetoprotein and/or liver ultrasonography for screening of hepatocellular carcinoma in patients with chronic hepatitis B. *Cochrane Database of Systematic Reviews*. 2012;9:CD002799.
- ¹² Poon RTP. Recent Advances in the Treatment of Hepatocellular Carcinoma. *Hong Kong J Radiol*. 2012;15(Suppl):S13-22.
- ¹³ Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *The Lancet*. 2003;363:1907-17.
- ¹⁴ Coon JT, Rogers G, Hewson P, et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health Technology Assessment*. 2007;11(34):1-206.
- ¹⁵ Bruix J, Sherman M: American Association for the Study of Liver Diseases:

Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020–1022.

¹⁶ Kudo M. The 2008 Okuda lecture: Management of hepatocellular carcinoma: from surveillance to molecular targeted therapy. *Journal of Gastroenterology & Hepatology*. 2010 Mar; 25(3):439-52.

¹⁷ Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC, et al. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. *J Med Screen*. 2003;10:204-9.

¹⁸ Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2004;130:417-22.

¹⁹ Kansagara D, Papak J, Pasha AS, et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. *Ann Intern Med* 2014;161:261–9.

²⁰ Yuen MF, Cheng CC, Laufer JJ, Lam SK, Ooi CG, Lai CL. Early Detection of Hepatocellular Carcinoma Increases the Chance of Treatment: Hong Kong Experience. *Hepatology*. 2000 Feb;31(2):330-5.

²¹ Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS Medicine / Public Library of Science*. 11(4):e1001624, 2014 Apr.