衞生防護中心
Centre for Health Protection

Cancer Expert Working Group on Cancer Prevention and Screening (CEWG)

Recommendations on Prevention and Screening for Pancreatic Cancer For Health Professionals

Local epidemiology

An increasing trend has been observed in the incidence and mortality of pancreatic cancer in Hong Kong.[1] The cancer often has a poor prognosis upon diagnosis, with an overall 5-year survival rate of 9% worldwide.[2]

2. In 2019, a total of 946 new pancreatic cancer cases (530 in males and 416 in females) were recorded, accounting for 2.7% of all newly diagnosed cancer cases locally. It was ranked as the 11th most common cancer in Hong Kong. The median age at diagnosis was 68 in males and 72 in females. The age-standardised incidence rates (ASIR)[a] were 7.0 for male and 4.3 for female per 100,000 standard population of the respective sex. The ASIR for both sexes rose from 3.1 per 100,000 population in 1991 to 5.6 per 100,000 population in 2019.[3]

[a] Rates were standardised to the Segi's world standard population (Segi, 1960).

3. There were 813 deaths (464 in males and 349 in females) due to pancreatic cancer in 2020, ranking it the fourth leading cause and constituting 5.5% of all cancer deaths. The crude mortality rates were 13.6 in males and 8.6 in females per 100,000 population in 2020, while the age-standardised mortality rates (ASMR)[a] were 5.7 in males and 3.1 in females per 100,000 standard population. The ASMR of pancreatic cancer showed an overall increasing trend over the past three decades.[3,4]

4. ASIR and ASMR of pancreatic cancer are in general higher in more developed countries.[5] Compared with the vast majority of developed western and neighbouring Asian countries such as Japan, Korea and Singapore, the ASIR and ASMR of Hong Kong remain low.[6]

Types of pancreatic cancer

5. The various types of exocrine pancreatic cancer (including adenocarcinoma or ductal carcinoma, squamous cell carcinoma, adenosquamous carcinoma and colloid carcinoma) make up more than 95% of all cancers of the pancreas, while less than 5% of all pancreatic cancer cases are pancreatic neuroendocrine tumors. The vast majority (over 90%) of all diagnoses are adenocarcinoma of the pancreas.[7]

Risk factors

6. Similar to many other cancers, pancreatic cancer has a multifactorial aetiology.[8] Although the causes of pancreatic cancer are still not fully understood, certain risk factors have been identified.[9]

(a) Tobacco smoking

Among the known modifiable risk factors, smoking is the best documented and has long been classified as causing cancer of the pancreas.[2,10] A summary review of meta-analytical studies concluded there being strong evidence showing a positive association between smoking and pancreatic cancer, 11-32% of all pancreatic cancer might be attributable to tobacco smoking.[8]

A meta-analysis of 82 published studies estimated the overall relative risks (RR) for current and former smokers were 1.74 (95% confidence intervals [95% CI] 1.61-1.87) and 1.2 (95% CI 1.11-1.29) respectively.[11] Another analysis also reported summary odds ratios (ORs) estimated from 12 studies as 2.20 (95% CI 1.71-2.83) and 1.17 (95% CI 1.02-1.34) for current and former smokers respectively.[12] The risk increases with the intensity and duration of smoking.[12,13]

(b) Overweight and obesity

The Working Group of the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence that the absence of excess body fatness would lower pancreatic cancer risk,[14] while the World Cancer Research Fund/American Institute for Cancer Research's Continuous Update Project Expert Panel also concluded greater body fatness as a convincing cause of pancreatic cancer.[15] Several large studies have consistently shown that obesity is a dose-dependent risk factor for pancreatic cancer.[16,17,18]

(c) Heavy alcohol consumption

Multiple meta-analyses and pooled analyses were conducted to investigate association between alcohol consumption and pancreatic cancer risk based on case-control studies and prospective cohort studies. Results consistently suggested that heavy drinking was associated with increased

pancreatic cancer risks.[19,20,21,22]

(d) Dietary factors

There is some evidence suggestive of positive association between unhealthy dietary habits and an increased risk of pancreatic cancer, yet inconclusive.[8,15]

(e) Diabetes mellitus

While diabetes can be a manifestation of early-stage pancreatic cancer, paradoxically, both type I and type II diabetes were shown to double the risk of pancreatic cancer. Meta-analyses demonstrated increased risks in patients with type I or type II diabetes compared to those without the condition (RR 2.00, 95% CI 1.37-3.01 for type I; OR 1.82, 95% CI 1.66-1.89 for type II).[23,24]

(f) Chronic pancreatitis and hereditary pancreatitis

Accumulating evidence suggests that longstanding pre-existing chronic pancreatitis as a strong risk factor for pancreatic cancer.[25,26,27,28] At the meantime, the lifetime risk of pancreatic cancer is about 40% in people with hereditary pancreatitis[29] and their risk is higher than patients with other forms of pancreatitis.[26,29,30]

(g) Family history and genetic susceptibility

A family history of pancreatic cancer was associated with around 80% increased risk.[31,32] The risk rises with increasing number of affected first-degree relatives to as high as 32-fold in individuals with three or more first-degree relatives with pancreatic cancer.[33] The lifetime risk of pancreatic cancer in familial pancreatic cancer kindreds increases with decreasing age of onset in the kindred (HR 1.55, 95% CI 1.19 - 2.03 per year).[34]

A number of familial cancer syndromes are found to be associated with an

increased risk of pancreatic cancer: familial atypical multiple mole melanoma syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, cystic fibrosis, hereditary breast and ovarian cancer, Fanconi anemia, familial adenomatous polyposis, Li-Fraumeni syndrome, and Lynch syndrome.[35,36] Meanwhile, up to 8–10% of patients with pancreatic cancer carry a pathogenic germline variant in a known cancer risk gene (including *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, and *TP53*).[2]

(h) Increasing age and gender

Increasing age positively correlates with risk of pancreatic cancer; most patients are diagnosed at ages 60 – 80, and pancreatic cancer is unusual in people young than 45 years.[2] Meanwhile, pancreatic cancer is more common in men than in women.[3,9]

Primary prevention

7. A number of the major risk factors associated with pancreatic cancer are potentially modifiable. The CEWG recommends the general population to adopt the following healthy lifestyle and behavioural changes to prevent pancreatic cancer:[37,38,39]

- Do not smoke, or quit smoking if one has already been smoking,
- Avoid alcohol consumption, and
- Maintain a healthy body weight and waist circumference by being physically active and adopting a healthy eating pattern that includes plenty of fruits, vegetables, and whole grains, and that limits or avoids red and processed meats, sugary beverages, and highly processed foods.

Awareness of pancreatic cancer symptoms and early detection[40,41]

8. Pancreatic cancer may not have any symptoms, or the symptoms might be non-specific and hard to notice, until the cancer has spread to other organs (i.e. metastasised). Some common symptoms include:

- jaundice that may be associated with dark urine, light-coloured stools and itchy skin,
- pain in the abdomen or back,
- weight loss or loss of appetite,
- pale and greasy stools,
- nausea and vomiting,
- fatigue,
- enlargement of the gallbladder, and
- blood clot in the leg.

Screening for the general population at average risk

9. A high-performing screening test with high sensitivity and specificity is essential to improve the accuracy of screening for a particular disease. However, such test for pancreatic cancer screening is currently not available. Elevated concentrations of carbohydrate antigen 19-9 (CA19-9) have been shown in blood samples taken before diagnosis of pancreatic cancer.[42] However, CA19-9 is insensitive for early invasive pancreatic cancer and does not identify high-grade pancreatic intraepithelial neoplasia (PanIN),[43] and elevated CA19-9 is not recommended for use as screening tool, because CA19-9 is not expressed in individuals with Lewis-negative genotype (i.e. false negative results), and there are also concerns over false positive elevation in the presence of other benign and malignant conditions, and the poor positive predictive value.[44,45]

10. Meanwhile, study findings concerning screening for pancreatic cancer are limited to high-risk populations.[46,47] A systematic review conducted by the United States Preventive Services Task Force (USPSTF) summarised that no studies had reported on the effect of screening on morbidity or mortality or on the effectiveness of treatment for screen-detected pancreatic adenocarcinoma, and there was also limited evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma,[46] the USPSTF then reaffirmed that the potential benefits of screening for pancreatic cancer in asymptomatic adults do not outweigh the potential harms.[48]

11. Given the relatively low incidence of pancreatic cancer in the general population, the absence of a suitable non-invasive test, and a lack of data on various aspects as demonstrated by USPSTF's systematic review, screening of pancreatic cancer in the average-risk population is generally not recommended.[44,46,47]

12. There is currently no recommendation or guideline from international and overseas organisations suggesting screening for pancreatic cancer in the general population. The IARC of the World Health Organization (WHO) stated in its report that there was no reliable screening test currently available for the early detection of pancreatic cancer in the general population.[2] The USPSTF and several organisations in the United States concordantly recommend against screening for pancreatic cancer in asymptomatic adults or average-risk individuals,[48,49,50,51] while the Cancer Australia also concludes that there are no reliable screening tests for pancreatic cancer for people who are at average risk.[52] In the United Kingdom, likewise the NHS does not have a national programme to screen the general population for pancreatic cancer.[53]

Surveillance and screening for the population at increased risk

13. Screening individuals in high-risk groups increases the rate of detection and reduces false-positive results.[44] Recent data from the International Cancer of the Pancreas Screening (CAPS) Consortium showed that 9 of 10 screen-detected pancreatic cancers were resectable, suggesting a benefit of screening in individuals at high risk.[54] Targeted screening was recommended for individuals whose lifetime risk of developing pancreatic cancer is higher than 5%, or five-fold increased RR. The CAPS Consortium agreed that the following high-risk groups were candidates for screening:[55]

- first-degree relatives (FDRs) of patients with pancreatic cancer from a familial pancreatic cancer kindred with at least two affected FDRs;
- patients with Peutz-Jeghers syndrome; and
- *p16*, *BRCA2* and hereditary non-polyposis colorectal cancer mutation carriers with one or more affected FDR.

14. The goal of screening for pancreatic cancer in asymptomatic high-risk patients is the early detection of small tumors (T1N0M0) or the identification of pre-cancerous lesions, including PanIN, specifically PanIN3, and intraductal papillary mucinous neoplasms (IPMN) with high-grade dysplasia.[56] In individuals with significantly increased risk of pancreatic cancer on the basis of family history and genetic risk factors, imaging of the pancreas such as endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) are used in the clinical setting for surveillance.[2]

15. EUS, MRI/MRCP and computed tomography (CT) identified pancreatic lesions in 42.6%, 33.3% and 11% of screened high-risk individuals (HRIs), respectively. However, incorrect diagnosis of lesions identified by EUS and /or MRI is a significant concern. After false positive findings of

screening tests, there is a risk of invasive investigation and over-treatment, particularly pancreatic surgery bears the risks of morbidity and mortality. Radiation exposure and the suboptimal detection rate precluded CT from being a routine pancreatic screening test. Abdominal ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) were also not recommended for screening, owing to their low diagnostic sensitivity and the risk of pancreatitis respectively.[55]

16. More importantly, there was a lack of evidence on whether screening HRIs would save lives, while available evidence supporting screening and surveillance was limited to observational studies. Screening may also lead to the discovery of incidental or indeterminate lesions, resulting in diagnostic confusion and uncertain management. [55]

17. An ongoing randomised controlled trial evaluates the outcomes of a risk-based screening strategy utilising a glycaemia-based model that was developed and validated to determine risk of pancreatic cancer in patients with new-onset diabetes. The results of another study that developed an early-stage cost-effectiveness model preliminarily suggested favorable cost-effectiveness of such risk-based screening strategy.[57,58,59]

18. Evidence about cost-effectiveness of pancreatic cancer screening in HRIs is emerging. A decision analysis, comparing one-time screening for pancreatic dysplasia with EUS to no screening in a hypothetical cohort of 100 members of familial pancreatic cancer kindreds, demonstrated that endoscopic screening was cost-effective, with an incremental cost-effectiveness ratio of $16,885/life-year saved. Endoscopic screening of carefully selected members appeared to increase patient life expectancy in a cost-effective manner.[60]

19. A systematic review of 16 studies found that pancreatic cancer

screening resulted in a high curative resection rate (60% vs 25%), longer median survival time (14.5 months vs 4 months), and higher 3-year survival rate (20% vs 15.0%, P > 0.05). Familial HRIs had a higher diagnostic rate of pancreatic tumors than controls through screening (34% vs 7.2%).[61]

20. Despite emerging evidence suggesting there is a window of opportunity to detect pre-cancer lesions and early pancreatic cancer in HRIs, the exact benefit of pancreatic cancer screening at this time remains unclear.[47] No single modality for screening has been well supported with high-level evidence. More trials and prospective research on cost-effectiveness, survival and mortality benefit, psychological burden, treatment consequences will hopefully shed light on the issue. Concerning people at increased risk of pancreatic cancer, recommendations by Western countries and overseas organisations vary, while the WHO, USPSTF, national health authorities of Canada and Singapore have not published any recommendations on screening of increased-risk populations for pancreatic cancer.

Conclusion

21. To date, no evidence has been found to support that screening for pancreatic cancer or treatment of screen-detected pancreatic cancer improves disease-specific morbidity or mortality, or all-cause mortality. While there being insufficient evidence to inform sensitivity, specificity, predictive value or false-positives of screening tests, WHO also concluded no reliable screening test was available for the early detection of pancreatic cancer in the general population. There is also a lack of evidence that demonstrates the effectiveness of screening by comparing the screened and unscreened populations. On the other hand, there exists a possibility that screening in the general population might lead to over-diagnosis and over-treatment.[48] Hence, advocating primary prevention and achieving early detection of pancreatic cancer remain

significantly important. Awareness of symptoms and signs, timely investigations and referral in primary care setting play a key role in early detection to improve the prognosis. There is also no local study on the effectiveness of pancreatic cancer screening for individuals at average or increased risk. Additional research is needed to better understand the risk factors or causes of pancreatic cancer in local Chinese population.

22. In summary, screening for pancreatic cancer (including screening by serum biomarker CA19-9) is not recommended in asymptomatic persons at average risk. For individuals at increased risk (e.g. with strong family history, specific genetic syndromes or carrying certain genetic susceptibility traits), while there is emerging evidence reported from some centres, more definitive research is necessary. As such, high-risk individuals are recommended to seek advice from doctors for assessment of their pancreatic cancer risk and the need for and approach of surveillance if necessary. The CEWG will keep in view the latest development and emerging evidence on this issue.

Recommendations by CEWG

23. Taking local epidemiology, emerging scientific evidence, local and overseas screening practices into consideration, the CEWG has formulated recommendations for pancreatic cancer screening which were endorsed by the Cancer Coordinating Committee at its 17th meeting on 7 June 2022. The recommendations for the local population are given below.

For persons at average risk	
1.	Screening for pancreatic cancer (including screening by serum biomarker CA19-9) is not recommended in asymptomatic persons at average risk.

For persons at increased risk	
2.	There is currently insufficient evidence to recommend screening of pancreatic cancer for persons at increased risk by any standardised protocol. Persons with strong family history of pancreatic cancer, specific genetic syndromes, or carrying genetic susceptibility traits that put them at significantly increased risk of pancreatic cancer may consider seeking advice from doctors for individual assessment.

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