

# INHERITED PANCREATIC CANCER

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## Abstract

Up to 10% of pancreatic cancer cases have a heritable component. Some of these are clearly defined tumour predisposition syndromes known as hereditary pancreatic cancers, but most are familial cases, defined by family history and where the underlying genetic causes remain unknown. Genetic counselling is important in suspected inherited pancreatic cancer cases, to enable risk assessment and relevant genetic testing. Screening trials are available for at-risk individuals (i.e. >5% lifetime risk), although more long-term data is required to determine the risks, benefits and optimal approaches to pancreatic cancer surveillance.

Pancreatic cancer is a lethal disease with an overall five-year survival rate of 6%. It is the fifth most common cause of cancer death in Australia.<sup>1</sup> Surgical resection offers the only potential for cure, but is limited because the majority of patients present with locally advanced or metastatic disease. Although early detection of pancreatic cancer is recognised as the best strategy to improve patient outcomes, population screening is not recommended because of low incidence and the lack of a robust screening test. Screening tests need to demonstrate validity, reliability yield, acceptable cost and the availability of accepted treatment to align with the World Health Organisation principles of early disease detection.<sup>2</sup>

Pancreatic cancer is aetiologically complex, arising from a combination of environmental and genetic factors. Established environmental risk factors include age, cigarette smoking, diabetes mellitus and obesity.<sup>3-5</sup> Up to 10% of pancreatic cancer has a heritable component, presenting in three different clinical settings: 1. Hereditary tumour predisposition syndromes which account for 15-20% of the burden of inherited disease; 2. Hereditary pancreatitis; 3. Familial pancreatic cancer, defined as a family with at least two first-degree relatives with pancreatic cancer who do not fulfill the diagnostic criteria for a hereditary tumour syndrome.

## Hereditary tumour predisposition syndromes

Germline mutations in the BRCA1 and BRCA2 genes cause approximately 45% of hereditary breast-ovarian cancer. In addition to an increased risk of breast and ovarian cancer, pathogenic germline BRCA2 mutations place carriers at modestly increased risk of pancreatic cancer.<sup>6</sup> In familial pancreatic cancer, the prevalence of pathogenic BRCA2 mutations increases with the number of affected relatives - 6-12% in families with two or more with pancreatic cancer and 16% in families with three or more with pancreatic cancer,<sup>7,8</sup> and within ethnicities known to carry founder mutations. BRCA2 prevalence

in unselected, likely sporadic pancreatic cancer cohorts range from 0.7 - 3.6%.<sup>9,10</sup> The relative risk of pancreatic cancer in BRCA2 mutation carriers is 3.5-6 fold (table 1).<sup>11</sup> The lack of reported pancreatic cancer or breast-ovarian family history in BRCA2 pancreatic cancer patients is likely due to reduced penetrance for pancreatic cancer rather than a pancreatic cancer specific genotype-phenotype correlation for BRCA2 mutations.

In contrast, the role of BRCA1 mutations and predisposition to pancreatic cancer is less well defined. Initial studies in BRCA1 mutation positive families with young-onset breast or ovarian cancer suggested a 2.26 fold (95% CI = 1.26-4.06) increased risk of pancreatic cancer, however BRCA1 mutations are uncommon in families reporting a history of pancreatic cancer alone.<sup>12</sup>

Familial melanoma is an autosomal dominant syndrome characterised by predisposition to melanoma and pancreatic cancer. Germline mutations in the CDKN2A gene have been reported in 25% of all melanoma prone families.<sup>13</sup> CDKN2A carriers have a 13 to 22-fold risk of developing pancreatic cancer (table 1), which may be a genotype-phenotype effect. The CDKN2A-pancreatic cancer relationship has not been demonstrated in Australia, likely due to a broad spectrum of mutations.<sup>13</sup> Reports of CDKN2A prevalence in familial pancreatic cancer vary (3.3% - 21.4%) and are not always associated with personal/family history of melanoma.<sup>14,15</sup>

Peutz-Jegher syndrome is an autosomal dominant disorder caused by germline STK11 mutations. Clinical presentation includes gastrointestinal tract polyposis and mucocutaneous pigmentation, often around the lips.<sup>16</sup> The pancreatic cancer risk in Peutz-Jegher syndrome individuals is 132 fold (95% CI = 44-261) (table 1).<sup>17</sup> Mutations in STK11 account for less than 1% of inherited pancreatic cancer.

Lynch Syndrome is caused by germline mutations in the DNA mismatch repair (MMR) genes MSH2, MLH1, MSH6

and PMS2. Patients have an increased risk of early-onset colorectal and endometrial cancer, as well as lower risk of other tumour types including pancreatic cancer. A prospective cohort study of 446 MMR mutation carriers identified two pancreatic cancer cases, corresponding to a SIR of 10.68 (95% CI 2.7 – 47.7) and a 10-year pancreatic cancer risk of 0.95% (table 1).<sup>18</sup> The prevalence of germline MMR gene mutations in pancreatic cancer patients with a personal or family history of colorectal cancer is as high as 10% but may represent selection bias.<sup>9,19</sup>

Familial adenomatous polyposis is primarily caused by mutations in the adenomatous polyposis coli (APC) gene. Patients are at risk for thyroid tumours, gastric, duodenal and ampullary adenocarcinoma. The relative risk for pancreatic cancer has been reported as 4.46 (95% CI 1.2 – 11.4),<sup>20</sup> but this may be due to coding errors as recent data suggests the prevalence of pancreatic cancer is low.<sup>21</sup>

Li-Fraumeni syndrome is a rare highly penetrant autosomal dominant cancer predisposition syndrome, frequently caused by mutations in the TP53 gene. It is characterised by early onset tumours including sarcoma, adrenocortical carcinoma, breast cancer, leukaemia and brain tumours. The risk of pancreatic cancer is increased but unquantified.<sup>22</sup>

## Hereditary pancreatitis

Hereditary pancreatitis is a rare autosomal dominant form of pancreatitis. Mutations in the cationic trypsinogen gene (PRSS1) are found in up to 80% of cases. Patients with hereditary pancreatitis have a significantly increased risk

of developing pancreatic cancer, estimated to be 58-fold (95% CI 23 – 105) (table 1).<sup>23</sup> Cigarette smoking is a major co-risk factor for pancreatic cancer development, increasing the risk by two-fold and lowering age at diagnosis by 20 years.<sup>24</sup>

## Familial pancreatic cancer

Familial pancreatic cancer is defined as a kindred, with at least two first-degree relatives with pancreatic cancer not otherwise fulfilling the diagnostic criteria for a hereditary tumour syndrome.<sup>25</sup> The relative risk of developing pancreatic cancer increases with each additional affected first-degree relative: one first degree relative 4.6 (CI 0.5 – 6.4); two first degree relative 6.4 (CI 1.8 – 16.4); three first degree relative 32.0 (CI 10.2 – 74.7) (table 1).<sup>26</sup> The risk is two to three times higher in smokers, particularly males under the age of 50.<sup>27</sup> The presence of pancreatic cancer cases <50 years confers an additional risk.<sup>28</sup> Furthermore, familial pancreatic cancer kindreds have other cancers including breast, ovarian, endometrial and melanoma.<sup>29,30</sup>

Many familial pancreatic cancer kindreds demonstrate probable autosomal dominant inheritance, yet less than 25% have a mutation identified. PALB2 and ATM are moderate risk familial pancreatic cancer susceptibility genes accounting for 4.2% and 3.6% respectively.<sup>31,32</sup> Whole genome sequencing technology holds the potential to identify additional lower-penetrance genes that contribute to the remaining familial pancreatic cancer cases.

**Table 1:** Genetic risk factors for pancreatic cancer.

Genetic risk group	Syndrome	Relative risk (95% CI)	Estimated lifetime pancreatic cancer risk (70 – 80 years)
STK11	Peutz Jeghers syndrome	132 (44-261)	11 – 32%
PRSS1	Hereditary pancreatitis	58 (23-105)	20 – 40% (higher range in smokers)
CDKN2A	Familial melanoma	38 (10-97)	17%
BRCA2	HBOC/familial pancreatic cancer	3.51 (1.87-6.58)	3 – 8 %
MSH2, MLH1, MSH6, PMS2	Lynch syndrome	8.6 (4.7-15.7)	3.6% <sup>33</sup>
BRCA1	HBOC	2.26 (1.26-4.06)	2.1%
APC	Familial adenomatous polyposis	4.46 (1.2 – 11.4)	Elevated but not defined
TP53	Li-Fraumeni Syndrome	Elevated but not defined	Elevated but not defined
PALB2	Familial pancreatic cancer	Elevated but not defined	Elevated but not defined
ATM	Familial pancreatic cancer (monallelic)	Elevated but not defined	Elevated but not defined
Clinical risk group	Syndrome	Relative risk (95% CI)	Estimated lifetime pancreatic cancer risk (70 – 80 years)
General Population	NA	1	0.96%
1 FDR pancreatic cancer	Familial pancreatic cancer	4.6 (0.5 - 6.4)	4%
2 FDR pancreatic cancer	Familial pancreatic cancer	6.4 (1.8 - 16.4)	8-12% <sup>26</sup>
≥3 FDR pancreatic cancer	Familial pancreatic cancer	32 (10.2 - 74.7)	16-30% <sup>26</sup>

## Genetic counselling and testing for inherited pancreatic cancer

Obtaining a complete three-generation pedigree of malignancy, including pathological confirmation where possible, is important as it can suggest an underlying genetic predisposition or common environmental factor. It also facilitates risk assessment and discussions of genetic testing and risk-reducing strategies in family members.<sup>29</sup> PancPro is a Bayesian model developed from National Familial Pancreatic Tumour Registry pedigree data. It calculates the risk that a person carries a high-penetrance pancreatic cancer gene and the age-related risk of developing cancer.<sup>34</sup> PancPro demonstrates an observed to predicted pancreatic cancer ratio of 0.83 (95% CI, 0.52 to 1.20).<sup>35</sup>

Testing for known pancreatic cancer susceptibility genes is carried out by local familial cancer clinics according to genetic testing and clinical management guidelines (e.g. eviQ,<sup>36</sup> National Comprehensive Cancer Network).<sup>37</sup> When clinically indicated (table 2), genetic testing is best offered to individuals with a confirmed diagnosis of pancreatic cancer. Because of the high mortality rate, storing DNA from pancreatic cancer cases with any family history is important. Genetic testing in unaffected individuals is informative only when the mutation in an affected relative is known.

Affected and unaffected family members may be eligible to participate in familial pancreatic cancer research projects. Familial pancreatic cancer registries have been established to further understand the aetiology of familial pancreatic cancer, identify candidate pancreatic cancer susceptibility genes and provide high-risk populations for early detection studies.<sup>38</sup>

of a suitable biomarker or imaging modality and lack of proven early interventions. However, it has been proposed that a high-risk population could benefit from early detection strategies. Global screening studies are underway to determine appropriate screening modalities and parameters.

The primary imaging modalities utilised in these studies are endoscopic ultrasound, magnetic resonance imaging with/without magnetic resonance cholangiopancreatography and computerised tomography. Findings from the pancreatic cancer screening studies to date are difficult to consolidate because of differing populations, imaging modalities and endpoints used. Many studies have successfully demonstrated that precursor lesions or invasive cancers can be detected in a significant proportion of at-risk individuals, but none to date have successfully demonstrated better outcomes for patients.

There is also no consensus as to the timing, inclusion criteria and initiation/cessation ages for pancreatic cancer surveillance programs. Guidelines suggest those with a minimum 5-10 fold-increased risk should be considered. An international consortium agreed that the following groups: familial pancreatic cancer with at least two first degree relatives affected; patients with Peutz-Jeghers syndrome; patients carrying BRCA1/2, CDKN2A, or MMR gene mutations with at least one FDR affected should be screened if eligible for surgical treatment.<sup>41</sup>

## Conclusion

Inherited cases of pancreatic cancer are rare, which hinders understanding of the genetic etiology and then

**Table 2:** Clinical indications for cancer predisposition assessment.<sup>39,40</sup>

Clinical criteria	Syndrome to consider	Gene(s) to consider
PC diagnosed any age, if any of the following criteria are met: <ul style="list-style-type: none"> <li>• ≥ 2 cases pancreatic cancer in close relatives</li> <li>• ≥ 2 cases breast, ovarian or prostate cancer in close relatives</li> <li>• Ashkenazi Jewish ancestry</li> </ul>	Familial pancreatic cancer, hereditary breast and ovarian cancer	BRCA1, BRCA2, PALB2, ATM BRCA1, BRCA2, PALB2 BRCA1, BRCA2
Pancreatic cancer and ≥1 PJ polyp	Peutz-Jegher syndrome	STK11
Pancreatic cancer and ≥ 2 additional cases of any Lynch syndrome associated cancer in the same person or close relative	Lynch syndrome	MSH2, MLH1, PMS2, MSH6
≥ 3 cases of pancreatic cancer and/or melanoma in close relatives or pancreatic cancer and melanoma in the same person	Familial melanoma	CDKN2A
Personal history of ≥2 attacks of acute pancreatitis of unknown aetiology, a family history of pancreatitis, or early age of onset of chronic pancreatitis	Hereditary pancreatitis	PRSS1

## Early detection in inherited pancreatic cancer

Screening the general population for pancreatic cancer is not feasible because of its low incidence, absence

introduction of clinical management guidelines for this complex disease. Family cancer clinics are important for assessing family history and identification of possible hereditary tumour predisposition syndromes. Familial pancreatic cancer research cohorts are vital for identification

of additional pancreatic cancer susceptibility genes and defining effective screening protocols translatable into clinical practice.

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Garvan Institute of Medical Research

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## Useful links

<https://www.eviq.org.au/>

<http://www.genetics.edu.au/>

<http://www.pancreaticcancer.net.au/afpacc>

<https://www.pancare.org.au/patient-support-services/clinical-trials/>

<http://bcf.dfc.harvard.edu/bayesmendel/pancpro.php>

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