Diagnosis and Management of Hereditary Pancreatic Cancer

Jeremy L. Humphris and Andrew V. Biankin

Abstract

Hereditary pancreatic cancer can be diagnosed through family history and/or a personal history of pancreatitis or clinical features suggesting one of the known pancreatic cancer predisposition syndromes. This chapter describes the currently known hereditary pancreatic cancer predisposition syndromes, including Peutz–Jeghers syndrome, familial atypical multiple mole melanoma, hereditary breast and ovarian cancer, Li–Fraumeni syndrome, hereditary non-polyposis colon cancer and familial adenomatous polyposis. Strategies for genetic testing for hereditary pancreatic cancer and the appropriate options for surveillance and cancer risk reduction are discussed. Finally, ongoing research and future directions in the diagnosis and management of hereditary pancreatic cancer will be considered.

Keywords

Pancreatic cancer · Inherited · Screening

J.L. Humphris (✉) · A.V. Biankin
The Kinghorn Cancer Centre, Cancer Research Program, 370 Victoria St., Darlinghurst, NSW 2010, Australia
e-mail: j.humphris@garvan.org.au

A.V. Biankin
Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Garscube Estate, Switchback Road, Glasgow Bearsden G61 1BD, United Kingdom

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Contents

1 Introduction

Up to 10 % of pancreatic cancers (PCs) have a hereditary component, but the underlying genetic cause has only been identified in a minority. Genetic counselling and testing are important in suspected inherited PC cases, to disseminate information regarding genetic testing and disease risk. Screening trials are available for high-risk individuals (i.e. >5–10 % lifetime risk), although more long-term data are required to determine the risks, benefits and optimal approaches to PC surveillance. Novel approaches are needed to define the missing heritability in PCs and to incorporate this into clinical practice.

2 Epidemiology

2.1 Demographics

2.1.1 Age

PC is largely a disease of advancing age with mean age at diagnosis of 71 years and is rarely diagnosed before 40 years of age (Ryan et al. 2014). Only 5–10 % of cases are diagnosed before 50 years, but this cohort may be enriched with individuals with an inherited genetic predisposition (Raimondi et al. 2009). The incidence increases exponentially in both sexes after age 40 from 2.3 cases per 100,000 for 40–44 year olds to 57 cases per 100,000 in those 70–74 years (AIHW 2014). Reports of younger age at diagnosis in familial PC cases are inconclusive (Barton et al. 2011), but some studies suggest earlier onset by 5 years and a higher proportion (≈16 %) of young-onset disease (Petersen et al. 2006). In familial pancreatic cancer (FPC) families with identified mutations, the median age of diagnosis was

60–62.8 years for BRCA2 and 66.7 years for PALB2 (Hahn et al. 2003a; Jones et al. 2009a). Anticipation has been reported in 32–85 % of FPC families with successive generations developing PC 10–20 years earlier (McFaul et al. 2006).

2.1.2 Ethnicity

The worldwide incidence of PC shows significant variability with the highest rates seen in the more developed regions of North America, Western and Central/Eastern Europe and Australia/New Zealand. The lowest rates are seen on less developed regions in Africa and South Asia. Subpopulation stratification shows variability with higher risk in people of African American and Ashkenazi Jewish heritage compare to those of Caucasian, Hispanic and Asian descent (Eldridge et al. 2011; Raimondi et al. 2009). This is likely the culmination of both genetic and non-genetic risk factors (Fig. 1).

2.1.3 Gender

In comparison with ethnicity, there are only small gender differences in the risk of developing PC. The lifetime risk of developing PC before age 75 for males is 0.9 and 0.6 % for females (AIHW 2014) which has been attributed to higher cigarette smoking rates in men (Raimondi et al. 2009).

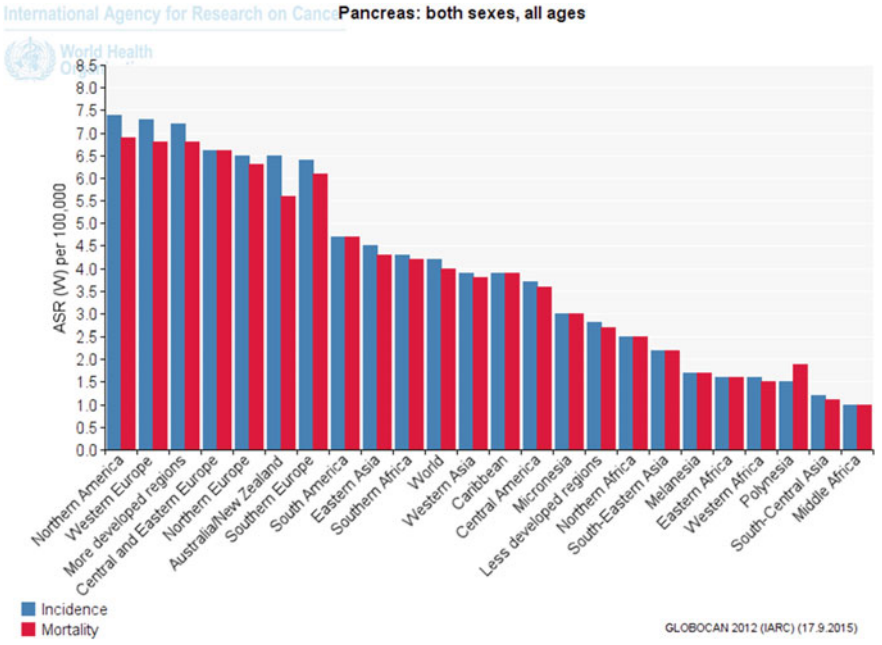

Fig. 1 Age-specific pancreatic cancer incidence and mortality in worldwide populations. The incidence to mortality ratio approaches 1 in all populations. Reproduced with permission (Ferlay J)

2.2 Non-genetic Risk Factors

Epidemiologic studies have identified several environmental and lifestyle risk factors for PC which frequently coexist and are likely to interact (Raimondi et al. 2009). These are summarised in Table 1.

2.2.1 Genetic Risk Factors

The conventional paradigm based on case–control and cohort studies is that 5–10 % of patients diagnosed with PC have a hereditary component based on family history of the disease (Ghadirian et al. 1991). Studies requiring histological confirmation have shown lower rates (1.9–2.7 %) of familial aggregation (Bartsch et al. 2004; Hemminki and Li 2003). The 5–10 % figure may be correct but as large sequence cohorts are beginning to show germline mutations in cancer predisposition genes frequently occur in the absence of family history, showing that while family history is predictive of carrier status, it is imperfect (Grant et al. 2014). Inherited predisposition to PC manifests as 3 distinct clinical scenarios (Bartsch et al. 2012): (1) hereditary tumour predisposition syndromes including hereditary breast–ovarian cancer (HBOC), Peutz–Jeghers Syndrome (PJS), familial atypical multiple mole melanoma (FAMMM), Li–Fraumeni, hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) which account for 15–20 % of the burden of inherited disease (Hruban et al. 2010) (2) hereditary pancreatitis due to mutations in *PRSS1* and 3. Familial PC (FPC) which is defined as a family with at least 2 first-degree relatives with PC, which do not fulfil the diagnostic criteria for an inherited tumour syndrome (Brand et al. 2007). The majority (80 %) of hereditary PC is attributed to FPC with a pattern consistent with autosomal dominant inheritance in 50–80 % of families (Lynch et al. 1990; McFaul et al. 2006) (Table 2).

Table 1 Non-genetic risk factors for PC

Risk factor	Estimated risk (95 % CI)
Active cigarette smoking (Bosetti et al. 2012)	OR 2.20 (1.71–2.83)
Ceased cigarette smoking (Bosetti et al. 2012)	
>1 but <10 years	OR 1.64 (1.36–1.97)
>10 years	OR 1.12 (0.86–1.44)
Diabetes mellitus (Li et al. 2011)	
<2 years duration	RR 7.94 (4.70–12.55)
>10 years duration	OR 1.51 (1.16–1.96)
BMI (>35 vs. <25) (Arslan et al. 2010)	OR 1.55 (1.16–2.07)
Heavy alcohol (≥6 drinks/day) (Genkinger et al. 2009; Anderson et al. 2012)	OR 1.46 (1.16–1.83)
Chronic pancreatitis (>2 years) (Duell et al. 2012)	OR 2.71 (1.96–3.74)
Allergy (hay fever and animal allergy) (Olson and Kurtz 2013; Cotterchio et al. 2014)	OR 0.73 (0.64–0.74)

Table 2 Genetic risk factors for PC–hereditary cancer syndrome and moderate- to high-penetrance genes

Clinical risk group	Syndrome	Relative risk (95 % CI)	Estimated lifetime PC risk (70–80 years)	Other associated tumours	Prevalence in FPC kindreds
General population	NA	1	0.96		
1 FDR PC	NA	4.6 (0.5–16.4)			
2 FDR PC	FPC	6.4 (1.8–16.4)			
≥3 FDR PC	FPC	32 (10.2–74.7)			
Genetic risk group					
BRCA2 (Grant et al. 2014; Couch et al. 2007a; Zhen et al. 2014)	HBOC/FPC	3.51	3.36 %	Breast, ovarian	0.7–6 %
PALB2 (Schneider et al. 2011a; Jones et al. 2009; Zhen et al. 2014)	FPC	Elevated but not defined	Elevated but not defined	Breast	0–3 %
BRCA1	HBOC	2.26	2.16 %	Breast, ovarian	0.3–1.2 %
MSH2, *MLH1*, *MSH6*, *PMS2*, *5′ EPCAM deletion* (Grant et al. 2014)	HNPCC	8.6	3.68 % (1.45–5.88 %)	Colon, endometrial	Each <1 %
PRSS1	Hereditary pancreatitis	58	30–40 % in smokers, 20 % in non-smokers	Pancreas only	NA
STK11 (Grant et al. 2014; Schneider et al. 2011b)	Peutz–Jeghers syndrome	132	11–32 %	Gastrointestinal, breast, gynaecologic, pancreas	0 %
CDKN2A (Zhen et al. 2014; Grant et al. 2014)	FAMMM	38	17 %	Melanoma	0–2.5 %[a]
ATM (monoallelic) (Roberts et al. 2012b)	Ataxia telangiectasia (bi-allelic)	Elevated but not defined	Elevated but not defined	Breast, colon	2.4 %
TP53	Li–Fraumeni syndrome	Elevated but not defined	Elevated but not defined	Sarcoma, breast, brain, adrenocortical	NA

[a]Higher prevalence in some populations, e.g. Italian (up to 30 % of FPC) (Ghiorzo et al. 2012)

3 Main Section

3.1 Hereditary Tumour Predisposition Syndromes

3.1.1 Hereditary Breast–Ovarian Cancer

Inherited pathogenic germline *BRCA2* mutations place carriers at increased risk of cancers of the pancreas, prostate, gallbladder, bile duct, stomach and melanoma in addition to breast and ovarian cancer (The Breast Cancer Linkage Consortium 1999; Moran et al. 2012). The prevalence of germline *BRCA2* mutations in patients with PC depends on the ethnic ancestry of the population studied and is higher in groups with founder mutations such as those of Ashkenazi Jewish descent. In an early report, Goggins et al. (1996) found *BRCA2* mutations in 7 % of patients with apparent sporadic PC (3 of 41) of which one was the Ashkenazi founder mutation. Studies have shown *BRCA2* mutations in 5–10 % of Ashkenazi Jews with PC (Ozcelik et al. 1997; Ferrone et al. 2009). In familial PC, the mutation prevalence increases with rising number of affected relatives: 6–12 % in families with two or more with PC and 16 % from families in which 3 or more have PC (Murphy et al. 2002; Couch et al. 2007b). The relative risk of developing PC in *BRCA2* mutation carriers is approximately 3.5–6 (The Breast Cancer Linkage Consortium 1999; Risch et al. 2006). A substantial proportion of mutation-positive PC patients report neither a history of PC nor breast–ovarian cancer (Goggins et al. 1996; Murphy et al. 2002). This is likely due to reduced penetrance for PC rather than there being PC-specific genotype–phenotype correlation for BRCA2 mutations as has been seen in some breast–ovarian cancers (Thompson and Easton 2001).

In contrast, the role of *BRCA1* mutations in predisposition to PC is less well established. Overall studies in *BRCA*1 kindreds with young-onset breast or ovarian cancer suggested a 2.26-fold (95 % CI = 1.26–4.06) increased risk of pancreatic cancer (Brose et al. 2002; Iqbal et al. 2012). *BRCA1* mutations are uncommon without a history of breast cancer (Skudra et al. 2007) or Ashkenazi heritage (Shi et al. 2009; Lucas et al. 2013). Other studies have found no increase in the prevalence of *BRCA1* mutations in patients with pancreatic cancer (Ferrone et al. 2009; Axilbund et al. 2009).

3.1.2 Familial Atypical Multiple Mole Melanoma

Familial atypical multiple mole melanoma (FAMMM) is a syndrome characterised by predisposition to melanoma and PC. Clinical diagnostic features include family history of melanoma in at least one close relative, multiple melanocytic naevi (often >50) some of which show visible atypical and characteristic microscopic features. FAMMM is caused by germline mutations in *CDKN2A* (p16), which encodes the tumour suppressors ARF and INK4A. Individuals with FAMMM have a 38-fold increased risk of developing PC compared to the general population, contributing to a lifetime risk of 17 % by age 75 (Rutter et al. 2004; Vasen et al. 2000).

3.1.3 Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an autosomal dominant disorder characterised by gastrointestinal tract hamartomatous polyps and mucocutaneous pigmentation (Beggs et al. 2010). In 80–94 % of individuals who meet the clinical criteria, pathogenic mutations (two-thirds single nucleotide variants and one-third large deletions) in *STK11* are identified (McGarrity et al. 2013). These individuals have a 132-fold increased risk of pancreatic cancer compared with the general population, and the lifetime risk of pancreatic cancer in these individuals has been estimated to be 11–32 % (Hearle et al. 2006; Korsse et al. 2013).

3.1.4 Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) is the result of germline mutations in the DNA mismatch repair genes *MSH2*, *MLH1*, *MSH6*, and *PMS2*. Recently, heritable somatic methylation of MSH2 has been described due to germline deletion of the last two exons of EPCAM which produces silencing of the adjacent gene, MSH2 (Ligtenberg et al. 2009; Kuiper et al. 2011). Patients are at increased lifetime risk for a wide range of tumour types, but the predominant malignancies are colonic and endometrial cancer. The other associated tumour types are lower risk with <5 % lifetime risk and include PC, gastric, small bowel, ureteric and skin tumours. A recent study of 147 families containing a mutation in a mismatch gene reported a 8.6-fold (95 % CI, 4.7–15.7) increased risk of pancreatic cancer compared with the general population (Kastrinos et al. 2009). This corresponds to a 3.68 % (95 % CI, 1.45–5.88 %) lifetime (by age 70) risk of pancreatic cancer (Kastrinos et al. 2009).

3.1.5 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterised by the early development of hundreds to thousands of colonic adenomatous polyps. The natural history is that untreated nearly all affected patients will develop colorectal carcinoma by age 40 (Vasen et al. 2009). In more than 70 % of patients who meet the clinical criteria, a germline mutation in the *APC* can be identified (Vasen et al. 2009; Groden et al. 1991). Patients with FAP are at increased risk for other neoplasms, including thyroid tumours, gastric, duodenal and ampullary adenocarcinoma. The relative risk for the development of PC is 4.46, and some evidence suggests precursor lesions progress through the intraductal papillary mucinous neoplasm (IPMN) pathway (Chetty et al. 2005).

3.1.6 Li–Fraumeni Syndrome

Li–Fraumeni syndrome (LFS) is an autosomal dominant highly penetrant cancer predisposition syndrome characterised by a variety of early onset tumours. The syndrome, described in 1969 by Li and Fraumeni based on a retrospective analysis of families with childhood rhabdomyosarcoma(Li and Fraumeni 1969), was characterised by the presence of five cancers: sarcoma, adrenocortical carcinoma, breast cancer, leukemia, and brain tumours (Li et al. 1988; Garber et al. 1991). Several

different clinical classification systems exist, but these tumour types form the core clinical features. Li–Fraumeni Syndrome is caused by germline mutations in the *TP53* gene and is inherited in an autosomal dominant pattern. The risk of PC is increased but has not been quantified (Birch et al. 2001; Ruijs et al. 2010).

3.1.7 Hereditary Pancreatitis

Hereditary pancreatitis is a rare autosomal dominant form of inherited pancreatitis. This typically manifests as recurrent acute pancreatitis by age 10, chronic pancreatitis by age 20 and increased risk of PC after age 40 (Howes et al. 2004). In families, meeting the clinical criteria gain-of-function mutations (missense and rarely duplications or triplications) in the cationic trypsinogen gene (*PRSS1*) are found in around 80 % (Whitcomb et al. 1996). Patients with hereditary pancreatitis have a 58-fold (95 % CI 23–105) increased risk of developing pancreatic cancer and a lifetime risk (by age 70) of 30–40 % (Lowenfels et al. 1997). Cigarette smoking increases the risk by twofold and brings the age at diagnosis forward 20 years (Lowenfels et al. 2001). The lifetime risk in non-smokers is estimated to be <20 % (Rebours et al. 2009).

3.1.8 Familial Pancreatic Cancer

In FPC kindreds, the relative risk of developing PC escalates with increasing number of affected first-degree relatives (FDR) from twofold with one affected FDR to sixfold and 14–32-fold (up to 57-fold) with 2 and 3 affected FDRs, respectively (Klein et al. 2004; Tersmette et al. 2001). FPC is likely to be a heterogeneous syndrome with phenotype determined by the underlying genetic predisposition and modified by environmental risk factors. Familial clustering can also occur through phenocopying as a result of shared or common environmental exposures within families, as suggested by a non-significant in FPC kindred's spouses (Klein 2013a, b). FPC kindreds also appear to be at increased risk of developing malignancy of the breast, ovary, colorectum and melanoma, particularly if the proband developed young-onset (<50 years) PC (Wang et al. 2009b; Brune et al. 2010). This finding is consistent with previous reports where in 40 % of FPC families PC was the sole tumour entity and in the remaining 60 % other tumour types, namely breast, colon and lung, were seen (Schneider et al. 2011a). Defining the precise organotypic distribution of tumours which cluster with PC is important because it (a) supports an underlying genetic predisposition or common environmental factor potentially even in the absence of multiple PC cases in the family, (b) allows a more precise definition and clinical recognition of the syndrome and (c) facilitates broader and more precise risk assessment and employment of risk reduction strategies in at-risk family members (Wang et al. 2009a). These results highlight the importance of complete family history of all cancer types in clinical assessment of FPC pedigrees (Cote et al. 2007). The underlying genetic basis of PC predisposition has been identified in less than 25 % of such families (Roberts et al. 2012a), despite 50–80 % of families demonstrating an autosomal dominant inheritance pattern (Lynch et al. 1990; McFaul et al. 2006). Overall, 0.6 % of the general population is estimated to

carry a mutation in a moderate- to high-risk pancreatic cancer predisposition gene with an attendant lifetime risk of developing pancreatic cancer (by the age of 85) of 32 % (Klein et al. 2002).

Studies to date have delineated the underlying genetic basis in at best 25 % of these families with mutations in *BRCA2*, *PALB2* (Partner And Localizer of BRCA2) and *ATM* (Ataxia telangiectasia) mutated accounting for 3.7–19 % (Hahn et al. 2003; Couch et al. 2007a), 4.2 % (Jones et al. 2009) and 3.6 % (Roberts et al. 2012a), respectively (Lal et al. 2000). The prevalence of *BRCA2* mutations in FPC as discussed above depends in part on enrichment with family history of other related cancers and ancestry particularly Ashkenazi Jewish heritage. *PALB2* and *ATM* are recently implicated as PC predisposition genes and demonstrate the capability of next-generation sequencing of PC cohorts to identify new risk genes. *PALB2* binds to *BRCA2* and stabilises it in the nucleus, truncating mutations are found in 0.6–3 % of familial PC probands particularly those families with an additional case(s) of breast cancer (Jones et al. 2009; Tischkowitz et al. 2009). Truncating *ATM* mutations segregated with disease 2 FPC kindreds and were subsequently identified in 2.5 % of FPC probands (Roberts et al. 2012b). The risk of developing PC due to pathogenic germline *PALB2* or *ATM* mutations and their contribution to sporadic disease has not been defined.

Palladin (*PALLD*) a cytoskeletal protein when mutated is overexpressed in non-neoplastic stromal cells where it facilitates tumour invasion and metastasis (Brentnall et al. 2012). A missense mutation (p.P239S) in the palladin (*PALLD*) gene was identified in a large FPC kindred which segregated with disease (Pogue-Geile et al. 2006), but subsequent studies have failed to replicate this finding in other FPC probands (Zogopoulos et al. 2007).

3.1.9 Low-Penetrance Susceptibility Variants

Seven PC genome-wide association studies have identified several relatively common but low-penetrant loci associated with PC risk, including the ABO locus. For a complete list of loci, see www.ebi.ac.uk/gwas.

4 Precursor Lesions and Progression to PC

Pancreatic cancer develops from solid and cystic precursor neoplasms through the serial acquisition of mutations, which provide a selective advantage to the cells. The evolution of PC progresses through several stages from non-invasive precursor lesions such as pancreatic intraepithelial neoplasia (PanIN) or cystic neoplasms in particular mucin-producing intraductal papillary mucinous neoplasm (IPMN) and mucinous cystadenoma (Hruban et al. 2000). Based on the genetic evolution of PC, it is estimated that it takes 10 years from the initiating mutation to the establishment of the founder non-metastatic cancer cell and a further 5 years for the development of metastatic potential (Yachida et al. 2010). The detection of PC precursors depends on the underlying lesion, PanINs arise in the smaller pancreatic ducts and the vast majority measure less than 5 mm, as such they are difficult to detect with current

imaging techniques (Hruban et al. 2008). In contrast, mucinous cyst adenomas (MCNs) and the duct obstruction and upstream dilatation produced by IPMN are typically detectable on imaging studies (Hruban et al. 2004).

5 PC Risk Assessment

The primary goal of developing PC risk prediction models is to be able to personalise PC risk and in doing so inform genetic testing and potential screening options (Klein 2013b). Multiple risk factors for PC have been identified, after increasing age the next major risk factor is a family history of the disease (Lennon et al. 2014). In those with a known mutation efforts have been made to quantitate this risk, but the majority of individuals at increased genetic risk do not have a known mutation and in effect each person presents with a unique risk factor profile. PancPro is a Bayesian model developed from pedigree data from the National Familial Pancreas Tumour Registry (NFPTR) and calculates the risk that a person carries a high-penetrance PC gene and their risk by age of developing PC (Klein 2013b). The input variables required from each at-risk individual include personal and family history of cancer, current age and age at cancer diagnosis. The model has been validated in an independent cohort and shown an observed to predicted pancreatic cancer ratio of 0.83 (95 % CI, 0.52–1.20) (Wang et al. 2007). PancPRO may be a useful strategy to rank families based on their PC risk and suitability for a screening programme (Leonardi et al. 2012).

6 Genetic Testing for Hereditary Pancreatic Cancer

6.1 Initial Approach

The initial assessment in the index patient should begin with a thorough personal and family history of malignancy. This should include the presence and type of cancer diagnoses in first- and second-degree relatives (±third-degree), age at diagnosis and maternal or paternal lineage (Lu et al. 2014, Network, Version 2.2015). Using this information, a comprehensive, three-generation pedigree should be generated and used to develop a preliminary determination of the risk of a familial predisposition to cancer (Lu et al. 2014). Hallmark features suggestive of an inherited predisposition include (a) personal history: early age at PC diagnosis (<50 years) and previous cancer or premalignant diagnoses with unusual quantity or histological appearance and (b) family history: kindreds with early onset cancer diagnoses (<50 years), members with multiple synchronous or metachronous primary tumours, rare tumours, ancestry with established founder mutations, e.g. Ashkenazi Jewish, and family history of multiple close relatives from the same lineage with PC or spectrum of genetically related cancers (Whitcomb et al. 2015; Syngal et al. 2015). Table 3 summarises the genes to consider for testing based on clinical criteria.

Table 3 Indications for cancer predisposition assessment and consideration of genetic testing (Whitcomb et al. 2015; Syngal et al. 2015; Network, version 2.2015; Hampel et al. 2014)

Clinical criteria	Syndrome to consider	Gene(s) to consider
1. PC diagnosed any age, if any of the following criteria are met – ≥2 cases PC in close relative (1st and 2nd degree)[a] – ≥2 cases breast, ovarian or aggressive prostate cancer in close relatives – Ashkenazi Jewish ancestry	FPC HBOC	*BRCA2* *BRCA1*, *BRCA2*, *PALB2* *BRCA1*, *BRCA2*
2. PC and ≥1 PJ polyp	PJS	*STK11*
3. PC and ≥2 additional cases of any Lynch syndrome-associated cancer in the same person or close relative (LS tumour: CRC, EC, urothelial, gastric, ovarian, SB cancer, glioblastoma, sebaceous adenocarcinoma, biliary tract and PC)	Lynch syndrome	*MSH2*, *MLH1*, *PMS2*, *MSH6*, *5′ EPCAM deletion*
4. ≥3 cases of PC and/or melanoma in close relatives or PC and melanoma in the same person	FAMMM	*CDKN2A*
5. Personal history of ≥2 attacks of acute pancreatitis of unknown aetiology, a family history of pancreatitis, or early age of onset of chronic pancreatitis	HP	*PRSS1*

[a]*BRCA1*, *PALB2* and *ATM* mutation testing has also been suggested for FPC but the clinical utility in this setting is not well established (Syngal et al. 2015)

The potential benefits of genetic testing to the proband, although not typically applicable in the PC setting, include provision of the risk estimation of developing another cancer and implementation of risk reduction and preventative options (Whitcomb et al. 2015). The result can also impact treatment with consideration of a more extensive pancreatic resection as patients with inherited predisposition frequently show multi-focal disease, and patients may benefit from a precision or personalised treatment regimen, for example DNA damaging agent and/or PARP inhibitor chemotherapy if a BRCA1/2 or PALB2 mutation is identified. Genes with established clinical utility can be tested in family members and if found to carry the mutation can be considered for early detection strategies for PC as part of a research protocol and for other at-risk organs undergo surveillance and consider preventative intervention in accordance with published guidelines.

The increasing access to and performance of genomic sequencing in clinical and research settings has shown that a significant proportion of individuals with germline cancer predisposing mutations do not fulfil the classic clinical diagnostic criteria (Holter et al. 2015). This results from variability in the clinical genotype–phenotype correlation and incomplete penetrance leading to limited sensitivity and specificity of the classic diagnostic criteria. It is therefore imperative that the clinical features and guidelines undergo revision and modification and incorporate new findings as they arise. One approach is to integrate family history with specific genomic feature in the tumour (Carnevale and Ashworth 2015), for example, somatic hypermutation as a marker of microsatellite instability (The Cancer

Genome Atlas Network 2012) or somatic genomic instability as a marker of defective homologous recombination (Waddell et al. 2015). This approach may optimise identification of individuals with genetic predisposition to cancer and provide information on effective therapies, for example DNA damaging agents or PARP inhibitors in BRCA deficient tumours and immune checkpoint inhibitors in MMR-deficient tumours (Kaufman et al. 2015).

6.2 Surveillance and Management

The current evidence supporting PC surveillance strategies is at this time limited to observational studies (Syngal et al. 2015). Although screening has intuitive appeal with the potential benefit of early diagnosis and as a consequence improved treatment and prognosis, it has not been demonstrated that this translates into better outcome for patients. Demonstrating a reduction in mortality in a rare disease like hereditary PC will take several years and a large number of patients (Syngal et al. 2015). Screening can be associated with lead-time and length bias, which can lead to false conclusions of benefit (Grimes and Schulz 2002; Barratt et al. 2002). PCs diagnosed in screening trials have predominantly but not universally been resectable. However as with sporadic disease, resected patients often progress to metastatic disease due to subclinical metastatic disease at diagnosis (Al-Sukhni et al. 2012).

Expert opinion has recommended that individuals with a relative risk of 5–10-fold compared to the general population should be considered for PC surveillance (Canto et al. 2013b; Del Chiaro et al. 2010) as summarised in Table 4. The majority of significant lesions are found in older patients (>65 years); in view of this, recent guidelines suggest screening begin at 50 years of age, or 10 years younger than the earliest age of PC diagnosis in kindreds. Patients with PJS should start surveillance at 35 years (Syngal et al. 2015). The majority of significant lesions are found in older patients in particular >65 years (Canto et al. 2013a).

Table 4 Summary of the Cancer of the Pancreas Screening (CAPS) consortium consensus statement of criteria for consideration of screening (Canto et al. 2013a)

Familial PC group
Individuals with three affected kindreds, of which at least one is an FDR
Individuals with at least two affected FDRs with PC
Individuals with two or more affected blood relatives with PC, with at least one affected FDR
Germline mutation carrier group
STK11 mutation carriers, regardless of family history of PC
CDKN2A carriers with one affected FDR
BRCA2 mutation carriers with one affected FDR
BRCA2 mutation carriers with two affected family members, neither of which is a FDR
PALB2 mutation carriers with one affected FDR
Mismatch repair gene mutation carriers with one affected FDR

Current PC screening trials are predominantly imaging based, which provides limited or no information on the biology of the lesion. Biomarkers, of which carbohydrate antigen 19.9 (CA19.9) is the only currently clinically used, have a poor sensitivity for small pancreatic tumours with only 50 % of tumours <3 cm having an elevated level (Steinberg 1990). As PC spreads outside the pancreas abnormalities that are not produced by or specific to PC cells accumulate such as inflammatory markers (Goggins 2011). These represent epiphenomena and are unlikely to provide prognostic or predictive value. In view of recent large-scale sequencing studies of PC, which highlight the significant heterogeneity of tumours, it brings into question whether it is possible to identify a "one-size-fits-all" biomarker of early PC. Other biomarkers in blood ((e.g. PAM4-based immunoassay) (Gold et al. 2010), MIC-1 (Koopmann et al. 2006), circulating-free DNA (Mulcahy et al. 1998) and microRNA (Liu et al. 2012)), pancreatic juice (Berthelemy et al. 1995) and cyst fluid (Jabbar et al. 2014), either alone or in combination require further prospective validation to determine their clinical utility.

In recent years, multiple PC surveillance programmes have been established and initial findings reported (as shown in Table 5). The primary modalities used include endoscopic ultrasound (EUS) and magnetic resonance imaging with/without magnetic resonance cholangiopancreatography (MRI/MRCP) as they do not involve radiation exposure. The sensitivity of these modalities to detect cystic pancreatic lesions is 93 % with EUS, 81 % with MRCP and 27 % by Computerised Tomography (CT) (Canto et al. 2012). The ability to detect PanIN is unknown but likely to be much lower due to the aforementioned limitations. Overall, the studies demonstrate that precursor lesions or invasive cancers can be demonstrated in a variable but significant proportion of at-risk individuals but no study has shown better outcomes for patients (Schneider et al. 2011b; Canto et al. 2012). The variable yield (1–50 %) is partly dependent on the definition of the target lesions, which range from early cancer and high-grade dysplastic precursor lesions to IPMN with low–intermediate dysplasia to PanIN with any grade of dysplasia. The prevalence of detectable neoplasia is also dependent on the risk in the population being studied, the modalities used, the duration of follow-up and the number that undergo definitive pathological assessment, i.e. surgical resection.

Therapeutic intervention if undertaken for precursor lesions in current clinical practice constitutes a pancreatic resection. Pancreatectomy for a precursor lesion with a low probability of progression is associated with significant morbidity and unlikely to change the outcome for the patient. Typically, the long-term survivors, after pancreatectomy for PC, are those with early-stage tumours (<2 cm and confined to the pancreas) and lymph node-negative cancers (Agarwal et al. 2008). However, even in this small group a high rate of nodal metastases and poor prognosis has been described (Franko et al. 2013). Currently, early-stage cancers along with the high-grade precursor lesions (IPMN, MCN and PanIN 3 and CIS), represent the best opportunity to reduce mortality from PC as they are likely to progress and are potentially curable. Improving our understanding of the inherited predisposition to PC will lead to more precise risk assessment and potentially better selection of candidates who will benefit from screening. Screening brings with it the

Table 5 Summary of PC screening trials using a predominantly imaging-based approach in high-risk individuals

Study	Risk category	Patients (n)	Follow-up (months)	Imaging modality	Findings				
					Yield	PC	IPMN	PanIN 2–3	Other
Brentnall et al. (1999) Ann Int Med	FPC	14	15	CT, EUS, ERCP ± KRAS analysis in pancreatic juice	50 %	–	–	7[a]	–
Kimmey et al. (2002) Gastrointest Endosc	FPC	46		EUS, ERCP	26 %	–	–	12[a]	–
Canto et al. (2004) Clin Gastro Hepatol	FPC, PJS	38	22	EUS	5 %	1	1	–	–
Canto et al. (2006) Clin Gastro Hepatol	FPC, PJS	78	12	EUS, CT	10 %	1	6	1	–
Poley et al. (2009) Am J Gastro	FPC, PJS, Other syndromes with ≥2 affected (BRCA, p16, p53, HP)	44	Initial finding	EUS	23 %	3	7	–	–
Langer et al. (2009) Gut	FPC, BRCA2	76		EUS, MR/MRCP	0.76 %	–	1	–	–
Verna et al. (2010) Clin Cancer Res	FPC, BRCA2, CDKN2A	51	Initial finding	EUS, MRI	12 %	2	4	–	4 EPM[c]
Ludwig et al. (2011) Am J Gastro	FPC, BRCA	109		MRCP followed by EUS	8.30 %	1	5	2	–
Vasen et al. (2011) Gastroenterology	CDKN2A	79	48	MRI/MRCP	20 %	7	9	–	–
Al-Sukhni et al. (2011) J Gastrointest Surg	FPC, BRCA, PJS, CDKN2A, HP	262	50	MRI/MRCP	7.30 %	3	15	–	1 PNET
Schneider et al. (2011) Familial Cancer	FPC, BRCA, PALB2	72	44	EUS, MR/MRCP	13 %	1	7	2	–
Canto et al. (2012) Gastroenterology	FPC, BRCA2, PJS	216	29	EUS, CT, MRI	43 %	0	82	5[b]	3 PNET

[a]Widespread dysplasia; [b]5 pancreatic resection and all had multi-focal IPMN and PanIN; [c]EPM extrapancreatic malignancies—2 ovarian cancers (in BRCA-1/2 mutation carriers), 1 retroperitoneal carcinoid, 1 papillary thyroid cancer

risk of overtreatment and additional controlled trials are needed to determine the risks, benefits and optimal approaches to PC screening. Most would agree that a solid mass or cyst meeting current clinical guidelines should be resected, but patients frequently have widespread abnormalities on EUS complicating this decision.

7 Ongoing Research and Future Developments

Our traditional approach to understanding cancer predisposition emerged because of limitations in our ability to sequence individual genes, let alone exomes or genomes. The pragmatic reality of only testing those with a high risk of developing a malignancy based on clinical history of malignancy has generated an acquisition bias to our understanding of cancer predisposition today. This approach has been successful and allowed definition of several highly penetrant cancer predisposition genes and corresponding syndromes associated with PC, but most are predominantly characterised by malignancy in other organs. In some cases, e.g. BRCA mutations, this has led to significant improvements in clinical management. This "forward genetics" approach has served us well for many years, yet has instilled a dogma that may limit progress in the emerging "reverse genetics" era. Now that the challenges have completely shifted from the technological limitations of DNA sequencing, to the far greater challenge of understanding the biological basis of cancer predisposition and defining clinical validity and clinical utility, and then delivering an appropriate and viable benefit to the community.

Several challenges and knowledge gaps materialised by the broader availability and lower threshold for genomic sequencing. These include the following: (1) our current knowledge allows us to accurately predict the relative risk of developing a cancer in the setting of a family history. What we do not know is the risk of carriers without a family history. The interpretation of deleterious variants and estimation of risk in the absence of a related phenotype or family history is currently unknown, and there is little evidence to guide counselling and clinical decision making. Even in the presence of a potentially related phenotype, it may be difficult to assign causality to a deleterious variant and additional evidence may be required (MacArthur et al. 2014). (2) Current disease models propose a complex genetic predisposition pattern for most PC, which results from the convergence of several inherited and acquired (genetic and non-genetic) risk factors which interact and increment leading to progression from precursor lesion to invasive cancer (Whitcomb et al. 2015). Another challenge will be unravelling the contribution of multiple loci, including combinations of different genes, coexistent variants within genes and gene-environment interactions (Walsh et al. 2011; Couch et al. 2014). (3) Approximately 80 % of the heritability of PC remains unexplained, this has been termed the "missing heritability" which may lie in common but low-penetrant variants identified in genome-wide association studies, structural variants and epigenetics (Manolio et al. 2009). (4) Currently, we only utilise limited endpoints to

assess for cancer predisposition: increased incidence and young age of onset. Some inherited deleterious variants may not substantially lower the age of onset, or dramatically increase the incidence of a particular cancer, but may lead to a poor prognosis cancer since the initiating mutation is still environmentally determined, but "progressor" mutations may already be present. To circumvent these hurdles, we need to identify other ways to gather the evidence required to impact on clinical management (MacArthur et al. 2014). We also need to define the role of other measures such as functional readouts, or surrogate measures of the consequences of specific genomic variants, an example is using whole-genome sequences to identify surrogates of genetic defects in tumours. Such examples include microsatellite instability and mutational signatures associated with defects in DNA maintenance. The latter is a specific signature of point mutations that are associated with defects in *BRCA1* and *BRCA2* function (Alexandrov et al. 2013). Variants associated with such surrogate measures can then focus experimental approaches to demonstrate the functional significance of these variants.

To circumvent these hurdles along with the substantial diversity of the human genome and the complexity of cancer genomes, infer that our traditional approach to identifying predisposition genes and quantifying relative risk will require even larger numbers. As we accumulate more cancer genomes through large-scale international efforts such as the International Cancer Genome Consortium (ICGC) (Hudson et al. 2010) and The Cancer Genome Atlas (TCGA), the germline sequences that accompany these genomes will provide insights into the prevalence of known predisposition loci in the germ line and perhaps point to novel candidates (Stadler et al. 2014). In addition, familial tumour registries such as the National Familial Pancreas Tumour Registry (NFPTR) (Klein 2013b) with detailed data and biospecimen acquisition provide an important resource for identification of candidate risk genes, clustering of related tumour types, the estimation of risk and the assessment of early detection strategies. Follow-up and biospecimen acquisition (germ line DNA, and where appropriate, tumour DNA) of patients and their families for index cases with variants of unknown significance may also bear fruit in the longer term. The concept of healthy controls of advanced age may be helpful and requires assessment; however, it is likely that only large-scale "knowledge bank" approaches that track generations over time with well-documented clinical histories will begin to unravel this complexity.

8 Summary and Key Points

- A total of 5–10 % of PCs have a heritable component based on family history.
- The majority (80 %) of the heritability is currently unexplained by known predisposition genes.
- Hereditary PC can occur in the setting of well-established inherited tumour predisposition syndromes, but the majority do not fulfil these criteria.

- Clinical genetic testing in probands fulfiling clinical criteria for genes with current direct clinical utility.
- Screening can be considered if >5 % lifetime risk in a ethically approved peer-reviewed research study.
- Improved genomic sequencing technology has led to greater throughput (cancer gene panels or exome/genome sequencing) with increased availability and lowering of testing thresholds. This posits several challenges and highlights knowledge gaps and advocated for new approaches to cancer predisposition assessment and incorporation into clinical care.

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