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TOPIC HIGHLIGHT

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Genetic predisposition to pancreatic cancer

Paola Ghiorzo

Paola Ghiorzo, Department of Internal Medicine and Medical Specialties, University of Genoa and IRCCS Azienda Ospedaliera Universitaria San Martino-IST Istituto Nazioanle per la Ricerca sul Cancro, 16132 Genoa, Italy
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Correspondence to: Paola Ghiorzo, PhD, Department of Internal Medicine and Medical Specialties, University of Genoa and IRCCS Azienda Ospedaliera Universitaria San Martino-IST Istituto Nazioanle per la Ricerca sul Cancro, V.le Benedetto XV 6, 16132 Genoa, Italy. paola.ghiorzo@unige.it
Telephone: +39-10-3538949 Fax: +39-10-3537543
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Abstract

Pancreatic adenocarcinoma (PC) is the most deadly of the common cancers. Owing to its rapid progression and almost certain fatal outcome, identifying individuals at risk and detecting early lesions are crucial to improve outcome. Genetic risk factors are believed to play a major role. Approximately 10% of PC is estimated to have familial inheritance. Several germline mutations have been found to be involved in hereditary forms of PC, including both familial PC (FPC) and PC as one of the manifestations of a hereditary cancer syndrome or other hereditary conditions. Although most of the susceptibility genes for FPC have yet to be identified, next-generation sequencing studies are likely to provide important insights. The risk of PC in FPC is sufficiently high to recommend screening of high-risk individuals; thus, defining such individuals appropriately is the key. Candidate genes have been described and patients considered for screening programs under research protocols should first be tested for presence of germline mutations in the BRCA2, PALB2 and ATM genes. In specific PC populations, including in Italy, hereditary cancer predisposition genes such as CDKN2A also explain a considerable fraction of FPC.

Key words: Pancreatic adenocarcinoma; Susceptibility genes; CDKN2A; Melanoma; Hereditary cancer syndromes; Screening

Core tip: Pancreatic adenocarcinoma is the most deadly of the common cancers. Identifying families with hereditary pancreatic cancer can aid appropriate selection of individuals who are at high risk and are good candidates for prevention and screening programs. Although genetic predisposition to pancreatic cancer remains largely unexplained, next-generation sequencing is likely to provide important insights. Candidate genes have been described and patients considered for screening protocols should first be tested for germline mutations in these genes. In specific pancreatic cancer populations, including Italy, hereditary cancer predisposition genes such as CDKN2A also explain a considerable fraction of hereditary pancreatic cancers.

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INTRODUCTION

Pancreatic adenocarcinoma (PC) is the deadliest among the common cancers. Its incidence is on the rise, especially in North America, Japan and Europe, where it represents the fourth to fifth most frequent cause of cancer mortality. Despite advances in therapy, diagnostic imaging and understanding of genetic factors, PC mortality rates have not declined appreciably in the past 20 years, and PC mortality still nearly equals its incidence (roughly

280000 new cases per year, 7000 of which are in Italy), leading to an estimated 227000 deaths per year worldwide[1-4]. The only potentially curative treatment for PC is surgical resection. Median survival following resection ranges from 13 to 21 mo, while without surgery, median survival is a mere 2.5-8 mo[5,6]. However, as most PCs are diagnosed late, and < 5% of tumors are resectable at the time of diagnosis, 5-year survival for PC remains low (< 5%). Early detection of stage 1 disease with curative resection has been shown to improve 5-year survival rates upwards to 60%[7].

The incidence of PC in the general population is not as high as that of other more common cancers (*e.g.*, colorectal cancer), therefore, nonselective screening is not recommended. However, targeted screening may hold promise for high-risk individuals (HRIs) identified by their family history or because of a known genetic predisposition. To date, no standard diagnostic approach or early detection method for PC has been developed, and screening remains challenging[8]. Accurate risk stratification and correct identification of HRIs with a genetic predisposition to the disease who may benefit from prevention and screening interventions in high-volume centers with ongoing research programs on PC[8,9] is thus crucial.

In recent years some excellent reviews have described susceptibility genes for PC, its biology and screening intervention protocols[8-12]. The aim of this review is to provide an update of recent findings on genetic susceptibility to PC, describing standard and novel approaches for the identification of susceptibility genes, as well as genetic data recently obtained for the first time in the Italian PC population.

RISK FACTORS FOR PANCREATIC ADENOCARCINOMA

Biological, lifestyle and environmental risk factors

PC incidence shows wide variations across countries, suggesting that biological, lifestyle and environmental factors are involved in determining increased PC risks, which range between two- and 13-fold[4]. PC is age dependent; in the United States, the median age at diagnosis is 72 years. Only 5%-10% of patients with PC develop the disease before the age of 50 years, and these are likely to include patients with an underlying genetic predisposition or who have previously undergone radiotherapy[4]. Sex and race also play a role, probably related to differences in smoking rates in men, as well as race-specific genetic differences in the ability to detoxify tobacco products, or vitamin D deficiency in blacks. Although these factors cannot be modified, lifestyle and environmental risk factors are controllable, cause 20%-25% of all PCs, and are thus of importance for HRIs. Heavy alcohol intake is associated with a modest increased risk of PC, while chronic pancreatitis, long-term diabetes, *Helicobacter pylori* infection, overweight, vitamin D deficiency and occupational exposures are associated with significantly increased risk. Conversely, atopic allergy and use of metformin to treat diabetes have been associated with a reduced risk.

Susceptibility genes in HRIs

Although lifestyle modifications are possible and may help reduce PC risk, high-risk factors are not controllable and are the ones that typically characterize candidates for prevention and screening interventions.

PC has a familial basis in as many as 10% of patients. Some of the familial aggregation of PC is due to chance, and some to shared environmental exposure such as cigarette smoking[6]. An inherited predisposition to PC is seen in a range of clinical settings. Several hereditary cancer syndromes are known to be associated with an increased risk of PC, mainly Peutz-Jeghers syndrome (PJS), melanoma pancreatic-cancer syndrome (MPCS) or familial atypical multiple mole melanoma (FAMMM)-PC, hereditary breast-ovarian cancer (HBOC), and to a lesser extent Lynch syndrome (LS) and familial adenomatous polyposis (FAP). In addition, an increased risk of PC is present in patients with hereditary pancreatitis or cystic fibrosis.

Approximately 20% of hereditary cases of PC are currently attributed to a known genetic syndrome. The term familial pancreatic cancer (FPC) applies to the remaining 80% of patients with an inherited predisposition: families in which at least two first-degree relatives (FDRs) have been diagnosed with PC but that do not meet the diagnostic criteria for the previous settings[13-16] (Table 1).

Genes for known hereditary cancer syndromes

As mentioned earlier, PC is known to occur in a range of hereditary diseases and syndromes.

PJS is an autosomal dominant hereditary disease with characteristic hamartoma polyps of the gastrointestinal tract, and mucocutaneous melanin pigmentation. Almost half of all PJS patients harbor germline STK11/LKB1 gene mutations. Affected individuals have a 36% cumulative lifetime risk of developing PC[17].

FAMMM is an autosomal dominant disease that is characterized by the occurrence of > 50 atypical nevi and malignant melanoma in two or more first- or second-degree relatives. Malignant melanoma, however, may also be familial in the absence of the FAMMM phenotype. Approximately 10% of melanomas have a familial aggregation pattern and mutations in the CDKN2A tumor suppressor gene are identified in roughly 40% of these families[18]. PC has been observed in a considerable proportion of kindreds with CDKN2A mutations. This is considered to be a distinct hereditary cancer syndrome, is termed FAMMM-PC or MPCS, and has been found to confer a 17% cumulative lifetime risk of developing PC. CDKN2A germline mutations account for 30%-40% of patients affected by MPCS or the FAMMM-PC syndrome[18-29].

HBOC is another autosomal dominant hereditary cancer syndrome and is caused by germline mutations in

Table 1 Syndromes and genes associated with hereditary predisposition to pancreatic adenocarcinoma, relative and lifetime risk

Settings of hereditary PC	RR of PC (-fold)	Cumulative lifetime risk by age 70 (%)	Genes identified
FPC syndrome			PALLD, CDKN2A, BRCA2, PALB2, ATM,....?
FDR with PC	2-3	2	
FDRs with PC	6	8-12	
or more FDRs with PC	14-32	40	
Hereditary cancer syndromes			
PJS	132	36	STK11/LKB1
MPCS/FAMMM	13-47	17	CDKN2A
HBOC	3.5-10	3-8	BRCA1, BRCA2
LS	8.6	< 5	MLH1, MSH2, MSH6
FAP	2-3	< 5	APC
Syndromes of chronic inflammation			
HP	50-80	40	PRSS1, SPINK1
CF	5	< 5	CFTR

HP: Hereditary pancreatitis; FAP: Familial adenomatous polyposis; PC: Pancreatic adenocarcinoma; FDR: First-degree relative; PJS: Peutz-Jeghers syndrome; MPCS: Melanoma pancreatic-cancer syndrome; FAMMM: Familial atypical multiple mole melanoma; HBOC: Hereditary breast-ovarian cancer; LS: Lynch syndrome; FPC: Familial PC; CF: Cystic fibrosis; HP: Hereditary pancreatitis.

the BRCA1 and BRCA2 genes. BRCA2 mutation carriers have an increased risk of breast, ovarian, and prostate cancer, as well as a 3.5-10-fold increased risk of PC[30,31], while the reported risk of PC for BRCA1 mutation carriers is about 2.5 times that of the normal population[32].

PC is also typical of LS, alternatively termed hereditary non-polyposis colorectal carcinoma syndrome. This syndrome is caused by mutations in the mismatch repair (MMR) genes MSH2, MLH1, MSH6 and PMS2. Individuals with mutations in the MMR genes have a risk of developing PC that ranges between 5% and 10%[33]. According to a recent study[34], PC risk is increased sevenfold in both MLH1 and MSH2 carriers belonging to LS families, especially at young ages, as noted by Lynch *et al*[35] as early as 1991.

Patients with FAP also have an increased risk of developing PC, with a relative risk of 4.6 (95%CI: 1.2-11.4)[36,37]. Finally, PC also occurs, if less frequently, in patients affected by Li-Fraumeni syndrome and ataxia telangiectasia.

Hereditary cancer syndromes in Italian PC patients

One of the difficulties in confirming that PC is a component of an inherited syndrome caused by germline mutations in a susceptibility gene is the lack of DNA from PC patients in families, which makes it impossible to conduct co-segregation analysis.

We recently investigated the contribution of hereditary cancer syndromes to PC in a hospital-based series of 225 Italian PC patients who were consecutively recruited at our center. Among these patients, 24% of those who presented with features suggestive of HBOC were BRCA1 or BRCA2 positive, and 10% of those who were suspected to be affected by LS carried mutations in the MMR genes[38,39]. Interestingly, 45% of the cases suspected for MPCS were found to harbor mutations in CDKN2A[40-42]. This result corroborates previous findings on the high occurrence of PC in Italian melanoma families with CDKN2A mutations[27,43-46]. The presence of CDKN2A mutations in PC patients selected from a case-control series shows that an unbiased association exists between PC and CDKN2A germline mutations. No other hereditary syndromes were observed in this series that could drive selective screening of other genes.

Genes for hereditary conditions associated with PC

Hereditary pancreatitis: Hereditary pancreatitis (HP) is currently considered to be an independent nosological unit. It is an autosomally dominant disease with 80% penetrance. In patients with HP, trypsin becomes activated while still in the pancreas. This leads to partial digestion of the pancreatic tissue, causing inflammation.

A strong genetic association exists between HP and germline mutations in the PRSS1, SPINK1 and CFTR genes[47]. Patients with HP have an about 80% relative risk and a 40% lifetime risk of developing PC. If these individuals are smokers, then PC develops, or rather is diagnosed, up to two decades earlier than in non-smokers. Similarly, alcohol consumption also leads to a 20-year earlier diagnosis of PC[48,49].

Cystic fibrosis: Cystic fibrosis (CF) is an autosomal recessive disease that is caused by mutations in the *CFTR* gene. CF is characterized by the production of viscous mucus, which blocks the airways and leads to obstruction of the pancreatic duct, thus increasing the risk of inflammation. Patients with CF are at increased risk of chronic pancreatitis and of PC[50].

FPC genes

FPC is mostly inherited in an autosomal dominant fashion, and presents with a heterogeneous phenotype. Prospective studies have reported an increased risk of developing PC in unaffected FDRs of PC patients, which depends on the number of relatives with PC in the family[51]. This risk has been estimated to be 6.4-fold greater in individuals with two FDRs with PC (lifetime risk 8%-12%) and 32-fold greater in individuals with three or more FDRs with PC (lifetime risk 40%) (Table 1). Among kindreds with FPC,

the risk is higher in kindreds with young-onset PC (age < 50 years, relative risk = 9.3) compared with kindreds without young-onset PC[15,52,53]. Furthermore, evidence indicates that the risk of PC is modestly increased in FDRs of patients with sporadic PC compared to the general population[53], in which the lifetime risk of developing PC is slightly less than 1% (0.5% at age 70 years). Anticipation has been described in 59%-85% of FPC families; indeed, patients in younger generations are affected by the disease about 10 years earlier than their affected relatives[54,55].

Studies focusing specifically on FPC genes have not been successful so far in clarifying the genetic basis of the disease[8,15,52]. Several genes underlying susceptibility to the cancer syndromes associated with PC have been investigated for their involvement in FPC predisposition. Although the genes responsible for PJS[56] and LS[57,58] do not seem to play a major role, BRCA2 and BRCA1 are interesting candidates.

BRCA2 has been considered an important PC predisposition gene since its discovery[59], and recent reports have estimated that it accounts for 6%-12% of FPC families[8,60,61]. BRCA1 gene mutations have been reported in a small number of patients with FPC[62,63]. Increasing evidence is emerging that points to CDKN2A as an FPC susceptibility gene[42,64] and other, novel candidate genes (and loci) are being discovered. Indeed, over the past decade, FPC families have been found to harbor mutations in several different genes.

PALLD: In 2002, linkage analysis of a large FPC pedigree from the United States showed significant linkage to chromosome 4q32-34[65]. Four years later, an oncogenic germline mutation at this locus, in the Palladin (*PALLD*) gene, which encodes a cytoskeletal protein, was identified in affected members of that family. It was therefore suggested that PALLD may be a major PC susceptibility gene[66]. But this hypothesis was not supported by later studies on Italian FPC families and on families from other European countries[42,67,68].

BRCA1 and BRCA2: Although germline mutations in the *BRCA1* gene have been reported in a small number of patients with FPC[62,63], mutations in BRCA2 have long been reported to be the most frequently identified genetic alterations in FPC. Early studies with small sample sizes found BRCA2 mutations in 15% of FPC families from Germany and the United Kingdom and in 17% of families from North America[59,60]. These results however could not be confirmed in larger cohorts, in which deleterious BRCA2 mutations were detected in 6% of moderate- and high-risk FPC families[58,61]. BRCA2 deficiency in PC seems to be of clinical importance, because PCs in BRCA2-positive patients are characterized by marked sensitivity to poly (ADP-ribose) polymerase inhibitors and mitomycin[69-71].

We recently assessed the role of BRCA1 and BRCA2 as FPC susceptibility genes in the Italian population[42] and found no germline mutations.

PALB2: PALB2, which binds to the BRCA2 protein, was reported to be a new PC susceptibility gene after whole genome sequencing identified truncating PALB2 mutations in 3.1% of a series of North American FPC patients[72]. PALB2 mutations were later detected in 3.7% of German and British FPC families[73]. Conversely, a Dutch study on 28 FPC families identified no mutations in PALB2[74]. These findings suggest that PALB2 mutations may explain FPC in a small subset of European families, especially in those with an additional occurrence of breast cancer. Indeed, PALB2 is increasingly considered a good candidate for clinical testing in BRCA1- and BRCA2-negative HBOC families[75]. PALB2 testing in a series of Italian PC patients suspected for HBOC described above, and in FPC patients, yielded no mutations, despite the fact that we screened the gene both by Sanger sequencing and by multiplex ligation-dependent probe amplification assay, in order to rule out large genomic rearrangements[38,42].

Germline mutations in other genes in the BRCA2 pathway, namely FANC-C and FANC-G, have been linked to early-onset PC, but segregating germline mutations in these genes have yet to be identified in FPC families[76].

ATM: Recently, heterozygous germline mutations in the ataxia telangiectasia mutated (ATM) gene have been identified in two kindreds with FPC[77]. Subsequent analysis of 166 additional FPC patients identified another four deleterious ATM germline mutations, while none were detected in 190 spouse controls. The prevalence of ATM mutations in the whole FPC cohort was 2.4% (4/166), and 4.6% (4/87) in families with three or more affected members[77]. These findings suggest that ATM mutations in these families may underlie PC, driven by the classic two-hit model for tumor suppressor genes.

CDKN2A: CDKN2A germline mutations account for 30%-40% of patients with MPCS or FAMMM-PC[18-29] and have generally been considered to play a minor role in FPC[61,78-80]. However, there is increasing evidence that CDKN2A (p16INK4a) mutations occur in FPC without metachronous or synchronous occurrence of melanoma in the family.

Two recent papers describing our Italian and the Dutch PC population suggest that CDKN2A may be an FPC susceptibility gene and that CDKN2A testing may be appropriate in FPC even when melanoma does not occur in the family[42,64]. Previously, a large North American study of 1537 unselected patients with PC found that 0.6% carried CDKN2A mutations. Among the 120 FPC cases in that study, four (3.3%) were CDKN2A positive. The authors concluded that screening of patients with PC for CDKN2A mutations should not be performed, but also that these mutations are especially penetrant among smokers[80].

Most CDKN2A mutations are missense mutations lo-

Table 2 Role of CDKN2A mutations in familial pancreatic adenocarcinoma and melanoma pancreatic-cancer syndrome

Study[1]	N° of FPC families	CDKN2A mutation found	Type of CDKN2A mutations	% of CDKN2A positive	N° of MPCS	CDKN2A mutation found	% of CDKN2A positive	Type of CDKN2A mutations
Slater *et al*[61] 2010; Bartsch *et al*[79] 2002	56	0	-	-	5	2	40	p.Q50X, p.E119X
McWilliams *et al*[80] 2010	119	3	c.-34G>T,p.V95fs, p.D153spl,	2.5	39	2	5.3	p.D153spl, pL16R
Ghiorzo *et al*[42] 2012	16	5	p.E27X,p.G67R, p.G101W, c. 201ACTC>CTTT	31	5	2	40	p.L65P, p.G101W
[2]Harinck *et al*[64] 2012	24	3	p.Ser8fs, p.Ala76fs	12	4	3	75	p.Ala76fs

[1]This table only includes studies that analyze CDKN2A mutations in pancreatic adenocarcinoma (PC) probands from familial PC (FPC) families comparing them with PC probands from Melanoma pancreatic-cancer syndrome (MPCS) families belonging to the same population. The prevalence of CDKN2A mutations in MPCS/FAMMM-PC e families, as analyzed in melanoma probands, is described in the text. [2]A melanoma was diagnosed in one FPC family after the proband was found to carry a mutation in CDKN2A.

cated in the coding sequences of exons 1 and 2, common to both the tumor suppressors encoded by this locus (p16INK4a and p14ARF). A number of these mutations seem to derive from ancestral founders[81]. We previously performed germline testing of CDKN2A in a series of unselected PC patients and found that 4% of these patients were CDKN2A positive[40,41]. In a subsequent study we extended the analysis to 225 PC patients and controls. The CDKN2A mutation rate in the 225 PC cases was 5.7%, ranging from 2.6% in patients without a family history of PC or melanoma, to 17% when two cancers occurred in the index patient or FDRs, and to 45% when three or more cancers occurred. Interestingly, 25% of the cases with one FDR with melanoma were mutation positive. Sixteen probands of FPC families were identified, defined for having at least two FDRs affected by PC, and no other manifestation of a hereditary cancer syndrome, or melanoma. Deleterious or potentially deleterious CDKN2A mutations were found in five of the probands (31%)[42]. The mutation frequency ranged from 20% in FPC families with two affected members to 50% in families with three, and was comparable to the mutation rate in melanoma families[46] (Table 2).

Within the PC families with no CDKN2A mutations, anticipation was observed, which is consistent with previous studies that reported anticipation for BRCA2 carriers in FPC families without CDKN2A mutations[55].

The CDKN2A mutation rate in our FPC cases was nearly 10 times that observed in the North American study by McWilliams and colleagues[80]. This result indicates that a sizeable subset of Italian FPC families may carry CDKN2A mutations, and likely reflects the prevalence of founder mutations in CDKN2A in our population[43-46,82,83].

Approaches to CDKN2A genetic testing

It has been proposed that individuals should be referred for CDKN2A testing when at least one of the following conditions is met: (1) a personal history of melanoma and an FDR with melanoma; (2) more than two confirmed primary melanomas; (3) more than three (first-degree or second-degree) relatives with melanoma; (4) a personal or a family history of PC and melanoma; (5) a personal history of melanoma; and (6) a personal and/or a family history of atypical moles[13]. Other recommendations have included patients with more than three melanomas, or families with at least one melanoma and two other instances of melanoma or PC in the family, with mutation yields ranging between 20% and 40%[84].

Had we followed these criteria we would have identified two out of five (40%) of our mutation-positive families with both melanoma and PC. However, as none of the criteria include FPC families, we would not have identified the CDKN2A-positive FPC kindreds. The North-American study mentioned earlier came to the same conclusion, because the majority of their mutations were identified in FPC families, despite their low overall mutation frequency[80]. Their finding is probably more generalizable than ours, both because of their sample size and because it was not influenced by the presence of founder mutations.

Taken together, our results confirm that the occurrence of at least three cancer events (including PC and melanoma) in the family is a good predictor of CDKN2A mutations (45%). Importantly, however, the likelihood of identifying a CDKN2A mutation may also be high in families with two or more instances of PC or with one instance of PC and one of melanoma among FDRs, because we found that 17% of such kindreds were positive for CDKN2A mutations[42].

Harinck and colleagues also performed CDKN2A mutation analysis in 28 FPC families. Unlike ours, their selection criteria included presence of melanoma, and indeed melanoma also occurred in four of their families (14%), Interestingly, CDKN2A mutations were identified in three of these melanoma-positive families, confirming that CDKN2A mutations are frequently found in families affected by both PC and melanoma. The prevalence of CDKN2A mutations in their FPC families with no occurrences of melanoma was 12% (n = 3). These CDKN2A-positive families would not have been identified had the recommendations mentioned above

been followed, which are based on studies that found no CDKN2A mutations in FPC families without melanoma[13,26,61,79]. The prevalence of CDKN2A mutations in the FPC families studied by Harinck *et al*[64] may have actually been underestimated. Indeed, affected relatives in some of the families in that study were unavailable for DNA testing, so unaffected FDRs were tested instead. In such cases a negative test does not rule out the presence of a pathogenic mutation unless a specific mutation has been found in another relative.

Harinck and colleagues concluded that CDKN2A mutations are found in a considerable proportion of families with FPC (Table 2), and therefore CDKN2A mutation analysis should be performed in FPC families even in the absence of reported melanomas. According to the authors this strategy will enhance the recognition of individuals at risk for PC and facilitate the early detection of melanomas.

A number of reports have suggested that BRCA2 mutation analysis should be performed in FPC families that do not meet the criteria for HBOC[59,61]. Similarly, our findings and those reported by Harinck and colleagues emphasize the need to include CDKN2A mutation analysis in genetic testing for FPC families, even in the absence of reported melanomas[42,64].

Novel predisposition genes: evidence from NGS and genome-wide association studie

The discovery of additional FPC genes is one of the most exciting opportunities in PC research. As the speed and ease of testing increase and costs fall as a result of NGS, we expect that a number of new FPC genes will be discovered in the coming years. Exome sequencing has already led to the identification of PALB2 and ATM mutations in FPC, and much hope is being placed in postgenomic studies[72,77]. Indeed, recent genome-wide association studie (GWAS) and post- GWAS analyses have identified chromosome regions containing novel susceptibility loci for PC.

One such study, the PanScan Project, has identified several common polymorphisms affecting PC susceptibility. In that study, single nucleotide polymorphisms (SNPs) in ABO, sonic hedgehog (SHH), telomerase reverse transcriptase, nuclear receptor subfamily 5, group A, member 2 were found to be associated with PC risk. The scan also identified loci on chromosomes 13q22.1 and 15q14, to which no known genes or other functional elements are mapped[85,86].

Another GWAS on PC risk has been performed in the Japanese population[87], and yielded three new loci on chromosomes 6p25.3 (SNP rs9502893, 25 kb upstream of FOXQ1), 12p11.21 (SNP rs708224, in the second intron of BICD1) and 7q36.2 (SNP rs6464375, in the first intron of DPP6). Another still has been conducted in the Chinese population[88] and identified five novel PC susceptibility loci at chromosomes 21q21.3 (SNPrs372883, in the 3' UTR of gene BACH1), 5p13.1 (SNP rs2255280, in intron 1 of gene DAB2), 21q22.3 (SNP rs1547374, upstream of gene TFF1), 22q13.32 (SNP rs5768709) and 10q26.11 (SNPrs12413624). The latter two SNPs are not located in the immediate vicinity of any gene.

Several recent reports have also shown associations between other genetic variants and PC risk and progression, and their impact on survival is currently being investigated[89-91].

The ABO gene in particular has been further investigated, and a link between ABO blood type and PC has been established. Non-O blood types have been found to account for 17% of all new PC cases, showing a protective effect of the O blood group. However, the exact mechanism that links PC and blood group remains unclear[92]. Whether genetic variability at the ABO locus may be involved in PC survival is currently under investigation[93].

Recent analysis of GWAS data has revealed that two pathways, the neuroactive ligand receptor interaction and olfactory transduction, are significantly associated with PC risk, and has shown that four genes are significantly associated with PC risk, adding OR13C4 to the previously identified ABO, HNF1A and SHH[2-4] genes. These findings provide new insights into the polygenic basis of PC susceptibility and etiology[94].

Gene-environment interaction

Among PC families, the risk of developing PC is higher in younger subjects and is likely modified by nongenetic risk factors such as exposure to tobacco smoke. Not only do smokers have a 2-3-fold greater risk of developing the disease compared to non-smokers, but they generally develop the disease at an earlier age[95,96].

An interesting example of gene-environment interaction for PC was shown for germline CDKN2A mutations in the large North American hospital-based study mentioned earlier, which investigated both the prevalence of germline mutations in PC patients, and their penetrance[80]. The authors found that penetrance for PC and melanoma was increased among mutation carriers, with PC risk estimates of 58% (95%CI: 8%-86%) by age 80 years and melanoma risk estimates of 39% (95%CI: 0%-80%) by age 80 years. Among ever-smokers, the risk of PC was higher for CDKN2A mutation carriers compared to non-carriers (HR = 25.8, $P = 2.1 \times 10^{-3}$), but among non-smokers the comparison did not reach statistical significance. The authors concluded that CDKN2A mutations in PC patients are rare but notably penetrant, and that CDKN2A mutation carriers, as well as being candidates for prevention and screening studies, should be counseled to avoid tobacco use.

Identification of HRIs: in silico analyses, genetic testing, role of registries

Genetic testing can identify a family's underlying genetic susceptibility to PC, but has limited scope because the genetic basis of much of the inherited susceptibility to this disease remains unexplained. Additional PC susceptibility genes may be discovered in the near future that should improve our ability to identify individuals who

Table 3 Proposed inclusion criteria for pancreatic adenocarcinoma screening programs in high-risk individuals, identified based on family history and possibly on genetic background

Current (based on family history alone or on genetic background):
Family history:
Three or more relatives in the same lineage affected by PC
Two relatives affected by PC, at least one of which is a FDR of the individual
Hereditary pancreatitis
> 10-fold increased risk as established by PancPRO
Genetic background:
Germline carrier of a mutation in a candidate gene with at least one FDR or SDR affected by PC
Mutation-positive individual in a PJS kindred
Proposed (based on family history and genetic background):
Family history: Identification of a hereditary syndrome or a 10-fold increased risk established by PancPRO
Genetic background: According to testing in candidate genes (CDKN2A, BRCA1-2, ATM, PALB2, STK11, PRSS1, SPINK1…)
Mutation identified: Propose screening to carriers of germline mutation
No mutation identified: Propose screening to all HRIs
In populations with a high prevalence of germline mutations in candidate genes (*e.g.*, CDKN2A founder mutations in Italy or the Netherlands)
The same as above + test candidate genes according to specific genetic background, even in the absence of all criteria for hereditary syndromes or of a PancPRO score > 10

PC: Pancreatic adenocarcinoma; FDR: First-degree relative; PJS: Peutz-Jeghers syndrome; HRIs: High-risk individuals.

would benefit most from pancreatic screening in the context of research protocols[11].

Family history remains the main tool to quantify PC risk. Risk stratification is determined by the number of affected individuals in the family and the degree of relatedness between those individuals and other family members. The phenotypic variance seen in FPC families and the heterogeneity of the hereditary cancer syndromes potentially involved require careful study of the family tree over at least three generations, and histopathological confirmation of all diagnoses.

A computer-based risk assessment tool, PancPRO (http://astor.som.jhmi.edu/BayesMendel/pancpro.html), which uses this type of information has been shown to provide an approximate risk assessment for FPC families[97,98]. Families with high PancPRO scores would generally be identified by standard criteria, but PancPRO has the advantage that it can assign a quantitative risk score to any family member, which also depends on the age at diagnosis (or death) of the affected relatives. PancPRO provides useful information about an individual's PC risk before he or she decides to undergo invasive screening. That information can also help identify appropriate candidates for research on screening protocols or genetic susceptibility. Indeed, according to a recent position paper by the Italian PC Registry, having a PancPRO risk score > 10 is one of the criteria for enrollment in screening programs for PC[99].

It is in the framework of these programs that our findings will be of value to establish the most appropriate criteria to select families for CDKN2A testing in Italy. We found that about 30% of our FPC patients with no occurrence of melanoma among relatives carried mutations in CDKN2A, and similar results have been reported in the Netherlands, therefore, we suggest that individuals considered at high risk because of their family history should undergo genetic testing for CDKN2A before they are enrolled in research surveillance programs, especially in populations such as these, in which founder effect CDKN2A mutations are predominant (Table 3).

Genetic testing for hereditary PC mandates full informed consent as recommended by national guidelines for genetic testing for cancer susceptibility[100] and should be initially performed in affected individuals[11,13]. Germline genetic testing of patients with PC is currently underused, not least because clinicians often fail to take a detailed history of cancer occurrence in the family. The possibility that a hereditary cancer syndrome may be present in the family is therefore frequently overlooked. However, our data show that a considerable proportion of FPC families carry CDKN2A mutations, even in the absence of melanoma in the family.

A combination of risk prediction tool analysis and genetic testing is likely to be the most successful approach to identify HRIs (Table 3). Based on the results reviewed here, genetic testing should be performed after PancPRO analysis to stratify better risk and identify the HRIs who may benefit from PC surveillance programs performed in the context of research protocols.

More generally, affected members of FPC families should be analyzed for BRCA2, PALB2, ATM and CDKN2A mutations. Genetic analyses of other genes (*e.g.*, LKB1 and BRCA1) should only be recommended if the family history is suggestive of the associated hereditary cancer syndromes[11].

CONCLUSION

PC remains one of the most challenging of all cancers. Numerous studies are currently under way to identify novel early detection tools for PC, and evidence is beginning to show that screening FDRs of individuals with several family members affected by PC can identify precursors of this malignant disease[8-13].

Prospective PC screening with endoscopic ultrasound, magnetic resonance imaging and magnetic resonance

cholangiopancreatography has been shown to detect precancerous lesions with a diagnostic yield ranging from 13%[101] to 76%[102], depending on study population (high or moderate risk, carriers or non-carriers of germline mutations), age at baseline screening, screening modalities, and definition of the diagnostic yield, with the highest yield obtained in confirmed carriers of CDKN2A germline mutations[103].

Appropriate inclusion of families at high risk of PC in registries provides an excellent tool to improve our clinical and genetic understanding of FPC[104]. Indeed, focused research projects can be conducted most efficiently when data from different FPC registries are combined.

Although much work is currently focused on clarifying the impact of common genetic variability on individual PC risk, much less is known about heritable susceptibility to PC compared to what is known about other heritable cancers. One viable option to expand our understanding of the genetic determinants of PC risk is to collect large sets of patients across different populations[91]. In this review we have described some important results on new susceptibility genes and loci that have been recently obtained by PC consortia[10].

Genetic risk factors are believed to play a major role, and several germline mutations have been identified that underlie hereditary susceptibility to PC in different settings, such as FPC and other hereditary cancer or chronic inflammation syndromes. The risk of PC in FPC is sufficiently high to recommend screening HRIs; therefore defining those HRIs appropriately is crucial.

In the general population, the lifetime risk of developing PC is 1%. Although they have a twofold increased risk of PC, the vast majority of individuals with a family history of PC will not develop the disease themselves. It is therefore important to explain the concepts of both relative and absolute risk to patients and their families. However, when an FDR of a PC patient is tested and found to carry a germline mutation in a high-risk gene, the risk is not negligible. Once penetrance and factors that modify penetrance have been taken into account, these individuals may be appropriate candidates for prevention or screening protocols, which should at all events only be directed at HRIs, defined to the best of our ability and possibly with genotypic data.

Utility analyses suggest that PC screening is most cost-effective in individuals whose lifetime risk of the disease is 16% or greater[9]. It can detect intraductal papillary mucinous neoplasm and pancreatic intraepithelial neoplasia, which are precursor lesions for FPC; importantly, the former are higher grade, more common, and multifocal in individuals with FPC compared with patients with sporadic PC[9].

In this review we emphasize the importance of testing CDKN2A in Italian patients with hereditary PC, even when there is no occurrence of melanoma in the family, in order to improve the accuracy of risk stratification and ensure appropriate selection of patients, which we think may be especially of value in populations with a high CDKN2A mutation rate (Table 3). Identifying high-risk family members is important to understand the biology of PC, to recommend risk reduction strategies and, in some cases, enrollment in cancer surveillance programs. Because the best methods for surveillance have yet to be established and given the overall complexities involved, HRIs and FPCs should be referred to, screened and managed by multidisciplinary teams with specific experience, in the context of research protocols at high-volume centers.

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