Published in final edited form as:
Cancer J. 2012 ; 18(6): 485–491. doi:10.1097/PPO.0b013e318278c4a6.

Inherited Pancreatic Cancer Syndromes

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Abstract

Pancreatic cancer remains one of the most challenging of all cancers. Genetic risk factors are believed to play a major role, but other than genes coding for blood group, genetic risks for sporadic cases remain elusive. However, several germline mutations have been identified that lead to hereditary pancreatic cancer, familial pancreatic cancer and increased risk for pancreatic cancer as part of a familial cancer syndrome. The most important genes with variants increasing risk for pancreatic cancer include *BRCA1, BRCA2, PALB2, ATM, CDKN2A, APC, MLH1, MSH2, MSH6, PMS2, PRSS1 and STK11.* Recognition of members of high-risk families is important for understanding pancreatic cancer biology, for recommending risk reduction strategies and, in some cases, initiating cancer surveillance programs. Because the best methods for surveillance have not been established the recommendation to refer at-risk patients to centers with ongoing research programs in pancreatic cancer surveillance is supported.

Keywords

Pancreatic cancer; genetic risk factors; germline mutations

Pancreatic cancer is a rapidly progressive and usually fatal disorder that has risen to be the 4th leading cause of cancer deaths in the U.S.[1]. Lifetime risk for developing pancreatic cancer is approximately one in 71 individuals, with the majority of cases diagnosed between ages 60 and 80 years[2]. More than a dozen types of pancreatic neoplasms have been classified by the world health organization, but ductal adenocarcinomas comprise nearly 90% of cases and are clearly the most lethal.

Inherited risk factors contribute to at least 5–10% of all pancreatic adenocarcinoma cases[3], but the recognized contribution of genetic risk is likely to rise dramatically as complex risk combinations are recognized. Genetic variants in several genes have been identified as strong dominant risk factors, however, not all cases of inherited pancreatic cancer can be linked to a known gene[4]. Thus, families of pancreatic cancer patients, and other individuals may be at increased risk of pancreatic cancer but no tests are available to determine whether or not these risk factors are present. However, in other cases risk factors have been identified and organs at highest risk of developing malignancies are known.

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Here we review clinical and genetic data on the inherited genetic syndromes associated with pancreatic cancer risk and current medical management options for pancreas surveillance in high risk populations. Further, we discussed allelic variants as they relate to specific patient populations.

Hereditary and Familial Pancreatic Cancers

Germline mutations conferring risk of pancreatic cancer are suggested in kindreds with multiple generations of pancreatic or related cancers, cancer diagnoses under the age of 50, individuals with synchronous and/or metachronous tumors, unusual or rare tumors including tumors more frequent in the opposite gender, and/or families with ethnicity known to have an increased mutation carrier frequency[5]. Furthermore, the presence of pancreatic cancer in a family increases pancreatic cancer risk for relatives regardless of the known gene mutation[3]. Thus, a good family history is critical to the management of pancreatic cancer risk.

Definition of Hereditary and Familial Pancreatic Cancer

Hereditary pancreatic cancer is defined as a genetic syndrome with an identifiable gene mutation associated with an increased risk for pancreatic cancer. Familial Pancreatic Cancer (FPC) is defined as a family with at least one pair of first-degree relatives (parent-child or sibling pair) with pancreatic cancer without an identifiable syndrome in the family[3]. Relatives meeting the FPC criteria have an increased risk over the general population for developing pancreatic cancer (Table 1). These individuals can be further stratified dependent on relationships to the affected relatives. An individual with three or more first-degree relatives with pancreatic cancer in a family meeting the FPC definition carries up to a 17 relative risk (RR) for pancreatic cancer[6]. Further, smoking history exacerbates pancreatic cancer risk in the FPC setting as well as reduces age of onset by up to a decade[7].

Surveillance for Early Pancreatic Cancer in FPC

Currently the best treatment option for pancreatic cancer is surgical excision. Pancreatic cancer metastasizes early and progresses rapidly. Therefore, the only cases that have a reasonable chance for a cure or prolonged survival are ones that are detected as high-risk lesions or very early (<2 cm) isolated tumors. At risk relatives who meet the FPC criteria, warrant pancreatic surveillance[3]. The type, frequency and age to begin surveillance are not yet well defined. Some centers utilize endoscopic ultrasound and/or MRI surveillance programs, both of which detect pancreatic lesions better than CT [8].

Inherited Cancer Syndromes Associated with Pancreatic Cancer (Table 2)

Hereditary Breast-Ovarian Cancer Syndrome (HBOC)

The HBOC Syndrome is an autosomal dominant disorder with increased risks for breast cancer (47–55% by age 70), ovarian cancer (17–39%), and other cancers including prostate, male breast, melanoma and pancreatic cancer. Cancer diagnoses are observed in multiple generations of a family often with diagnoses before age 50[9]. The majority of cases of HBOC are due to mutations in the *BRCA1* or *BRCA2* genes.

The *BRCA1-BRCA2* HBOC is the most common form of inherited breast and ovarian cancer, accounting for 90–95% of inherited breast and ovarian cancers, respectively[10–12]. The incidence of HBOC in the general population is approximately 1 in 500 individuals. Carrier frequency is increased among patients with Ashkenazi (Eastern European) Jewish ethnicity, with 1 in 40 individuals at risk. Specifically, there are three founder mutations in this population: 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*[13].

BRCA1—The *BRCA1* gene, located at 17q21.31 (OMIM: 113705) codes for a protein complex regulating DNA repair, cell cycle checkpoint controls and maintaining genomic stability. Mutations in *BRCA1* are primarily associated with early onset breast and ovarian cancer risks, though other cancer risks do occur at higher rates than expected in the general population including pancreatic cancer. Brose and coworkers[14] reported a relative risk of 2.8 compared to the general population risk of 1.3% for pancreatic cancer in *BRCA1* mutation carriers. In chronic pancreatitis, which is a risk factor for pancreatic cancer, and in pancreatic cancer tumors there is a down-regulation of BRCA1 mRNA and protein[15]. This suggests that BRCA1 may play a role in protecting the pancreas from cancer development. However, Moran and coworkers[16] reported a series of 268 *BRCA1* families, in which increased pancreatic cancer risk was not recognized. Further, Axilbund and coworkers sequenced the *BRCA1* gene in 66 pancreatic cancer patients meeting the FPC definition and did not identify any mutations[17]. Taken together these data suggest that the risk of pancreatic cancer for carriers of BRCA1 mutations is relatively small, and does not warrant inclusion of at-risk subjects in a pancreatic cancer surveillance program.

BRCA2—*BRCA2,* located on 13q13.1 (OMIM #600185), was identified in 1995 as an associated candidate gene in familial breast cancer[18]. The *BRCA2* protein product functions as a tumor suppressor by way of interactions with rad51-dependent DNA repair[19]. *BRCA2* mutations increase breast and ovarian cancers risk, and other cancers including male breast, prostate, melanoma and pancreatic cancer[16]. *BRCA2* mutations are the most common form of inherited pancreatic cancer risk[20]. Kindreds with at least 3 or more cases of pancreatic cancer have a 15–17% chance for carrying a *BRCA2* mutation[21]. Analysis of 222 *BRCA2* families identified a statistically significant increased risk for pancreatic cancer (RR 4.1, 95% CI 1.9–7.8)[16]. The Breast Cancer Linkage Consortium indicated that *BRCA2* mutation carriers have a 3.5 RR compared to non-mutation carriers (5–7% lifetime risk) for developing pancreatic cancer[22]. In a genomic sequencing study of unselected, apparently sporadic pancreatic cancers, 3/41 (7.3%) were found to harbor germline *BRCA2* mutations, none of which had family history of pancreatic cancer, indicating that multiple underlying genetic factors increase the risk for pancreatic cancer.

Animal studies confirm a major role for *BRCA2* in a mouse model of FPC. Feldmann and coworkers[23] developed a double conditional BRCA2 knockout mouse with and without the Trp53 (R172H) deregulating variant. Mice with the *BRCA2* (−/−) background resulted in widespread DNA damage throughout the exocrine pancreatic cells, with development of pancreatic intraepithelial neoplasia (PanIN lesions) in most mice and invasive pancreatic ductal adenocarcinoma in about 15% of mice. Combining *BRCA2* (−/−) and the Trp53 (R172H) variants accelerated carcinogenesis. The authors conclude that loss of BRCA2 function predisposes the exocrine pancreas to profound DNA damage, and the frequency of invasive neoplasia is accentuated by the concomitant deregulation of p53[23]. However, in humans, Brose and coworkers[14] did not see the common loss of *BRCA2* mRNA expression and protein in sporadic tumors as they had seen with BRCA1. Taken together, these data suggest that patients with BRCA2 mutations are at increased risk for pancreatic cancer, but that this pathway is not essential or common in sporadic pancreatic cancers.

The high risk of pancreatic cancer in *BRCA2* warrants consideration for possible surveillance. For reasons that are not yet understood, some large BRCA2 kindreds have multiple cases of pancreatic cancer, while others have none. Therefore, pancreatic surveillance is only recommended for *BRCA2* mutation carriers with a family history of pancreatic cancer. Surveillance may include endoscopic ultrasound or MRI evaluations. Currently there are no formal guidelines for pancreatic cancer surveillance or medical management in the HBOC patient population. However, for other cancers associated with

HBOC, the National Comprehensive Cancer Network set forth aggressive, early onset management guidelines for breast and ovarian cancers.

Familial Pancreatic Cancers associated with the Fanconi Anemia DNA repair pathway

PALB2

The partner and localizer of *BRCA2 (*PALB2*) gene* (OMIM # 610355), was originally identified as a breast cancer susceptibility gene associated within the Fanconi anemia DNA repair pathway (FANCN). Rahman and coworkers[24] identified mono-allelic truncating mutations in 10 out of 923 patients with familial breast cancer indicating a 2.3-fold high risk for breast cancer. In 2009, the first paper was published reporting *PALB2* as a FPC susceptibility gene[25]. Jones and coworkers[25] estimated that approximately 3–4% of FPC families may harbor a mutation in *PALB2*[25]. Analysis of *PALB2* in *BRCA*-negative families identified a 4-fold increased risk for male breast cancer and a 6-fold increased risk for pancreatic cancer in relatives of the mutation carrier [26].

The importance of *PALB2* is yet to be established in larger populations. Recommendations for surveillance have not been established, but individuals from FPC kindreds should be counseled according to the FPC risk, with greater risk assumed if *PALB2* tracks with cancer in the family.

Ataxia Telangiectasia (AT)

ATM

Ataxia Telangiectasia (AT) is a rare autosomal recessive condition characterized by early onset progressive cerebellar ataxia, telangiectasia of the skin, ionizing radiation sensitivity and immunodeficiency. AT presents during the first decade of life in biallelic mutation carriers and these individuals carry a 38% risk for cancer. The gene affected is the ATM gene. Monoallelic mutation carriers harbor cancer risks including breast and pancreas. Female mutation carriers are reported to have an increased risk for breast cancer equal to that of having one first-degree relative with breast cancer[27].

The possible importance of ATM in pancreatic cancer was highlighted in BxPC-3 cells (containing wild type *K-ras*) which were treatment with curcumin[28]. Curcumin resulted in phosphorylation of ATM at Ser-1981, G2/M cell cycle arrest and apoptosis of the tumor cells[28]. This beneficial effect of curcumin was eliminated with SiRNA silencing of ATM.

In a recent analysis of 166 unrelated FPC patients, 2.4% were identified as *ATM* mutation carriers[29]. Further, 4.6% of FPC patients carried an *ATM* mutation if there were more than three cases of pancreatic cancer in their relatives[29]. Analysis of gene function are necessary to elucidate pancreatic cancer relationship to AT.

Genetic counseling and specific medical management is warranted for families with *ATM* mutations, and guidance is available[30]. Pancreatic cancer surveillance is not clearly defined in this population, though patients meeting the FPC definition may consider pancreatic surveillance programs.

Familial Atypical Multiple Mole Melanoma Syndrome

CDKN2A

The Familial Atypical Multiple Mole Melanoma syndrome (FAMMM) is characterized by an increased predisposition toward dysplastic nevus and early onset melanoma in an

autosomal dominant inheritance pattern. *CDKN2A*, a cell cycle regulator gene coding for the p16 protein product, has functional effects in melanoma and pancreatic cancer cell lines, thus implicating it as a potential risk factor for inherited pancreatic cancer risk[31]. Vasen and coworkers[32] determined that a germline founder mutation in a Dutch cohort was associated with up to a 17% lifetime risk for pancreatic cancer in this FAMMM family. In other FPC kindreds, mutations throughout *CDKN2A* have been observed without melanomas[33]. In a series of 120 American non-Hispanic pancreatic cancer cases with a family history of pancreatic cancer, 3.3% carried a *CDKN2A* mutation. Further, the penetrance for developing pancreatic cancer was estimated at 58% by age 80 for mutation carriers.

Medical management is rigorously suggested to begin in childhood due to the rapid and early onset development of atypical nevi. Recommendations include semi-annual dermatology evaluations including baseline photography beginning in childhood as well as pancreatic cancer surveillance consideration. Lifestyle modification includes applying SPF lotions and limiting sun exposure. Pancreatic cancer risk appears to be especially high in smokers[33], and minimizing such exposure is recommended.

Familial Adenomatous Polyposis (FAP)

APC

Familial Adenomatous Polyposis (FAP) syndrome is classically known for the multitude of early onset gastrointestinal adenomas. In this autosomal dominant condition, symptoms present on average at age 16 years[34]. Inherited mutations in the tumor suppressor gene, *APC*, account for the majority of cases. Though the primary cancer risk in FAP is colon cancer, extra-colonic risks including duodenal, thyroid, hepatic and pancreatic cancers exist. Small bowel cancers occur in 50–90% of patients with FAP and are usually periampullary[35]. Hepatoblastoma is observed in early childhood and poses a risk of 1.6%. Thyroid cancers are observed in approximately 2% of patients with FAP. Pancreatic cancer is considered a low risk cancer, though it is observed in FAP families with higher incidence than the general populations. Surveillance for FAP-related cancer include an intensive medical regimen consisting of yearly colonoscopies starting in the second decade until the presence of polyps is too numerous to remove via polypectomy. Total colectomy is recommended for treatment of polyps and prevention of colon cancer. Esophagogastroduodenoscopy (EGD) is recommended starting by age 25 years every one to three years or before colectomy. Extracolonic surveillance includes hepatoblastoma evaluations for pediatric patients and complete physical examination annually[36]. Pancreas surveillance may be considered for such families where pancreatic cancer is present.

Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer)

Lynch syndrome accounts for approximately 2–5% of all colorectal cancers diagnoses and is the most common cause of inherited colon cancer. Substantially increased cancer risks for colon and extra-colonic tumors exist in patients with Lynch syndrome. The lifetime colorectal cancer risk ranges from 52–82% with a mean diagnosis age of 44 years. Other lifetime cancer risks include endometrial cancer (25–60%), ovarian cancer (4–12%), gastric (6–13%) and pancreatic cancer (1.3–4%)[37,38]. Pancreatic cancer was observed in 2 out of 282 cancers diagnosed in a series of 121 families with known germline mutations. While this report identified a low cumulative incidence, others have identified higher risks for Lynch syndrome associated pancreatic cancer. Geary and coworkers[39] identified a 30-fold increased risk for pancreatic cancer before the age of 50 years and an almost nine times as likely overall risk in a cohort of 147 families with Lynch syndrome.

Lynch syndrome tumors arise from germline mutations in mismatch repair genes such as *MLH1, MSH2, MSH6* and *PMS2*. As such, the mismatch repair dysfunction results in loss of protein expression and microsatellite instability (MSI) in tumors. Analysis of tumor tissue may establish or exclude a Lynch syndrome diagnosis. However, approximately 10–15% of sporadic colon tumors display this phenotype, leaving clinicians to utilize family history as a means for risk assessment in some cases. It is anticipated that with the growing practice of universal testing of newly diagnosed colon cancers, many new cases of Lynch syndrome will be diagnosed.

Hereditary Pancreatitis (HP)

PRSS1

While rare, hereditary pancreatitis (HP) is among the only known inherited cancer predisposition syndrome for which pancreatic cancer is the sole cancer risk factor. HP is an inherited form of chronic pancreatitis, in which a subset of families carries gain-of-function mutations in *PRSS1*[43]. Symptom onset begins in the first to second decade of life, though penetrance is estimated at 80%[44]. Recurrent acute pancreatitis attacks develop into chronic pancreatitis and pain leading to pancreas dysfunction, diabetes and pancreatic cancer risk. Rebours et al. described that the pancreatic cancer risk ranges from 18–53% in a French cohort [45].

PRSS1 codes for cationic trypsinogen, a digestive enzyme. Premature activation of trypsin within the pancreas is believed to cause activation of the other digestive enzymes, resulting in pancreatic auto-digestion and chronic inflammation[46]. The incidence of pancreatic cancer in these families increases after 20–40 years of chronic pancreatitis, with earlier onset and higher incidence in smokers and diabetics[47,48]. The importance of inflammation in initiating the epithelial to mesenchymal transition and pancreatic cancer, especially in the presences of *KRAS* G12D mutations has recently been published[49,50].

The challenge with surveillance of HP patients for pancreatic cancer is the gross distortion of the pancreatic architecture by chronic pancreatitis. One option for patients at high risk is total pancreatectomy[51], with or without islet autotransplantation (TPIAT)[52]. With recognition that risk is markedly reduced in non-smokers and in non-diabetics, and that some large HP families have never had a case of pancreatic cancer, caution is required in recommending this irreversible and potentially dangerous procedure.

Peutz-Jeghers Syndrome (PJS)

STK11

Peutz-Jeghers syndrome (PJS) is caused by mutations in *STK11* and presents with mucocutaneous hyperpigmentation and hamartomatous polyposis. Pancreatic cancer risk has been reported as high as a 132-fold risk in patients with PJS[53]. Though a rare syndrome, PJS currently confers the greatest defined inherited risk factor for pancreatic cancer.

Genetic Counseling and Risk Assessment

Patient identification for pancreatic cancer risk stratification due to inherited factors is complex (Table 2). Pedigree analysis, molecular tumor studies and germline mutation testing collectively offer patients the most accurate risk assessment. In addition to the medical complexities, a family history of pancreatic cancer can be emotionally trying for the high risk healthy relative. In a series of high risk family members, Maheu and coworkers [54] evaluated perception of cancer risk and identified that relatives who had increased worry prior to beginning pancreatic cancer surveillance may benefit from a comprehensive risk

assessment and counseling program. Because no consensus guidelines exist for patients at high risk for inherited pancreatic cancer syndromes, clinical judgment and personalized counseling may be considered for this population. At the time of publication, patients meeting the FPC definition or those with known inherited cancer syndromes with a family history pancreatic cancer may consider a pancreatic cancer surveillance program. Thus it is generally recommended that surveillance of these patients only be performed in centers experienced in caring for these high-risk patients, ideally enrolling them into research protocols.

References

1. Lewis ZK, Frost CJ, Venne VL. Pancreatic cancer surveillance among high-risk populations: knowledge and intent. Journal of genetic counseling. 2009; 18:229–238. [PubMed: 19263198]
2. Lillemoe KD, Yeo CJ, Cameron JL. Pancreatic cancer: state-of-the-art care. CA: a cancer journal for clinicians. 2000; 50:241–268. [PubMed: 10986966]
3. Brand RE, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut. 2007; 56:1460–1469. [PubMed: 17872573]
4. Klein AP, et al. Evidence for a major gene influencing risk of pancreatic cancer. Genetic epidemiology. 2002; 23:133–149. [PubMed: 12214307]
5. Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. Journal of the National Cancer Institute. 1998; 90:1039–1071. [PubMed: 9672254]
6. Brune KA, et al. Importance of age of onset in pancreatic cancer kindreds. Journal of the National Cancer Institute. 2010; 102:119–126. [PubMed: 20068195]
7. Rulyak SJ, et al. Risk for the Development of Pancreatic Cancer in Famililal Pancreatic Cancer Kindreds. Gastroenterology. 2003; 124:1292–1299. [PubMed: 12730869]
8. Canto MI, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012; 142:796–804. quiz e714–795. [PubMed: 22245846]
9. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007; 25:1329–1333. [PubMed: 17416853]
10. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer. 1996; 77:2318–2324. [PubMed: 8635102]
11. Pal T, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer. 2005; 104:2807–2816. [PubMed: 16284991]
12. Risch HA, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. American journal of human genetics. 2001; 68:700–710. [PubMed: 11179017]
13. Struewing JP, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. The New England journal of medicine. 1997; 336:1401–1408. [PubMed: 9145676]
14. Brose MS, et al. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. Journal of the National Cancer Institute. 2002; 94:1365–1372. [PubMed: 12237282]
15. Beger C, et al. Down-regulation of BRCA1 in chronic pancreatitis and sporadic pancreatic adenocarcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2004; 10:3780–3787. [PubMed: 15173085]
16. Moran A, et al. Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Familial cancer. 2012; 11:235–242. [PubMed: 22187320]
17. Axilbund JE, et al. Absence of germline BRCA1 mutations in familial pancreatic cancer patients. Cancer biology & therapy. 2009; 8:131–135. [PubMed: 19029836]
18. Wooster R, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995; 378:789–792. [PubMed: 8524414]
19. Sharan SK, et al. Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2. Nature. 1997; 386:804–810. [PubMed: 9126738]

20. Goggins M, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer research. 1996; 56:5360–5364. [PubMed: 8968085]
21. Murphy KM, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer research. 2002; 62:3789–3793. [PubMed: 12097290]
22. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. Journal of the National Cancer Institute. 1999; 91:1310–1316. [PubMed: 10433620]
23. Feldmann G, et al. Inactivation of Brca2 cooperates with Trp53(R172H) to induce invasive pancreatic ductal adenocarcinomas in mice: a mouse model of familial pancreatic cancer. Cancer biology & therapy. 2011; 11:959–968. [PubMed: 21455033]
24. Rahman N, et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nature genetics. 2007; 39:165–167. [PubMed: 17200668]
25. Jones S, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science. 2009; 324:217. [PubMed: 19264984]
26. Casadei S, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer research. 2011; 71:2222–2229. [PubMed: 21285249]
27. Geoffroy-Perez B, et al. Cancer risk in heterozygotes for ataxia-telangiectasia. International journal of cancer Journal international du cancer. 2001; 93:288–293. [PubMed: 11410879]
28. Sahu RP, Batra S, Srivastava SK. Activation of ATM/Chk1 by curcumin causes cell cycle arrest and apoptosis in human pancreatic cancer cells. British journal of cancer. 2009; 100:1425–1433. [PubMed: 19401701]
29. Roberts NJ, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer discovery. 2012; 2:41–46. [PubMed: 22585167]
30. Gatti, R. Ataxia-Telangiectasia. In: Pagon, RA.; Bird, TD.; Dolan, CR.; Stephens, K.; Adam, MP., editors. GeneReviews. Seattle (WA): 1993.
31. Kanda M, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. Gastroenterology. 2012; 142:730–733. e739. [PubMed: 22226782]
32. Vasen HF, et al. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). International journal of cancer Journal international du cancer. 2000; 87:809–811. [PubMed: 10956390]
33. McWilliams RR, et al. Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling. European journal of human genetics : EJHG. 2011; 19:472–478. [PubMed: 21150883]
34. Petersen GM, Slack J, Nakamura Y. Screening guidelines and premorbid diagnosis of familial adenomatous polyposis using linkage. Gastroenterology. 1991; 100:1658–1664. [PubMed: 1673441]
35. Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the Heidelberg Polyposis Register. International journal of colorectal disease. 2001; 16:63–75. [PubMed: 11355321]
36. Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. Gastroenterology. 2001; 121:198–213. [PubMed: 11438509]
37. Barrow E, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. Clinical genetics. 2009; 75:141–149. [PubMed: 19215248]
38. Kastrinos F, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009; 302:1790–1795. [PubMed: 19861671]
39. Geary J, et al. Gene-related cancer spectrum in families with hereditary non-polyposis colorectal cancer (HNPCC). Familial cancer. 2008; 7:163–172. [PubMed: 17939062]
40. Handra-Luca A, Couvelard A, Degott C, Flejou JF. Correlation between patterns of DNA mismatch repair hmlh1 and hmsh2 protein expression and progression of dysplasia in intraductal papillary mucinous neoplasms of the pancreas. Virchows Archiv : an international journal of pathology. 2004; 444:235–238. [PubMed: 14760534]
41. Arnason T, et al. Loss of expression of DNA mismatch repair proteins is rare in pancreatic and small intestinal neuroendocrine tumors. Archives of pathology & laboratory medicine. 2011; 135:1539–1544. [PubMed: 22129180]

42. House MG, et al. Prognostic value of hMLH1 methylation and microsatellite instability in pancreatic endocrine neoplasms. Surgery. 2003; 134:902–908. discussion 909. [PubMed: 14668721]
43. Whitcomb DC, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nature genetics. 1996; 14:141–145. [PubMed: 8841182]
44. Amann ST, Gates LK, Aston CE, Pandya A, Whitcomb DC. Expression and penetrance of the hereditary pancreatitis phenotype in monozygotic twins. Gut. 2001; 48:542–547. [PubMed: 11247900]
45. Rebours V, Levy P, Ruszniewski P. An overview of hereditary pancreatitis. Dig Liver Dis. 2011
46. Whitcomb DC. Genetic aspects of pancreatitis. Annu Rev Med. 2010; 61:413–424. [PubMed: 20059346]
47. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA. 2001; 286:169–170. [PubMed: 11448279]
48. Rebours V, et al. Mortality rate and risk factors in patients with hereditary pancreatitis: uni- and multidimensional analyses. The American journal of gastroenterology. 2009; 104:2312–2317. [PubMed: 19550412]
49. Rhim AD, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012; 148:349–361. [PubMed: 22265420]
50. Daniluk J, et al. An NF-kappaB pathway-mediated positive feedback loop amplifies Ras activity to pathological levels in mice. The Journal of clinical investigation. 2012; 122:1519–1528. [PubMed: 22406536]
51. Ulrich CD II. Pancreatic cancer in hereditary pancreatitis – Consensus guidelines for prevention, screening, and treatment. Pancreatology. 2001; 1:416–422. [PubMed: 12120218]
52. Sutton JM, et al. Total pancreatectomy and islet cell autotransplantation as a means of treating patients with genetically linked pancreatitis. Surgery. 2010; 148:676–685. discussion 685–676. [PubMed: 20846557]
53. Giardiello FM, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000; 119:1447–1453. [PubMed: 11113065]
54. Maheu C, et al. Pancreatic cancer risk counselling and screening: impact on perceived risk and psychological functioning. Familial cancer. 2010; 9:617–624. [PubMed: 20623197]
55. Klein AP, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer research. 2004; 64:2634–2638. [PubMed: 15059921]
56. Ghiorzo P, et al. Contribution of germline mutations in the BRCA and PALB2 genes to pancreatic cancer in Italy. Familial cancer. 2012; 11:41–47. [PubMed: 21989927]
57. Stadler ZK, et al. Prevalence of BRCA1 and BRCA2 mutations in Ashkenazi Jewish families with breast and pancreatic cancer. Cancer. 2012; 118:493–499. [PubMed: 21598239]
58. Ferrone CR, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27:433–438. [PubMed: 19064968]
59. Hahn SA, et al. BRCA2 germline mutations in familial pancreatic carcinoma. Journal of the National Cancer Institute. 2003; 95:214–221. [PubMed: 12569143]
60. Ghiorzo P, et al. CDKN2A is the main susceptibility gene in Italian pancreatic cancer families. Journal of medical genetics. 2012; 49:164–170. [PubMed: 22368299]
61. Bartsch DK, et al. CDKN2A germline mutations in familial pancreatic cancer. Annals of surgery. 2002; 236:730–737. [PubMed: 12454511]
62. Moore PS, et al. Role of disease-causing genes in sporadic pancreatic endocrine tumors: MEN1 and VHL. Genes, chromosomes & cancer. 2001; 32:177–181. [PubMed: 11550286]
63. Park JH, et al. Germline mutations of the MEN1 gene in Korean families with multiple endocrine neoplasia type 1 (MEN1) or MEN1-related disorders. Clinical genetics. 2003; 64:48–53. [PubMed: 12791038]

64. Ohye H, et al. A novel germline mutation of multiple endocrine neoplasia type 1 (MEN1) gene in a Japanese MEN1 patient and her daughter. Endocrine journal. 1999; 46:325–329. [PubMed: 10460018]

65. Bartsch D, et al. MEN1 gene mutations in 12 MEN1 families and their associated tumors. European journal of endocrinology/European Federation of Endocrine Societies. 1998; 139:416–420. [PubMed: 9820618]

66. Gargiulo S, et al. Germline MLH1 and MSH2 mutations in Italian pancreatic cancer patients with suspected Lynch syndrome. Familial cancer. 2009; 8:547–553. [PubMed: 19728162]

67. Lindor NM, et al. Pancreatic cancer and a novel MSH2 germline alteration. Pancreas. 2011; 40:1138–1140. [PubMed: 21926548]

68. Banville N, et al. Medullary carcinoma of the pancreas in a man with hereditary nonpolyposis colorectal cancer due to a mutation of the MSH2 mismatch repair gene. Human pathology. 2006; 37:1498–1502. [PubMed: 16996571]

69. Slater EP, et al. PALB2 mutations in European familial pancreatic cancer families. Clinical genetics. 2010; 78:490–494. [PubMed: 20412113]

70. Tischkowitz MD, et al. Analysis of the gene coding for the BRCA2-interacting protein PALB2 in familial and sporadic pancreatic cancer. Gastroenterology. 2009; 137:1183–1186. [PubMed: 19635604]

71. Gorry MC, et al. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology. 1997; 113:1063–1068. [PubMed: 9322498]

Table 1

Pancreatic Cancer Risk in FPC Families

Number First Degree Relatives with Pancreatic Cancer	Risk for Developing Pancreatic Cancer
0	1–2%
1	4–6%
2	4–7%
3+	17–32%

Based on Klein [55] and Brune [6].

Table 2

Gene	Mutation	Reference	Type of population
ATM	c.8266A>AT p.K2756X (only confirmed germline mutation) c.170G>GA p.W57X c.3214G>GT p.E1072X c.6095G>GA p.R2032K IVS41-1G>GT c.3801delG	Roberts 2012[29]	US Caucasian
BRCA1	c.514delC p. Gln172AsnfsX62 c.1687C>T p.Gln563Stop c.3756_3759delGTCT p.Ser253ArgfsX10 c.5030_5033delCTAA p.Thr1677IlefsX2	Ghierzo 2012[56]	Italian
	185delAG 5382insC	Stadler 2012[57] Ferrone 2009[58]	Ashkenazi Jews
BRCA2	c.514delC p.Gln172AsnfsX62 c.5796_5797delTA p.His1932GlnfsX12 c.6468_6469delTC p.Glu2157IlefsX18	Ghierzo 2012[56]	Italian
	6174delT	Stadler 2012[57] Ferrone 2009[58] Murphy 2002[21] Goggins 1996[20]	Ashkenaji Jews US Caucasian
	6672insT 6819delTG 4075delGT R2034C G3076E 10323delCins11	Hahn 2003[59]	German/European
	IVS 16-2A>G (splice acceptor site of intron 16) IVS 15-1G>A (splice donor site of intron 15) M192T K3326X	Murphy 2002[21]	US Caucasian Ashkenaji Jews
	2458insT	Goggins 1996[20]	N/A
CDKN2A/p16	p.E27X p.L65P c.201 ACTC>CTTT (promoter) p.G67R p.R144C p.G101W p.E27X	Ghierzo 2012[60]	Italian
	−34G>T (initiation codon) c.47T>G p.L16R c.71G>C p.R24P c.192G>C L64L c.238_251del p.R80fs c.283del p.V95fs c.318G>A p.V106V c.457G>T D183spl	McWilliams 2011[33]	US Caucasian
	c.324T>A p.V95E c.482G>A p.A148T c.323_324insG p.E119X	Bartsch 2002[61]	German
MEN1	c.304G>T p.R102S c.723 to 724 del 320 CCC to C 68 CCC to CC 179 GAG to GTG c.249–252 del c.183G>A p.W61X c.196G>T p.V66F c.482delG	Moore 2001[62]	Italian
	c.1213C>T p.Q405X c.969C>A p.Y323X	Park 2003[63]	Korean

Gene	Mutation	Reference	Type of population
	c.973G>C p.A325P 210–211insAGCCC		
	c.712delA p.K201R	Ohye 1999[64]	Japanese
	c.CCT>CCGG, p.55fs64aaX c.GAG>AAG, p.E26K c.AGC>AAAC p. 66fs50aaX c. CGG>CAG p.R171Q c.CTG>CCG p.L168P c.GTG>GTTG p.236 fs12aaX c.TAT>TAG p.T268X c.GCC>CC p.437 fs15aaX c.GCA>G p.510fs19aaX c.CCG>GG p.493fs65aaX	Bartsch 1998[65]	German
MLH1	K618A	Garguilo 2009[66]	Italian
MSH2	Q402X G322D E205Q V367I	Garguilo 2009[66]	Italian
	c.1046C>T p.P349L	Lindor2011[67]	Northern European
	c.1147C>T p.R383X	Banville2006[68]	Ireland
PALB2	c.1240C>T p.R414X c.508-9delAG p.R170I,183X c.3116delA, p.N1039fs	Slater 2010[69]	European including German, UK, Latvian, Italian, Greek, Hungarian and Spanish
	heterozygous 6.7kb deletion of exon 12 & 13	Tischkowitz2009[70]	Canadian
	c. 172-5delTTGT	Jones et al. 2009 [25]	US Caucasian
PRSS1	p.N29I p.R22H	Gorry 1997 [71] Whitcomb 1996 [43]	US Caucasian -do-