Genetic Testing by Cancer Site

Pancreas

Jennifer E. Axilbund, MS and Elizabeth A. Wiley, MS

Abstract: It is estimated that 5% to 10% of pancreatic cancer is familial. Although there is evidence of a major pancreatic cancer susceptibility gene, the majority of families with multiple cases of pancreatic cancer do not have an identifiable causative gene or syndrome. However, a subset of pancreatic cancer is attributable to known inherited cancer predisposition syndromes, including several hereditary breast cancer genes (*BRCA1*, *BRCA2*, and *PALB2*), *CDKN2A*, hereditary pancreatitis, hereditary nonpolyposis colorectal cancer, and Peutz-Jeghers syndrome. In addition to explaining a proportion of familial pancreatic cancer, individuals with these conditions are at increased risk for pancreatic cancer. Relatives from familial pancreatic cancer kindreds without one of these identifiable syndromes may have as high as a 32-fold risk of pancreatic cancer, depending on the number of affected first-degree relatives. Such high-risk individuals may benefit from increased surveillance, and strategies for early detection of pancreatic cancer are under evaluation.

Key Words: Pancreatic cancer, genetics, hereditary syndrome, familial cancer

(*Cancer J* 2012;18: 350–354)

It is estimated that 5% to 10% of pancreatic cancer (adenocarcinoma) is familial,[1,2] and individuals with a family history of pancreatic cancer are at greater risk of developing pancreatic cancer, themselves.[3] Although there is evidence of a major pancreatic cancer susceptibility gene,[4] it remains elusive. Therefore, the majority of families with multiple cases of pancreatic cancer do not have an identifiable causative gene or syndrome, making risk assessment and counseling challenging. However, a subset of pancreatic cancer is attributable to known inherited cancer predisposition syndromes (Table 1).

BRCA2

The *BRCA2* gene is associated with hereditary breast and ovarian cancer syndrome and often presents as premenopausal breast cancer, ovarian cancer, and/or male breast cancer. The Breast Cancer Linkage Consortium[5] reported a 3.5-fold (95% confidence interval [CI], 1.9–6.6) increased risk of pancreatic cancer in *BRCA2* gene mutation carriers. Subsequent studies in the United Kingdom and the Netherlands showed a relative risk of 4.1 and 5.9, respectively.[6,7] In a United States–based study, 10.9% (17/156) of families with a *BRCA2* mutation reported a family history of pancreatic cancer. The median ages at diagnosis for males and females were 67 and 59 years, respectively, which differed statistically from the SEER (Surveillance, Epidemiology and End Results) database (70 years old for males and 74 years old for females; $P = 0.011$).[8] Although genotype-phenotype data remain sparse, the *BRCA2* K3326X variant was found in 5.6% (8/144) of familial pancreatic cancer patients compared with 1.2% (3/250) of those with sporadic pancreatic cancer (odds ratio [OR], 4.84; 95% CI, 1.27–18.55; $P < 0.01$).[9]

Approximately 17% of pancreatic cancer patients who have at least 2 additional relatives with pancreatic cancer carry deleterious mutations in the *BRCA2* gene.[10] Estimates for the prevalence of *BRCA2* mutations with 2 first-degree relatives with pancreatic cancer are 6% to 12%,[11,12] and *BRCA2* mutations also explain a portion of apparently sporadic pancreatic cancers.[13] However, prevalence varies between populations. Six (4.1%) of 145 of Ashkenazi Jews with pancreatic cancer were found to have a deleterious *BRCA2* mutation when compared with cancer-free controls (OR, 3.85; 95% CI, 2.1–10.8; $P = 0.007$), although no differences were noted in age at diagnosis or clinical pathological features.[14] An earlier, smaller study found a deleterious *BRCA2* mutation in 3 (13%) of 23 Ashkenazi Jews with pancreatic cancer, unselected for family history.[15] Among Ashkenazi Jewish probands with breast cancer who reported a family history of pancreatic cancer, 7.6% (16/211) had a *BRCA2* mutation.[16] By comparison, no *BRCA2* mutations were found in studies of pancreatic cancer in Korea or Italy.[17,18]

BRCA1

Similar to *BRCA2*, mutations in *BRCA1* are associated with markedly increased risk for premenopausal breast cancer and ovarian cancer. The Breast Cancer Linkage Consortium reported a 2.26-fold (95% CI, 1.26–4.06) increased risk of pancreatic cancer in families with a *BRCA1* mutation,[19] and Brose and colleagues[20] estimated a 3-fold higher lifetime risk. However, more recently, Moran and colleagues[6] in the United Kingdom found no elevation in pancreatic cancer risk in 268 families with a known *BRCA1* mutation. A United States–based study reported that 11% (24/219) of their families with a *BRCA1* mutation had at least 1 individual with pancreatic cancer, with median ages at diagnosis of 59 years for males and 68 years for females. Again, this was significantly younger than reported in the SEER database ($P = 0.0014$).[8] Molecularly, Al-Sukhni et al[21] evaluated pancreatic tumors from 7 known *BRCA1* mutation carriers and found loss of heterozygosity of *BRCA1* in 5 (71%), with confirmed loss of the wild-type allele in 3 of the 5 compared with only 1 (11%) of 9 sporadic controls. This suggests that *BRCA1* germline mutations do, in fact, predispose to pancreatic cancers in at least some individuals.

Familial breast cancer registries in the United States and Israel have evaluated the mutation status of families that reported pancreatic cancer in addition to breast cancer and ovarian cancer. In the US study, of 19 families with breast, ovarian, and pancreatic cancer, 15 carried a deleterious mutation in *BRCA1* and 4 in *BRCA2*,[22] whereas the Israeli study reported an equal number of *BRCA1* and *BRCA2* families.[23] Another study, specifically of Ashkenazi Jewish families, reported a *BRCA1* mutation in 7% of probands with breast

From the Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, MD.

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Reprints: Jennifer E. Axilbund, MS, The Johns Hopkins School of Medicine, 550 North Broadway, Suite 410, Baltimore, MD 21205. E-mail: axilbund@jhmi.edu.

ISSN: 1528-9117

TABLE 1. Inherited Cancer Predisposition Syndromes That Increase the Risk for Pancreatic Cancer

Syndrome	Gene(s)	Risk of PC	Predominant Features
Hereditary breast and ovarian cancer	*BRCA1*	RR, 2.26–3.0	Malignancies: breast (particularly premenopausal), ovary, male breast, prostate
	BRCA2	RR, 3.5–5.9	Malignancies: breast (particularly premenopausal), ovary, male breast, prostate, melanoma (cutaneous and ocular)
Familial atypical multiple mole and melanoma	*CDKN2A*	RR, 7.4–47.8	Malignancies: melanoma (often multiple and early onset) Other: dysplastic nevi
Hereditary pancreatitis	*PRSS1*	SIR, 57	Other: chronic pancreatitis
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	*MLH1* *MSH2* *MSH6* *PMS2* *EPCAM*	SIR, 0–8.6	Malignancies: colorectum, endometrium, ovary, stomach, small bowel, urinary tract (ureter, renal pelvis), biliary, brain (glioblastoma), skin (sebaceous)
PJS	*STK11*	SIR, 132	Malignancies: colorectum, small bowel, stomach, breast, gynecological Other: melanin pigmentation (mucocutaneous), small-bowel intussusception

SIR indicates standardized incidence ratio; RR, relative risk.

cancer who also had a family history of pancreatic cancer,[16] which was, again, equal to the prevalence of *BRCA2* mutations. Thus, within the Ashkenazi Jewish population, *BRCA1* and *BRCA2* mutations may contribute more equally to risk in families with both breast and pancreatic cancer. However, these studies all examined cohorts of families selected because of clustering of breast and/or ovarian cancer with pancreatic cancer. When families were selected on the basis of familial pancreatic cancer, alone, *BRCA1* mutations were less prevalent. Zero of 66 families with 3 or more cases of pancreatic cancer had a deleterious *BRCA1* mutation, including those who also reported a family history of breast and/or ovarian cancer.[24] Evaluation of Ashkenazi Jewish patients ascertained on the basis of pancreatic cancer, alone, showed a 1.3% (2/145) prevalence of *BRCA1* mutations.[14] Therefore, *BRCA1* may explain a small subset of families showing a clustering of pancreatic cancer with breast and/or ovarian cancer, but is unlikely to explain most families with site-specific pancreatic cancer.

PALB2

PALB2 (partner and localizer of *BRCA2*) was recognized as the *FANCN* gene in 2007, and biallelic mutation carriers develop Fanconi anemia.[25,26] Monoallelic mutation carriers were shown to be at increased risk for breast cancer (relative risk [RR], 2.3; 95% CI, 1.4–3.9).[27] Prevalence of *PALB2* mutations among familial breast cancer cases is low across ethnicities; *PALB2* mutations are relatively nonexistent in breast cancers in the Irish and Icelandic populations and are found in approximately 1% of Italians, US African Americans, Chinese, and Spanish breast cancer families and in 2% of young South African breast cancer patients.[28–35] Analysis of 1144 US familial breast cancer cases found a *PALB2* mutation in 3.4% (33/972) of non-Ashkenazi Jews and none (0/172) of Ashkenazi Jews. The estimated risk for breast cancer was 2.3-fold by age 55 years (95% CI, 1.5–4.2) and 3.4-fold by age 85 years (95% CI, 2.4–5.9). There was also a 4-fold risk for male breast cancer ($P = 0.0003$) and a 6-fold risk for pancreatic cancer ($P = 0.002$).[36] Among French Canadian woman with bilateral breast cancer, a *PALB2* mutation was found in 0.9% (5/559) compared with none of 565 women with unilateral breast cancer ($P = 0.04$), and first-degree relatives of *PALB2* mutation carriers had a 5.3-fold risk for breast cancer (95% CI, 1.8–13.2).[37]

PALB2 founder mutations have been identified in several populations, including the c.2323 C>T (Q775X) mutation in French Canadians.[38] Another example is the Finnish founder mutation c.1592delT. This mutation was found in 2.7% (3/113) of familial breast and/or breast/ovarian cancer families compared with 0.2% (6/2501) of controls (OR, 11.3; 95% CI, 1.8–57.8; $P = 0.005$).[39] One percent (18/1918) of breast cancer cases, unselected for family history, also had this founder mutation. The hazard ratio for breast cancer was estimated at 6.1 (95% CI, 2.2–17.2; $P = 0.01$), with a penetrance of 40% by age 70 years.[40]

PALB2 has not been shown to be a significant contributor to familial clustering of other cancers, including melanoma, ovarian cancer, and prostate cancer,[41–43] but has been identified in familial pancreatic cancer kindreds. Specifically, Jones et al[44] identified a *PALB2* mutation in a familial pancreatic cancer proband, and subsequently found *PALB2* mutations in 3 of 96 additional families, suggesting that 3% to 4% of familial pancreatic cancer may be attributed to this gene. Other populations have found lower mutation frequencies, ranging from absent in Dutch (0/31) to 3.7% (3/81) in Germans.[45,46] When ascertained on the basis of co-occurrence of breast and pancreatic cancer in the same individual or family, prevalence varied, again, from absent in Dutch (0/45) and United States–based studies (0/77) to 4.8% (3/62) in Italians.[42,47,48]

CDKN2A

The p16 transcript of the *CDKN2A* gene is an important cell cycle regulator. Germline mutations in the *CDKN2A* gene predispose to multiple early-onset melanomas. Somatic *CDKN2A* mutations are also frequently identified in pancreatic adenocarcinomas and precursor lesions, indicating a role for this gene in pancreatic cancer development and progression.[49–51]

The risk of pancreatic cancer with *CDKN2A* mutations varies based on genotype. In a study of 22 families with the Dutch founder mutation, p16-Leiden, which is a 19-base-pair

deletion in exon 2, the relative risk of pancreatic cancer was 47.8 (95% CI, 28.4–74.7).[52] The age-related risks have been shown to be less than 1%, 4%, 5%, 12%, and 17% by ages 40, 50, 60, 70, and 75 years, respectively.[53] Regarding other mutations, the Genes, Environment and Melanoma study assessed relative risks for nonmelanoma cancers in 429 first-degree relatives of 65 melanoma patients with a *CDKN2A* mutation. Five pancreatic cancers were reported compared with 41 pancreatic cancers among 23,452 first-degree relatives of 3,537 noncarriers, for a relative risk of 7.4 (95% CI, 2.3–18.7; $P = 0.002$).[54] A United States–based study estimated penetrance to be 58% by age 80 years (95% CI, 8%–86%) and noted a hazard ratio of 25.8 ($P = 2.1 \times 10^{-13}$) in those who ever smoked cigarettes.[55]

Mutation prevalence in pancreatic cancer families varies by population. In an Italian study, 5.7% of 225 consecutive patients with pancreatic cancer had an identified *CDKN2A* mutation.[56] The predominant mutations were the E27X and G101W founder mutations, although others were also represented. Five (31%) of 16 patients classified as having familial pancreatic cancer carried *CDKN2A* mutations, leading the authors to conclude that this gene may account for a sizeable subset of Italian familial pancreatic families. By comparison, no *CDKN2A* mutations were found in 51 Polish pancreatic cancer patients diagnosed at younger than 50 years.[57] Similarly, analysis of 94 German pancreatic cancer patients, who had at least 1 other first-degree relative with pancreatic cancer, revealed no *CDKN2A* mutations.[58] However, 2 of 5 families with at least 1 pancreatic cancer and at least 1 melanoma had an identified mutation.[59] Similarly, a Canadian study found a *CDKN2A* mutation in 2 of 14 families with both pancreatic cancer and melanoma.[60] Finally, a United States–based study found 9 *CDKN2A* mutations in an unselected series of 1537 pancreatic cancer cases (0.6%). The prevalence increased to 3.3% and 5.3% for those who reported a first-degree relative with pancreatic cancer or melanoma, respectively.[55] Thus, in the majority of populations, co-occurrence of melanoma appears to be a significant indicator of an underlying *CDKN2A* mutation.

Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer (HNPCC), also referred to as Lynch syndrome, is the most common form of hereditary colon cancer, and it accounts for 2% to 5% of colorectal cancers. In addition to a high lifetime risk for colorectal cancer, affected individuals are at increased risk for multiple other cancers. Hereditary nonpolyposis colorectal cancer results from mutations in mismatch repair (MMR) genes, and colon cancers that arise in Lynch syndrome typically demonstrate microsatellite instability (MSI). Four percent of all pancreatic adenocarcinomas demonstrate MSI.[61] Yamamoto and colleagues[62] assessed tumor characteristics in 3 *MLH1* mutation carriers with both colon and pancreatic cancer and found that both tumor types had similar properties, including high MSI, loss of MLH1 protein expression, wild-type *K-RAS* and *p53*, and poor differentiation. These findings support an inherited basis for the development of both types of cancer.[62]

Pancreatic cancer has been described in HNPCC kindreds as early as 1985, although data regarding risk of pancreatic cancer in HNPCC have varied.[63–68] Barrow and colleagues[64] studied 121 families with known MMR mutations; 2 of 282 extracolonic cancers were pancreatic, leading to a 0.4% cumulative lifetime risk for pancreatic cancer (95% CI, 0%–0.8%). By comparison, Geary et al[65] studied 130 families with MMR mutations and found 22 cases of pancreatic cancer, half of which were in confirmed or in obligate carriers. Pancreatic cancer in these families was 7 times more common than expected, and the familial relative risk was 3.8 ($P = 0.02$). In addition, these tumors were 15 times more common in individuals younger than 60 years, suggesting an earlier average age at diagnosis as compared with the general population.[65] Another United States–based study of HNPCC families found the lifetime risk for pancreatic cancer to be 1.31% by age 50 years (95% CI, 0.31%–2.32%) and 3.68% by age 70 years (95% CI, 1.45%–5.88%). These risks are higher than those from the SEER data of 0.04% and 0.52% at ages 50 and 70 years, respectively.[66]

Regarding the prevalence of HNPCC in pancreatic cancer, Gargiulo and colleagues[69] assessed 135 pancreatic cancer patients. Nineteen of these patients had a family history that was suggestive of HNPCC, and of the 11 patients whose DNA was available for analysis, only 1 deleterious MMR mutation was found. Thus, MMR mutations presumably account for only a small proportion of pancreatic cancer patients.

Hereditary Pancreatitis

Hereditary pancreatitis (HP) is rare form of chronic pancreatitis. Several genes have been linked to chronic pancreatitis, including *SPINK1*, *CTFR*, and *CTRC*, but the *PRSS1* gene on chromosome 7q35 accounts for the majority of hereditary cases. *PRSS1* mutations are inherited in an autosomal dominant fashion and have an 80% penetrance for pancreatitis. Affected individuals begin experiencing symptoms of pancreatic pain and acute pancreatitis early in life. Several studies have shown an increase in pancreatic cancer risk associated with HP, and cumulative lifetime risk estimates range from 18.8% to 53.5%.[70–72] Lowenfels et al[71] observed an increased risk associated with paternal inheritance. Tobacco use in patients with HP has been shown to increase the risk for pancreatic cancer 2-fold (95% CI, 0.7–6.1), pancreatic and HP patients who smoke developed cancer 20 years earlier than did their nonsmoking counterparts.[73]

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition characterized by mucocutaneous pigmentation and hamartomatous polyps of the gastrointestinal tract. Peutz-Jeghers syndrome is caused by mutations on the *STK11* (*LKB1*) gene. The lifetime risk to develop any cancer has been estimated to be as high as 93%,[74] with no sex difference in cancer risk noted.[74,75] Risk for pancreatic cancer in PJS is estimated to be 8% to 36% by age 70 years.[74–76] Grützmann et al[77] analyzed 39 individuals with familial pancreatic cancer, and none were found to carry mutations in *STK11*. In 2011, Schneider and colleagues[58] confirmed these findings in their study of 94 familial pancreatic cancer kindreds. Therefore, although *STK11* mutations confer a high lifetime risk for pancreatic cancer in individuals with PJS, germline *STK11* mutations are not thought to account for hereditary pancreatic cancer.

TABLE 2. Risk of Pancreatic Cancer in Familial Pancreatic Cancer Kindreds Based on Number of Affected First-Degree Relatives (FDRs)

No. Affected FDRs	SIR (95% CI)
1	4.5 (0.54–16.3)
2	6.4 (1.8–16.4)
3	32 (10.4–74.7)

Empiric Risk Counseling and Management

Having a first-degree relative with apparently sporadic pancreatic cancer has a moderate effect on risk (OR, 1.76; 95% CI, 1.19–2.61).[78] In familial pancreatic cancer kindreds (defined as a family with a pair of affected first-degree relatives), the risk of pancreatic cancer increases with the number of affected first-degree relatives[3] (Table 2.) These findings suggest that high-penetrance genes may be causing the clustering of pancreatic cancer in families with 2 or 3 pancreatic cancer cases. Thus, individuals with multiple affected first-degree relatives are at appreciably increased risk for pancreatic cancer and may be candidates for increased surveillance.

Ideally, high-risk patients would be able to undergo noninvasive, inexpensive pancreatic cancer screening; however, to date, a highly sensitive and specific method for pancreas surveillance has not been recognized. Screening of high-risk patients with endoscopic ultrasound, magnetic resonance imaging, and/or magnetic resonance cholangiopancreaticogram has been shown to be effective at identifying early neoplasms, both benign and malignant.[79–82] However, it is unknown if these methods actually prevent pancreatic cancer or improve overall survival by detecting presymptomatic disease. In addition, there is great interest in developing a biomarker for premalignant or early-stage disease, although none, including CA-19-9, has been proven effective.[83] Thus, whenever possible, it is recommended that high-risk patients undergo pancreatic screening through a research study.

REFERENCES

1. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. *Semin Oncol*. 1996;23:251–275.
2. Klein AP, Hruban RH, Brune KA, et al. Familial pancreatic cancer. *Cancer J.* 2001;7:266–273.
3. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res*. 2004;64:2634–2638.
4. Klein AP, Beaty TH, Bailey–WilsonJE, et al. Evidence for a major gene influencing risk of pancreatic cancer. *Genet Epidemiol*. 2002;23:133–149.
5. The Breast Cancer Linkage Consortium. Cancer risks in *BRCA2* mutation carriers. *J Natl Cancer Inst*. 1999;91:1310–1316.
6. Moran A, O'Hara C, Khan S, et al. Risk of cancer other than breast or ovarian in individuals with *BRCA1* and *BRCA2* mutations [published online ahead of print December 21, 2011]. *Fam Cancer.*
7. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in *BRCA2* families: estimates for sites other than breast and ovary. *J Med Genet*. 2005;42:711–719.
8. Kim DH, Crawford B, Ziegler J, et al. Prevalence and characteristics of pancreatic cancer in families with *BRCA1* and *BRCA2* mutations. *Fam Cancer*. 2009;8:153–158.
9. Martin ST, Matsubayashi H, Rogers CD, et al. Increased prevalence of the *BRCA2* polymorphic stop codon K3326X among individuals with familial pancreatic cancer. *Oncogene*. 2005;24:3652–3656.
10. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and *BRCA2* in familial pancreatic cancer: deleterious *BRCA2* mutations in 17%. *Cancer Res*. 2002;62:3789–3793.
11. Hahn SA, Greenhalf B, Ellis I, et al. *BRCA2* germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst*. 2003;95:214–221.
12. Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of *BRCA2* mutations in familial pancreatic cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16:342–346.
13. Goggins M, Schutte M, Lu J, et al. Germline *BRCA2* gene mutations in patients with apparently sporadic pancreatic carcinomas. *Cancer Res*. 1996;56:5360–5364.
14. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. *J Clin Oncol*. 2009;27: 433–438.
15. Figer A, Irmin L, Geva R, et al. The rate of the 6174delT founder Jewish mutation in *BRCA2* in patients with non-colonic gastrointestinal tract tumours in Israel. *Br J Cancer*. 2001;84:478–481.
16. Stadler ZK, Salo-Mullen E, Patil SM, et al. Prevalence of *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish families with breast and pancreatic cancer. *Cancer*. 2012;118:493–499.
17. Cho JH, Bang S, Park SW, et al. *BRCA2* mutations as a universal risk factor for pancreatic cancer has a limited role in Korean ethnic group. *Pancreas*. 2008;36:337–340.
18. Ghiorzo P, Pensotti V, Fornarini G, et al. Contribution of germline mutations in the BRCA and *PALB2* genes to pancreatic cancer in Italy. *Fam Cancer*. 2012;11:41–47.
19. Thompson D, Easton DF. Cancer Incidence in *BRCA1* mutation carriers. *J Natl Cancer Inst*. 2002;94:1358–1365.
20. Brose MS, Rebbeck TR, Calzone KA, et al. Cancer risk estimates for *BRCA1* mutation carriers identified in a risk evaluation program. *J Natl Cancer Inst*. 2002;94:1365–1372.
21. Al-Sukhni W, Rothenmund H, Borgida AE, et al. Germline *BRCA1* mutations predispose to pancreatic adenocarcinoma. *Hum Genet*. 2008;124:271–278.
22. Lynch HT, Deters CA, Snyder CL, et al. *BRCA1* and pancreatic cancer: pedigree findings and their causal relationships. *Cancer Genet Cytogenet*. 2005;158:119–125.
23. Danes BS, Lynch HT. A familial aggregation of pancreatic cancer. An in vitro study. *JAMA*. 1982;247:2798–2802.
24. Axilbund JE, Argani P, Kamiyama M, et al. Absence of germline *BRCA1* mutations in familial pancreatic cancer patients. *Cancer Biol Ther*. 2009;8:131–135.
25. Reid S, Schindler D, Hanenberg H, et al. Biallelic mutations in *PALB2* cause Fanconi anemia subtype FA-N and predispose to childhood cancer. *Nat Genet*. 2007;39:162–164.
26. Xia B, Dorsman JC, Ameziane N, et al. Fanconi anemia is associated with a defect in the *BRCA2* partner *PALB2*. *Nat Genet*. 2007;39:159–161.
27. Rahman N, Seal S, Thompson D, et al. *PALB2*, which encodes a *BRCA2*-interacting protein, is a breast cancer susceptibility gene. *Nat Genet*. 2007;39:165–167.
28. McInerney NM, Miller N, Rowan A, et al. Evaluation of variants in the CHEK2, BRIP1 and *PALB2* genes in an Irish breast cancer cohort. *Breast Cancer Res Treat*. 2010;121:203–210.
29. Gunnarsson H, Arason A, Gillanders EM, et al. Evidence against *PALB2* involvement in Icelandic breast cancer susceptibility. *J Negat Results Biomed*. 2008;7:5.
30. Papi L, Putignano AL, Congregati C, et al. A *PALB2* germline mutation associated with hereditary breast cancer in Italy. *Fam Cancer*. 2010;9:181–185.
31. Ding YC, Steele L, Chu LH, et al. Germline mutations in *PALB2* in African-American breast cancer cases. *Breast Cancer Res Treat*. 2011; 126:227–230.
32. Zheng Y, Zhang J, Niu Q, et al. Novel germline *PALB2* truncating mutations in African American breast cancer patients. *Cancer*. 2012;118:1362–1370.
33. Cao AY, Huang J, Hu Z, et al. The prevalence of *PALB2* germline mutations in *BRCA1*/*BRCA2* negative Chinese women with early onset breast cancer or affected relatives. *Breast Cancer Res Treat*. 2009;114:457–462.
34. Blanco A, de la Hoya M, Balmaña J, et al. Detection of a large rearrangement in *PALB2* in Spanish breast cancer families with male breast cancer. *Breast Cancer Res Treat*. 2012;132:307–315.
35. Sluiter M, Mew S, van Rensburg EJ. *PALB2* sequence variants in young South African breast cancer patients. *Fam Cancer*. 2009;8:347–353.
36. Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the *BRCA2*-interacting protein *PALB2* to familial breast cancer. *Cancer Res*. 2011;71:2222–2229.
37. Tischkowitz M, Capanu M, Sabbaghian N, et al. Rare germline mutations in *PALB2* and breast cancer risk: a population-based study. *Hum Mutat*. 2012;33:674–680.
38. Foulkes WD, Ghadirian P, Akbari MR, et al. Identification of a novel truncating *PALB2* mutation and analysis of its contribution to early-onset breast cancer in French-Canadian women. *Breast Cancer Res*. 2007;9:R83.

39. Erkko H, Xia B, Nikkilä J, et al. A recurrent mutation in *PALB2* in Finnish cancer families. *Nature*. 2007;446:316–319.
40. Erkko H, Dowty JG, Nikkilä J, et al. Penetrance analysis of the *PALB2* c.1592delT founder mutation. *Clin Cancer Res*. 2008;14:4667–4671.
41. Sabbaghian N, Kyle R, Hao A, et al. Mutation analysis of the *PALB2* cancer predisposition gene in familial melanoma. *Fam Cancer*. 2011;10: 315–317.
42. Adank MA, van Mil SE, Gille JJ, et al. *PALB2* analysis in *BRCA2*-like families. *Breast Cancer Res Treat*. 2011;127:357–362.
43. Tischkowitz M, Sabbaghian N, Ray AM, et al. Analysis of the gene coding for the *BRCA2*-interacting protein *PALB2* in hereditary prostate cancer. *Prostate*. 2008;68:675–678.
44. Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies *PALB2* as a pancreatic cancer susceptibility gene. *Science*. 2009;324:217.
45. Harinck F, Kluijt I, van Mil SE, et al. Routine testing for *PALB2* mutations in familial pancreatic cancer families and breast cancer families with pancreatic cancer is not indicated. *Eur J Hum Genet*. 2012;20: 577–579.
46. Slater EP, Langer P, Niemczyk E, et al. *PALB2* mutations in European familial pancreatic cancer families. *Clin Genet*. 2010;78:490–494.
47. Stadler ZK, Salo-Mullen E, Sabbaghian N, et al. Germline *PALB2* mutation analysis in breast-pancreas cancer families [published online ahead of print March 17, 2011]. *J Med Genet*. 2011;48:523–525.
48. Peterlongo P, Catucci I, Pasquini G, et al. *PALB2* germline mutations in familial breast cancer cases with personal and family history of pancreatic cancer. *Breast Cancer Res Treat*. 2011;126:825–828.
49. Kanda M, Matthaei H, Wu J, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. *Gastroenterology*. 2012;142:730–733.
50. Remmers N, Bailey JM, Mohr AM, et al. Molecular pathology of early pancreatic cancer. *Cancer Biomark*. 2011;9:421–440.
51. Bartsch D, Shevlin DW, Tung WS, et al. Frequent mutations of CDKN2 in primary pancreatic adenocarcinomas. *Genes Chromosomes Cancer*. 1995;14:189–195.
52. de Snoo FA, Bishop DT, Bergman W, et al. Increased risk of cancer other than melanoma in *CDKN2A* founder mutation (p16-Leiden)–positive melanoma families. *Clin Cancer Res*. 2008;14:7151–7157.
53. Vasen HF, Gruis NA, Frants RR, 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). *Int J Cancer*. 2000;87: 809–811.
54. Mukherjee B, Delancey JO, Raskin L, et al. Risk of non-melanoma cancers in first-degree relatives of *CDKN2A* mutation carriers [published online ahead of print April 24, 2012]. *J Natl Cancer Inst*. 2012.
55. McWilliams RR, Wieben ED, Rabe KG, et al. Prevalence of *CDKN2A* mutations in pancreatic cancer patients: implications for genetic counseling. *Eur J Hum Genet*. 2011;19:472–478.
56. Ghiorzo P, Fornarini G, Sciallero S, et al. *CDKN2A* is the main susceptibility gene in Italian pancreatic cancer families. *J Med Genet*. 2012;49:164–170.
57. Debniak T, van de Wetering T, Scott R, et al. Low prevalence of *CDKN2A*/ARF mutations among early-onset cancers of breast, pancreas and malignant melanoma in Poland. *Eur J Cancer Prev*. 2008;17: 389–391.
58. Schneider R, Slater EP, Sina M, et al. German national case collection for familial pancreatic cancer (FaPaCa): ten years experience. *Fam Cancer*. 2011;10:323–330.
59. Bartsch DK, Sina-Frey M, Lang S, et al. *CDKN2A* germline mutations in familial pancreatic cancer. *Ann Surg*. 2002;236:730–737.
60. Lal G, Liu L, Hogg D, et al. Patients with both pancreatic adenocarcinoma and melanoma may harbor germline *CDKN2A* mutations. *Genes Chromosomes Cancer*. 2000;27:358–361.
61. Goggins M, Offerhaus GJ, Hilgers W, et al. Pancreatic adenocarcinomas with DNA replication errors (RER^+) are associated with wild-type K-ras and characteristic histopathology. Poor differentiation, a syncytial growth pattern, and pushing borders suggest RER^+. *Am J Pathol*. 1998; 152:1501–1507.
62. Yamamoto H, Itoh F, Nakamura H, et al. Genetic and clinical features of human pancreatic ductal adenocarcinomas with widespread microsatellite instability. *Cancer Res*. 2001;61:3136–3144.
63. Lynch HT, Voorhees GJ, Lanspa SJ, et al. Pancreatic carcinoma and hereditary nonpolyposis colorectal cancer: a family study. *Br J Cancer*. 1985;52:271–273.
64. Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet*. 2009;75:141–149.
65. Geary J, Sasieni P, Houlston R, et al. Gene-related cancer spectrum in families with hereditary non-polyposis colorectal cancer (HNPCC). *Fam Cancer*. 2008;7:163–172.
66. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA*. 2009;302:1790–1795.
67. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer*. 1999;81:214–218.
68. Vasen HF, Offerhaus GJ, den Hartog Jager FH, et al. The tumor spectrum in hereditary non-polyposis colorectal cancer: a study of 24 kindreds in the Netherlands. *Int J Cancer*. 1990;46:31–34.
69. Gargiulo S, Torrini M, Ollila S, et al. Germline *MLH1* and *MSH2* mutations in Italian pancreatic cancer patients with suspected Lynch syndrome. *Fam Cancer*. 2009;8:547–553.
70. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol*. 2004;2:252–261.
71. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst*. 1997;89:442–446.
72. Rebours V, Boutron-Ruault MC, Schnee MF, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. *Am J Gastroenterol*. 2008;103:111–119.
73. Lowenfels AB, Maisonneuve P, Whitcomb DC, et al. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *JAMA*. 2001;286:169–170.
74. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology*. 2000; 119:1447–1453.
75. Lim W, Olschwang S, Keller JJ, et al. Relative frequency and morphology of cancers in *STK11* mutation carriers. *Gastroenterology*. 2004; 126:1788–1794.
76. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res*. 2006;12: 3209–3215.
77. Grützmann R, McFaul C, Bartsch DK, et al. No evidence for germline mutations of the *LKB1*/*STK11* gene in familial pancreatic carcinoma. *Cancer Lett*. 2004;214:63–68.
78. Jacobs EJ, Chanock SJ, Fuchs CS, et al. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Int J Cancer*. 2010;127:1421–1428.
79. Canto MI, Hruban RH, Fishman EK, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology*. 2012;142:796–804.
80. Ludwig E, Olson SH, Bayuga S, et al. Feasibility and yield of screening in relatives from familial pancreatic cancer families. *Am J Gastroenterol*. 2011;106:946–954.
81. Verna EC, Hwang C, Stevens PD, et al. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clin Cancer Res*. 2010;16:5028–5037.
82. Langer P, Kann PH, Fendrich V, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut*. 2009;58:1410–1418.
83. Goggins M. Markers of pancreatic cancer: working toward early detection. *Clin Cancer Res*. 2011;17:635–637.