The Prevalence of BRCA2 Mutations in Familial Pancreatic Cancer

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Abstract

Mutations in the *BRCA2* gene have been implicated in pancreatic cancer susceptibility through studies of high-risk breast and ovarian cancer families. To determine the contribution of mutations in *BRCA2* to familial pancreatic cancer, we screened affected probands from 151 high-risk families identified through pancreatic cancer clinics for germ-line *BRCA2* mutations. Of these families, 118 had two or more first- and second-degree relatives with pancreatic cancer, and an additional 33 had two or more affected second-degree relatives. The average age of onset for pancreatic cancer was 62.8 years. Five *BRCA2* truncating mutations were identified, three in families with two or more first- and second-degree relatives with pancreatic cancer. Three of the families with mutations had a history of breast cancer but not ovarian cancer. Four of five families with mutations were identified through probands with early-onset (<55 years) pancreatic cancer. The results of this study were combined with those from a *BRCA2* mutation study of 29 other families from the same Johns Hopkins University National Familial Pancreatic Tumor Registry to estimate the frequency of *BRCA2* mutations. A total of 10 carriers from 180 families were identified, suggesting that *BRCA2* mutations account for 6% of moderate and high-risk pancreatic cancer families. (Cancer Epidemiol Biomarkers Prev 2007;16(2):342–6)

Introduction

Pancreatic cancer ranks fourth as a cause of death from cancer in the United States. Pancreatic cancer has one of the worst prognoses among human malignancies with an overall 5-year survival rate of <4%. Familial clustering or a family history of pancreatic cancer is a significant risk factor for the disease (1, 2), suggesting that susceptibility to pancreatic cancer can be inherited. It has been estimated that 5% to 10% of patients with pancreatic cancer have a first-degree relative with pancreatic cancer and that 10% to 20% of pancreatic cancers arise due to a significant inherited component (3).

Familial pancreatic cancer has been associated with germ-line mutations in *p16* (familial atypical melanoma mole syndrome; ref. 4), *STK11* (Peutz-Jeghers syndrome; ref. 5), *hMLH1* (hereditary nonpolyposis colon cancer; ref. 6), *FANCC* (7, 8), and *PRSS1* (hereditary pancreatitis; ref. 9). In addition, germ-line mutations in the *BRCA2* breast and ovarian cancer predisposition gene have been implicated in predisposition to pancreatic cancer. An increased incidence of pancreatic cancer relative to the general population (relative risk, 3.51) was observed in a study by the Breast Cancer Linkage Consortium of 3728 individuals from 173 breast ovarian cancer families carrying *BRCA2* mutations or showing linkage to the *BRCA2* locus (10). The risk of pancreatic cancer was even greater when the analysis was restricted to individuals <65 years of age (relative risk, 5.54; ref. 10). The association between *BRCA2* mutations and pancreatic cancer has also been evaluated by studying the number of germ-line *BRCA2* mutations in unselected cohorts of pancreatic cancer patients. Several independent studies have suggested that germ-line *BRCA2* mutations are associated with 10% of unselected, sporadic pancreatic cancers in the Ashkenazi Jewish population but <1% of sporadic cancers in non-Ashkenazi Caucasians (11-13). The mutations were not associated with a family history of breast, ovarian, or pancreatic cancer, suggesting that the penetrance of the gene may be low in some kindreds. More recently, *BRCA2* germ-line mutations were identified in 17% of families with three or more cases of pancreatic cancer among first- and second-degree relatives ($n = 29$; ref. 14) and in 12% of cases with two or more first- and second-degree relatives with pancreatic cancer ($n = 26$; ref. 15).

These findings implicate *BRCA2* as an important pancreatic cancer predisposition gene. However, the actual prevalence of *BRCA2* mutations in these families remains uncertain because of the small size of the study populations. As *BRCA2* and other Fanconi Anemia gene/DNA repair–deficient pancreatic cancer cell lines are now known to be more susceptible to cross-linking agents than other forms of chemotherapy (16), a more accurate estimate of the prevalence of *BRCA2* mutations will prove important in the development of clinical trials aimed at treating *BRCA2* mutation carriers with pancreatic cancer. In this study, we undertook a *BRCA2* mutation screen of 151 high-risk pancreatic cancer families in an effort to better define the prevalence of *BRCA2* mutations in this population.

Materials and Methods

Subjects. Familial pancreatic cancer cases for this study were identified through Institutional Review Board–approved protocols and followed similar procedures for case identification, enrollment, and data collection (17). At the Mayo Clinic, patients were ultrarapidly identified and consented to a prospective pancreatic cancer patient registry through Pancreatology and

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Table 1. Description of 151 high-risk pancreatic cancer families

	Mayo Clinic, n = 41 (%)	Johns Hopkins, n = 101 (%)	Toronto, n = 9 (%)	Total, n = 151 (%)
No. pancreatic cancers				
2	37 (90)	77 (76)	7 (78)	121 (80)
3	3 (7)	16 (16)	2 (22)	21 (14)
≥4	1 (3)	8 (8)	0 (0)	9 (6)
Family history of pancreatic cancer				
≥2 First-degree relatives	24 (59)	89 (88)	5 (56)	118 (78)
≥2 Second-degree relatives	17 (41)	12 (12)	4 (44)	33 (22)
Other cancers				
Breast	17 (41)	32 (32)	3 (33)	52 (34)
Ovarian	5 (12)	7 (7)	0 (0)	12 (8)
Prostate	13 (32)	16 (16)	0 (0)	29 (19)
Proband age of onset				
≤55	12 (29)	28 (28)	3 (33)	43 (28)
>55	29 (71)	73 (72)	6 (67)	108 (72)

Oncology Clinics at the time of diagnosis from 2000 to 2003. All patients were asked to provide blood samples and family history of cancer, to complete risk factor questionnaires, and to provide access to medical records. Approximately 76% of patients with subsequently confirmed pancreatic adenocarcinoma were consented to the Registry. For this study, eligible families were identified through probands with histologically proven pancreatic adenocarcinoma. A total of 41 families with a minimum of two first- or second-degree relatives with pancreatic cancer and with a DNA sample available on one of the affected family members were selected for this study. All 41 Mayo probands were non-Hispanic and non-Latino Caucasian race and none reported Ashkenazi Jewish heritage. The mean number of relatives in reported kindreds was 28, including the proband (range, 11-75).

Similarly, 101 high-risk pancreatic cancer families were identified through the Johns Hopkins University National Familial Pancreatic Tumor Registry (NFPTR).[8] These families contained a minimum of two second-degree relatives with pancreatic cancer, were recruited into the registry before December 2003, had DNA samples from affected family members available for analysis, and had not been previously screened for *BRCA2* mutations. A total of 97 probands were Caucasian, with 10 reporting Ashkenazi Jewish heritage, three probands were Hispanic, and one was African American. Family size (number of relatives) ranged from small to greater than 30 relatives.

A total of nine families fulfilling these same recruitment criteria were identified for the study through the Familial Gastrointestinal Cancer Registry at Mount Sinai Hospital in Toronto, Ontario, Canada. Probands with histologically confirmed pancreatic adenocarcinoma were recruited from local oncology clinics or referred to the registry due to a family history of pancreatic cancer between 1998 and 2003. Consented patients provided DNA samples and family history information. Of the nine probands, one reported Ashkenazi Jewish heritage, one was African-American, and the remaining seven were Caucasian. Four families included more than 20 relatives, four had from 10 to 20 relatives, and one had less than 10 relatives. At all sites, clinical histories of probands and the pathology reports for all proband tumors were reviewed and verified. Family histories of cancer, including breast and ovarian cancer, were provided by the probands in a standardized fashion and whenever possible, medical record confirmation of cancers were sought. A description of the families is provided in Table 1. Genomic DNA was extracted from peripheral blood mononuclear cells by standard techniques.

Mutational Analysis. Coding regions and exon/intron boundaries of the *BRCA2* gene were PCR amplified in 52 independent reactions using previously described primers (18, 19). Briefly, 10 ng of genomic DNA template from each of the probands of the 151 pancreatic cancer families were amplified in 20 μL PCRs with 1.25 units of Amplitaq Gold DNA polymerase (PE Applied Biosystems, Foster City, CA) on an MJ Research PTC-200 Thermocycler (MJ Research, Waltham, MA) according to the manufacturer's instructions. PCR products were denatured for 5 min at 95°C and reannealed at 65°C, and heteroduplexes were evaluated for alterations by WAVE denaturing high-pressure liquid chromatography (dHPLC) analysis (Transgenomics, Inc., Carpinteria, CA) using PCR product-specific melting temperatures and solvent gradients (18). Samples showing abnormal elution profiles were reamplified from genomic DNA and the products were sequenced in the Mayo Clinic DNA Sequencing Facility. Only mutations that result in truncation of the *BRCA2* gene were categorized as deleterious. The functional and clinical relevance of the missense mutations in BRCA2 identified in this study remains unclear. Thus, these missense mutations were categorized as unclassified variants, also termed variants of uncertain significance, and excluded from further analysis.

Results

To address the hypothesis that *BRCA2* mutations account for a substantial proportion of high-risk pancreatic cancer families, we conducted a mutation screen across all exons and exon/intron boundaries of the *BRCA2* gene using dHPLC analysis. Although mutation screening of *BRCA2* by dHPLC analysis is highly sensitive (18), a validation study was nonetheless conducted to ensure that a high proportion of *BRCA2* mutations could be detected by this method. In brief, 34 DNA samples from individuals carrying 126 known *BRCA2* sequence alterations, including small insertions and deletions, intronic variants, splice site alterations and single nucleotide alterations scattered throughout the coding regions of *BRCA2*, were screened for *BRCA2* mutations. A total of 124 of the 126 alterations were detected by the dHPLC analysis with only two single nucleotide alterations being overlooked. These results indicated that the dHPLC mutation detection approach was highly sensitive.

Subsequently, the entire *BRCA2* coding region and all exon/intron boundaries were screened for the presence of *BRCA2* mutations in DNA samples from affected probands of 151 high-risk pancreatic cancer families. Five truncating mutations (1983delGAAAA, 1242insA, 5950delCT, 390delCAAC, and 4065delT) were identified (Table 2). No additional family members were tested for the presence of the mutations. As the estimated prevalence of *BRCA2* mutations in the Caucasian

[8] http://www.path.jhu.edu/pancreas_NFPTR

Table 2. Prevalence of BRCA2 mutations according to family characteristics

	Families, *n*	Mutations, *n* (%)	Families,* *n*	Mutations,* *n* (%)	Combined †	
					Families, *n*	Mutations, *n* (%)
Total	151	5 (3)	29	5 (17)	180	10 (6)
No. pancreatic cancers						
2	121	4 (3)	0	0 (0)	121	4 (4)
3	21	1 (5)	13	4 (31)	34	5 (15)
≥4	9	0 (0)	16	1 (6)	25	1 (4)
Family history						
≥2 First-degree relatives	118	3 (3)	28	5 (18)	146	8 (6)
≥2 Second-degree relatives	33	2 (6)	1	0 (0)	34	2 (6)
Other cancers						
1-2 Breast	39	2 (5)	12	2 (17)	54	4 (7)
≥3 Breast	5	1 (20)	3	0 (0)	8	1 (13)
Breast and ovarian	4	0 (0)	4	0 (0)	8	0 (0)
1 Prostate	25	1 (4)	8	1 (13)	33	2 (6)
≥2 Prostate	4	2 (50)	1	1 (100)	5	3 (60)
Young age of onset						
≤55	43	5 (12)	6	3 (50)	49	8 (16)
>55	108	0 (0)	23	2 (9)	131	2 (2)
Average age of onset (proband)	63.5	48.0	66.7	65.4	64.0	56.7

*Numbers of high-risk pancreatic cancer families and number of BRCA2-inactivating mutations identified in Murphy et al. (14).
†Pooled data from this study and from Murphy et al. (14).

population is 0.2% (20), this result suggests a substantial enrichment for *BRCA2* mutations in pancreatic cancer families. *BRCA2* mutations (IVS16-2A>G, IVS15+1G>A, and 6174delT) were also detected in three blinded control DNA samples, further verifying the sensitivity of the mutation screen. All five mutations were identified in families with two or three pancreatic cancers, whereas no mutations were observed in the nine larger families with four or more pancreatic cancers (Table 2). Of these five mutations, three (3%) were detected in the 118 families with two or more first- and second-degree relatives with pancreatic cancer and two (6%) were detected in the 33 families with only second-degree relatives with pancreatic cancer (Table 2). None of the 12 families with three or more first-degree relatives with pancreatic cancer carried *BRCA2* mutations. These results indicate that although germline *BRCA2* mutations contribute to the familial aggregation of pancreatic cancer, these mutations account for only a small portion of familial pancreatic cancer families. In addition, despite small numbers, the results suggest that *BRCA2* mutations are associated with moderate-risk but not high-risk pancreatic cancer families.

In parallel with this study, 25 other families with a history of pancreatic cancer that did not include two or more first- or second-degree relatives were screened for *BRCA2* mutations and one variant (IVS2-7delT), which causes an in-frame skipping of exon 3 in the resulting mRNA, was identified. These families and this deleterious mutation were not included when estimating the prevalence of *BRCA2* mutations in high-risk pancreatic cancer families because of the limited history of pancreatic cancer, but the detection of another *BRCA2* deleterious mutation is further confirmation of an association between *BRCA2* mutations and pancreatic cancer.

Given that *BRCA2* mutations are associated with a family history of breast and ovarian cancer, we assessed whether the truncating mutations occurred in families with this type of cancer history. As shown in Table 2, one mutation was found in one of the five families with three or more members with breast cancer. One other mutation was identified in a family from a group of 27 that presented with a single case of breast cancer. The proband in this family had a personal history of breast, ovarian, and pancreatic cancer. Another mutation came from 1 of 12 families with two cases of breast cancer. Thus, three of the five pancreatic cancer families with *BRCA2* mutations displayed some history of breast cancer. This finding suggests that members of high-risk pancreatic cancer families with *BRCA2* mutations are at increased, but as yet undefined, risk for breast cancer. As three of the families with *BRCA2* mutations in this study qualify as moderate- or high-risk breast cancer families, the results also seem to be consistent with the previous observation that *BRCA2* mutation carriers from high-risk breast cancer families are at increased risk of pancreatic cancer (10). In addition, three families with mutations were found to contain individuals with prostate cancer (Table 2). Two of these had two or more members with prostate cancer. Whether these observations reflect the known association between prostate cancer risk and *BRCA2* mutations (10) or are unrelated to the presence of *BRCA2* mutation is unclear. However, the detection of *BRCA2* mutations in two of four families with two or more prostate cancer cases is suggestive of the former.

Interestingly, none of the four families with a history of breast and ovarian cancer and only one of five families with a significant history of breast cancer (three or more cases) carried *BRCA2* mutations. Empirical evaluation of the likelihood of a *BRCA2* mutation in these families based on family cancer history using the Myriad II tables[9] indicated that members of these families had a 10% to 20% chance of carrying a *BRCA2* mutation. Thus, it is not unreasonable that only one of nine high-risk families was found to carry a mutation.

BRCA2 mutations are associated with young-onset (<50 years) breast cancer (21). In contrast, *BRCA2* mutations are not associated with early-onset ovarian cancer and no association between *BRCA2* mutations and young-onset pancreatic cancer, defined as disease onset at 55 years or younger, has been observed (14, 15). In this study, four of five truncating mutations were identified in individuals with young-onset pancreatic cancer. These four carriers accounted for 10% of all young-onset probands, indicating an enrichment for *BRCA2* mutations among young-onset pancreatic cancer cases in this series of patients.

In addition to stop codon and frameshift mutations that cause truncation of the *BRCA2* protein, several rare *BRCA2* missense mutations were also detected. These were T582P, F599S, H962Y, L1522V, and V2049A. The functional significance of these variants is unknown. However, only the L1522V mutation occurs in a residue that is perfectly conserved

[9] http://www.myriadtests.com/provider/brca-mutation-prevalence.htm

throughout evolution from frogs and pufferfish to humans, suggesting that this mutation may alter *BRCA2* function and predispose to cancer. This mutation was detected in a family with two first-degree relatives with pancreatic cancer and a distant relative with breast cancer. Further studies of this variant will be needed to establish its relevance to pancreatic cancer predisposition.

To more accurately define the prevalence of *BRCA2* deleterious mutations in high-risk pancreatic cancer families, we combined the results of this study with those from a *BRCA2* mutation screen of 29 other high-risk pancreatic cancer families from the Johns Hopkins University NFPTR. All 29 families contained at least three pancreatic cancer cases and had two or more first-degree relatives with pancreatic cancer (Table 2) and accounted for the majority of the large pancreatic cancer kindreds in the NFPTR. As these families were recruited in the same time frame as the 118 NFPTR families in our study, they were included to account for the entire NFPTR collection in our estimation of the frequency of *BRCA2* mutations in the high-risk pancreatic cancer population. A previous mutation analysis of probands from these 29 families identified five deleterious *BRCA2* mutations (14). As before, the *BRCA2* mutations were predominantly observed in families with a moderate history of pancreatic cancer (Table 2). Two of five mutations were detected in families with breast cancer and two in families with prostate cancer, again suggesting a link between *BRCA2* mutations and breast and prostate cancer (Table 2). However, the average age of pancreatic cancer onset in probands with *BRCA2* mutations was 65.4 years, although three families contained at least one individual with young-onset pancreatic cancer (Table 2). When combining the results of this study with our own mutation study, we find that *BRCA2* mutations account for 10 of 180 (6%) of high-risk pancreatic cancer families (Table 2).

Discussion

In an effort to define better the prevalence of *BRCA2* mutations in the familial pancreatic cancer population, an analysis of 151 high-risk families was conducted. As reported above, five mutations were detected. Three of these were in families with two or more first-degree relatives with pancreatic cancer and two in families with two or more second-degree relatives with pancreatic cancer. The results suggested that 3% of high-risk pancreatic cancer families carry *BRCA2* mutations. However, on adjusting for other large pancreatic cancer families from the NFPTR that were previously tested for *BRCA2* mutations (14), we estimate that *BRCA2* mutations account for 6% (10 of 180) of high-risk pancreatic cancer families and 6% (8 of 146) of families fulfilling the criteria of familial pancreatic cancer (two or more affected first-degree relatives). This is substantially lower than previous estimates, which suggested that *BRCA2* germ-line mutations account for 17% of families with three or more cases of pancreatic cancer among first- and second-degree relatives ($n = 29$; ref. 14) and 12% of families with two or more first- and second-degree relatives with pancreatic cancer ($n = 26$; ref. 15). As the dHPLC mutation screening technique used in this study is highly sensitive, it seems unlikely that overlooked mutations account for the differences. One possible explanation for the differences in mutation frequency is that the small sample sizes in the other studies may have resulted in inflated estimates of mutation frequency. In addition, the use of moderate-risk families in our study compared with high-risk families only in the other studies may account for some of the difference. The majority of the 151 families that we studied contained only two first-degree or second-degree relatives with pancreatic cancer (Table 1) and can be classified as moderate risk. In contrast, many of the families used for the other studies (14, 15) contained three or more first- or second-degree relatives and can be classified as high risk. Thus, although the overall frequency of *BRCA2* mutations is 6%, it is clear that the frequency approaches 15% for families with many cases of pancreatic cancer but can be as low as 3% for families with smaller numbers of pancreatic cancer cases.

The families with *BRCA2* mutations that were identified in this study provide some interesting insights into the nature of *BRCA2*-associated cancer. Five of 10 families contained at least one prostate cancer case and 3 of 5 families with two or more prostate cancers carried *BRCA2* mutations. This is in keeping with a well-defined association between *BRCA2* mutations and prostate cancer risk (10). Another aspect of the families found to carry *BRCA2* mutations is that 8 of the 10 families exhibited at least one early onset pancreatic cancer. Although the average age of onset of pancreatic cancer did not always differ from non-*BRCA2* families (Table 2), the presence of one young-onset case in a pancreatic cancer family may be somewhat predictive of the presence of a *BRCA2* mutation.

Interestingly, 5 of 10 families with *BRCA2* mutations also exhibited a history of breast cancer. It has long been known that *BRCA2* mutations predispose to breast cancer and that female carriers of mutations have an ~65% chance of developing breast cancer in their lifetime. Population-based studies have also shown that only ~20% of breast cancer cases with *BRCA2* mutations fail to display a family history of breast cancer (22). However, the five families described here have a limited history of breast and ovarian cancer and these cancers are absent from five other families with *BRCA2* mutations identified in this study. Based on these data, it seems that the penetrance for breast and ovarian cancer due to *BRCA2* mutations in families selected based on pancreatic cancer is low. This finding suggests that a *BRCA2* mutation in a family can result in either a predominantly pancreatic cancer phenotype or a predominantly breast cancer–associated phenotype. It also raises the question of whether there are other cancer phenotypes associated with *BRCA2* mutations that have not been well defined. As most *BRCA2* mutation studies have been conducted using high-risk families, it is possible that the presence of mutation carriers in the population exhibiting low penetrance for certain cancers, such as pancreatic cancer, has been overlooked. Thus, many carriers with a personal history but a limited family history of cancer may remain unrecognized. However, the more likely explanation for these alternative phenotypes is that other genetic factors or environmental factors may determine whether a family exhibits a stronger pancreatic cancer phenotype or a breast cancer–associated phenotype. Further population-based studies of *BRCA2* mutations are needed to address this issue.

The finding that ~6% of moderate-risk pancreatic cancer families and >10% of high-risk pancreatic cancer families contain *BRCA2*-truncating mutations suggests that all high-risk families and moderate-risk families with a history of breast or prostate cancer should be clinically screened for the presence of *BRCA2* mutations. Only ~10% of high-risk breast cancer families that undergo *BRCA1* and *BRCA2* mutation testing are found to have mutations, so the prevalence of mutations in high-risk breast and pancreatic cancer populations is not significantly different. Importantly, only two of the probands found to carry mutations in this study would have been selected for clinical *BRCA2* mutation screening based on a personal or family history of breast and/or ovarian cancer. Thus, the results of this study strongly suggest that clinical *BRCA2* mutation testing of the familial pancreatic cancer population, based on family history of pancreatic cancer and not just on breast or ovarian cancer, should receive more emphasis.

The advantages of testing are numerous. Carriers may be closely followed for the development of pancreatic, breast, prostate, or ovarian cancer. Although prophylactic surgery to reduce the risk of breast and ovarian cancer onset is acceptable

for carriers from families with multiple individuals affected with breast and ovarian cancers, the risk reduction conferred by similar surgery in women with mutations from families that only display a history of pancreatic cancer is unclear. Individuals in families with detectable mutations who do not themselves carry mutations can be assured that they are at no more risk of these cancers than the general population. Furthermore, *BRCA2* carriers with pancreatic cancer may benefit from more specific cancer therapy because it has been shown recently that *BRCA2*-deficient pancreatic cancer cells are hypersensitive to DNA cross-linking agents, such as mitomycin C, cisplatin, and carboplatin (16).

References

1. Lynch HT, Fusaro L, Lynch JF. Familial pancreatic cancer: a family study. Pancreas 1992;7:511–5.
2. Schenk M, Schwartz AG, O'Neal E, et al. Familial risk of pancreatic cancer. J Natl Cancer Inst 2001;93:640–4.
3. Petersen GM, Hruban RH. Familial pancreatic cancer: where are we in 2003? J Natl Cancer Inst 2003;95:180–1.
4. Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. N Engl J Med 1995;333:970–4.
5. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447–53.
6. Yamamoto H, Itoh F, Nakamura H, et al. Genetic and clinical features of human pancreatic ductal adenocarcinomas with widespread microsatellite instability. Cancer Res 2001;61:3139–44.
7. van der Heijden MS, Yeo CJ, Hruban RH, Kern SE. Fanconi anemia gene mutations in young-onset pancreatic cancer. Cancer Res 2003;63:2585–8.
8. Couch FJ, Johnson MR, Rabe K, et al. Germ line Fanconi anemia complementation group C mutations and pancreatic cancer. Cancer Res 2005;65:383–6.
9. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993;328:1433–7.
10. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:1310–6.
11. Goggins M, Schutte M, Lu J, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res 1996; 56:5360–4.
12. Ozcelik H, Schmocker B, Di Nicola N, et al. Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. Nat Genet 1997; 16:17–8.
13. 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;84:478–81.
14. 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;62:3789–93.
15. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003;95:214–21.
16. van der Heijden MS, Brody JR, Dezentje DA, et al. *In vivo* therapeutic responses contingent on Fanconi anemia/BRCA2 status of the tumor. Clin Cancer Res 2005;11:7508–15.
17. Petersen GM, de Andrade M, Goggins M, et al. Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium. Cancer Epidemiology Biomarkers and Prev 2006;15:704–10.
18. Wagner T, Stoppa-Lyonnet D, Fleischmann E, et al. Denaturing high-performance liquid chromatography detects reliably BRCA1 and BRCA2 mutations. Genomics 1999;62:369–76.
19. Sinclair CS, Berry R, Schaid D, Thibodeau SN, Couch FJ. BRCA1 and BRCA2 have a limited role in familial prostate cancer. Cancer Res 2000;60:1371–5.
20. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 2000;83:1301–8.
21. Tavtigian SV, Simard J, Rommens J, et al. The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. Nat Genet 1996;12:333–7.
22. Malone KE, Daling JR, Doody DR, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black american women ages 35 to 64 years. Cancer Res 2006; 66:8297–308.