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Genetics of Pancreatic Cancer: Where Are We Now? Where Are We Going?

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Pancreatic adenocarcinoma represents about 90% of all pancreatic tumors [1]. In Italy, the incidence of ductal adenocarcinoma is about 7,000 new cases per year and the mortality rate is about 95% [2]. For this reason, pancreatic cancer is the fifth cause of death from cancer in Italy [3]. The only chance of cure is represented by surgical resection, and it is feasible in less than one half of the patients [4]. The poor prognosis of the disease is the result of several concurrent factors: the aggressive biological behavior of this histological type of malignancy, the relative delay of clinical evidence of the disease, and the lack of criteria for selecting individuals at risk who could benefit from clinical screening. Many efforts have been made in the past few years for assessing the mechanisms of the carcinogenesis of pancreatic cancer in order to identify individuals at increased risk, and for establishing diagnostic tools for screening and early diagnosis.

The Molecular Progression of Pancreatic Cancer

Like in other neoplasms, cellular changes leading to dysplasia, carcinoma in situ and invasive pancreatic carcinoma are related to mutations in oncogenes and tumor suppressor genes [5]. Although many experimental models have identified mutations occurring in oncogenes and/or tumor suppressor genes leading to pancreatic cancer, we do not have a definitive experimental model of pancreatic cancer capable of defining the molecular and prognostic markers of the disease [6]. K-*ras* mutations are reported in about 90% of sporadic pancreatic carcinomas [7]. However, a mutated K-*ras* gene may be associated with several non-neoplastic pancreatic disorders (e.g., chronic pancreatitis), and, according to the experimental models [8, 9, 10], it characterizes the earliest phases of dysplasia; for this reason, this gene does not seem not to be suitable for use as a diagnostic marker. Mutations in the *p-53* gene are described in about 75% of cases of pancreatic ductal carcinoma [6], and are present in about 50% of all cancers. The function of this gene is to stop cells in the G1 phase in the presence of DNA damage; the encoded proteins also play a role in apoptosis. Mutations in the p-16 protein are also frequently found. This gene also modulates cellular progression through the G1 phase [11]. P-16 mutations are described in about 80% of cases of pancreatic cancer. Recent studies have demonstrated that the p-16 wild type mutation in pancreatic adenocarcinoma human cells can decrease cellular proliferation, thus being an potential marker for gene therapy [12]. The DPC4 mutation is present in about 50% of cases of

pancreatic cancer [13]. The role of this alteration has not yet been well defined in pancreas cancer.

Genetic Susceptibility to Pancreatic Carcinoma

The first description of familial pancreatic cancer was reported at the end of the 1970s [14]. Nevertheless, the first study on a group of families diagnosed with familial pancreatic carcinoma was published in 1989 [15]. Familial pancreatic cancer was of great interest in subsequent years, and National Registers were established both in the USA [16, 17] and in Europe [18, 19, 20], to in order to better understand and monitor the disease. After enrolling families in registries, the individuals identified to be at higher risk for pancreatic carcinoma can be enrolled in screening programs, in order to try to prevent the disease or, at least, to arrive at an early diagnosis [21]. About 10-15% of the incident cases of pancreatic cancer have a positive family history for this tumor [21, 22]. This percentage includes three different clinical conditions: the first condition is represented by the genetic syndromes of cancer which include the pancreas in their cancer spectrum; the second condition is familial pancreatitis, in which pancreatic cancer represents the malignant phenotype of the disease, and the third condition is the properly named familial pancreatic cancer, in which two or more relatives are diagnosed with pancreatic cancer and the family does not fulfil the criteria of inclusion in other known genetic syndromes [23]. In this study, we will briefly review the current knowledge regarding these three aspects of familial pancreatic cancer and will address the question of possible screening and prevention measures.

1) Hereditary Neoplastic Syndromes Associated with Pancreatic Cancer

Hereditary breast and ovarian cancer (HBOC). This syndrome is predominantly caused by mutations of the BRCA1 or BRCA2 genes. The frequency of mutations in these two genes increases proportionally to the number of the members of the family diagnosed with ovarian or breast cancer. Families diagnosed with HBOC show an increased frequency of pancreatic cancer [24]. The risk of pancreatic cancer is increased 2.26-fold in carriers of BRCA1 mutations [25] and from 3.5- to 8-fold in BRCA2 carriers with respect to the general population [26, 27]. BRCA2 may also play a role in familial pancreatic cancer which is not associated with known hereditary neoplastic syndromes. This association is stronger in individuals of Ashkenazi Jewish descent [28]. Two studies, from America and Europe respectively, identified BRCA2 mutations in 13 to 17% of the families diagnosed with familial pancreatic cancer who did not meet the inclusion criteria of known hereditary neoplastic syndromes [29, 30]. Thus, BRCA2 might play an important role in the diagnosis of familial pancreatic cancer [31].

Peutz-Jeghers syndrome (PJS). Peutz-Jeghers syndrome is an autosomal dominant hereditary disease which causes increased susceptibility to several kinds of tumors. This syndrome is caused by a mutation in the STK11 gene [32]. The cumulative risk of developing a PJS tumor for mutation carriers at 20, 30, 40, 50, 60 and 70 years of age is 1%, 3%, 19%, 32%, 63% and 81%, respectively. In particular, the risk of gastrointestinal tumors such as esophageal, small bowel, colorectal and pancreatic cancer is increased; the risk for these malignancies at 30, 40, 50 and 60 years of age is 1%, 10%, 18%, and 42%, respectively. A particular mutation occurring in exon 3 of the STK11 gene seems to be associated with an increased risk of malignancy more than mutations located elsewhere in the gene [33]. The risk of developing pancreatic cancer for those with PJS is about 132 times the risk of the standard population [34].

Familial atypical multiple mole melanoma syndrome (FAMMM). This syndrome is associated with a mutation of the CDKN2A gene. It is often associated with extra-cutaneous neoplasms and pancreatic cancer is present in about 25% of cases [35]. FAMMM

is phenotypically expressed in about 12% of families diagnosed with familial pancreatic cancer [36]. The overall risk of pancreatic cancer for patients diagnosed with FAMMM and CDKN2A mutation is about 15 times higher with respect to the general population, and the cumulative risk of developing pancreatic cancer is about 17% at 75 years of age [37]. Lynch *et al*. described the phenotypic expression of FAMMM in 19 of 159 families diagnosed with pancreatic cancer. In 8 of these families, FAMMM and pancreatic cancer were associated with a CDKN2A germinal mutation simultaneously. This association was described as a new hereditary neoplastic syndrome, named FAMMM-pancreatic carcinoma (FAMMM-PC) [38].

Hereditary non-polyposis colorectal cancer syndrome (HNPCC). HNPCC is a syndrome caused by a germinal mutation of one of several mismatch repair (MMR) genes [39]. Although the association between pancreatic cancer and MMR gene mutation is not strong, some cases of pancreatic cancer occurring in families having HNPCC have been described [40]. Peltomaki *et al*. found that about 1% of MMR gene mutations could lead to pancreatic cancer [41]. In addition, some studies showed a larger prevalence of colorectal cancer in families having a history of pancreatic cancer [40].

2) Hereditary Pancreatitis

Hereditary pancreatitis (HP) is an autosomal dominant disease with variable expression and an estimated penetrance of 80%, which is associated with an increased risk of pancreatic cancer [42]. This disease is characterized by recurrent episodes of acute pancreatitis or a previous history of chronic pancreatitis in several members of the same family. In 1996, the first HP-associated mutation was identified in the cationic trypsinogen gene PRSS1. In subsequent years, several different mutations of the same gene have been found in a large number of families investigated. The disease is caused by a PRSS1 gene mutation in 70% of cases [43]; mutations in the serine protease inhibitor SPINK1 gene, a pancreatic trypsin inhibitor, have also been identified in a smaller number of families [44] and in patients with chronic pancreatitis. HP patients have more than a 50-fold increased risk of pancreatic ductal cancer in comparison to the expected incidence of pancreatic cancer in the general population. Risk is increased by paternal-line transmission and smoking [45]. The estimated cumulative risk of pancreatic cancer at 70 years of age in patients with hereditary pancreatitis approaches 40%; for patients with a paternal inheritance pattern, the cumulative risk of pancreatic cancer is approximately 75% [46].

3) Familial Pancreatic Cancer

In some patients diagnosed with pancreatic cancer, the familial distribution of the disease suggests an autosomal dominant transmission with reduced penetrance. This modality of transmission characterizes about 70% of "hereditary" pancreatic carcinomas not otherwise attributable to known genetic syndromes [47, 48]. A gene of susceptibility to pancreatic cancer has not yet been identified, though a susceptibility locus was located by linkage analysis in the q32-34 region of chromosome 4 [49]. This analysis was carried out in a family composed of 43 members over 4 generations, including 20 subjects affected with pancreatic cancer. The definition of familial pancreatic cancer is still a matter of debate. The most common definition refers to a family in which two first degree relatives are diagnosed with histologically confirmed pancreatic cancer and do not fulfil the inclusion criteria of another known hereditary neoplastic syndrome [50]. According to other authors, familial pancreatic cancer refers to families with three or more affected members, regardless of the degree of relationship and the age of occurrence (before or after 50 years of age) [47]. The phenomenon of anticipation for familial pancreatic cancer, although described in some studies, has not been confirmed in others [20, 51]. In a recent study based on the National Familial Pancreatic

Tumor Registry (Johns Hopkins University) [52], the risk of pancreatic cancer for members of affected families increased proportionally to the number of patients affected in the family. The risk was 4.5-fold higher when only one relative was affected by pancreatic cancer, 6.4-fold higher in the case of two affected relatives and 32-fold higher in the case of 3 or more affected relatives. Another interesting observation regarding patients diagnosed with pancreatic cancer at a young age without family history is the possibility of a germinal mutation of the Fanconi genes FANCC and FANCG [53].

Screening and Prevention in Hereditary Pancreatic Cancer

Familial pancreatic cancer (FPC) is a new clinical entity and only a few clinical institutions provide patients with specific information on this issue. When a family is diagnosed with a known hereditary syndrome, screening for pancreatic tumors is clearly justified, depending on the increase of risk determined by that syndrome and by the probability that the subject at risk is a gene carrier. The situation is more complex for subjects at risk of FPC. Mutational screening is not possible, as no gene has been identified so far. In addition, the diagnostic tools which are available to detect early pancreatic malignancies, such as dysplasia, are still limited. Nevertheless, some institutions have published results of clinical screening carried out in patients having an increased risk of pancreatic cancer. Rulyak and Brentnall [54] have recently reported data concerning the screening of 35 subjects in 13 families diagnosed with FPC. They were able to detect presumptive dysplastic lesions by means of US-endoscopy, abdominal CT-scan, MNR, and endoscopic retrograde cholangiopancreatography (ERCP) in 12 cases. These patients underwent total pancreatectomy and the dysplasia was histologically confirmed in all cases, in the absence of pancreatic cancer. More recently, Canto *et al*. [55] reported the experience of their group regarding screening for FPC by means of US-endoscopy. Further diagnostic assessments (CT, EUS-FNA and ERCP) were carried out only when US-endoscopy had shown a suspect pre-malignant or malignant lesion. Using this approach, 6 out of 38 patients were diagnosed with pancreatic lesions (1 invasive adenocarcinoma, 1 intraductal papillary mucinous neoplasm (IPMN) , 2 serous cystadenomas and 2 non-neoplastic masses). The patient with early diagnosis of pancreatic cancer is still alive more than 5 years after intervention.

Future Prospects for the Screening of "Hereditary" Pancreatic Cancer

In individuals at risk for a known hereditary neoplastic syndrome, screening should begin by the search for germline mutations in the known genes. The BRCA1 gene, and particularly the BRCA2 gene [56] should always be screened in all patients who fulfill the inclusion criteria of HBOC; mutations of STK11 [32] in patients diagnosed with or at risk of PJS; mutations in CDKN2A [37] in patients at risk of FAMMM; mutations in the MMR genes [39] in patients at risk of HNPCC; mutations in SPINK1 and PRSS1 [43, 44] in patients at risk of familial pancreatitis. If a mutation is identified in one of these genes, an estimate of the individual risk can be obtained not only for pancreatic cancer, but also for the other tumors included in the spectrum of the syndrome. This makes it possible to select those patients who should undergo specific surveillance protocols as, for example, in cases of hereditary breast or colorectal malignancies. The situation is more complex for individuals at risk of FPC as they have an indefinite degree of risk and because mutations occurring in the susceptibility gene are still unknown. In consideration of the aggressive biological behavior of pancreatic carcinoma, we need to develop new diagnostic tools capable of identifying premalignant lesions or in situ carcinomas. Screening protocols for individuals considered at risk has been proposed, but some of these protocols are invasive and potentially dangerous. For example, some

authors consider ERCP inappropriate because of the high incidence of complications. Other groups consider US endoscopy a valid alternative, whereas some authors, like Tanaka *et al*. [57], consider abdominal US a valid option.

Another open issue in FPC involves the decisions to be taken in case of the early diagnosis of pancreatic diseases other than cancer. Pancreatectomy seems to be justified in individuals diagnosed with a small solid pancreatic mass or a premalignant lesion such as IPMN. Nevertheless, the management of patients diagnosed with suspicious pancreatic dysplasia is difficult; pancreatic FNA is informative only in the case of positive histology. In other cases, we cannot exclude a pancreatic malignancy. In these cases, the aggressive approach would be total pancreatectomy which implies a relatively high degree of morbidity and mortality. In addition to that, we would expect, at the least, a worsening in the quality of life (unstable diabetes, bowel disorders, etc). Charpentier *et al*. [58] recently suggested, as a possible therapeutic choice, pancreas transplantation associated with pancreatectomy. In our opinion, this interesting approach presents some difficulties which should be evaluated carefully. First, associating pancreas transplant with a pancreatectomy increases the overall surgical risk and substantially inflates the demand for organs; second, the necessary immunosuppressive therapy could represent a specific carcinogenic factor for these patients, some of whom may be more susceptible to neoplasias because of a genetic predisposition.

Keywords Carcinoma, Pancreatic Ductal; Genetic Predisposition to Disease; Genetic Screening; Pancreatic Neoplasms

Abbreviations ERCP: endoscopic retrograde cholangiopancreatography; FAMMM: familial atypical multiple mole melanoma syndrome; FPC: familial pancreatic cancer; HBOC: hereditary breast and ovarian cancer; HNPCC: hereditary non-polyposis colorectal cancer syndrome; HP: hereditary pancreatitis; IPMN: intraductal papillary mucinous neoplasm; MMR: mismatch repair; PJS: Peutz-Jeghers syndrome

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References

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer Statistics 2003. CA Cancer J Clin 2003; 53:5-26. [PMID 12568441]

2. Zanetti R, Buiatti E, Federico M, Micheli A. In: Fatti e Cifre dei Tumori in Italia. 1a Edizione. Rome, Italy: Il Pensiero Scientifico Editore; 1998:9-29.

3. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Survival after resection for ductal adenocarcinoma of the pancreas. Br J Surg 1996; 83:625-31. [PMID 8689203]

4. Richter A, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 2003; 27:324-9. [PMID 12607060]

5. Cowgill SM, Muscarella P. The genetics of pancreatic cancer. Am J Surg 2003; 186:279-86. [PMID 12946833]

6. Rozenblum E, Schutte M, Goggins M, Hahn SA, Panzer S, Zahurak M, et al. Tumor-suppressive pathways in pancreatic carcinoma. Cancer Res 1997; 57:1731-4. [PMID 9135016]

7. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 1998; 53:549-54. [PMID 2453289]

8. Kalthoff H, Schmiegel W, Roeder C, Kasche D, Schmidt A, Lauer G, et al. p53 and K-ras alterations in pancreatic epithelial cell lesions. Oncogene 1993; 8:289-98. [PMID 8426738]

9. Cerny WL, Mangold KA, Scarpelli DG. K-ras mutation i san early event in pancreatic duct carcinogenesis in Syrian golden hamster. Cancer Res 1992; 52:4507-13. [PMID 1643642]

10. Scarpa A, Capelli P, Mukai K, Zamboni G, Oda T, Iacono C, Hirohashi S. Pancreatic adenocarcinomas frequently show p53 gene mutations. Am J Pathol 1993; 142:1534-43. [PMID 8494051]

11. Caldas C, Hahn SA, da Costa LT, Redston MS, Schutte M, Seymour AB, et al. Frequent somatic mutations and homozygous deletions of p16 (MTS1) gene in pancreatic adenocarcinoma. Nat Genet 1994; 8:27-32. [PMID 7726912]

12. Ghaneh P, Greenhalf W, Humphreys M, Wilson D, Zumstein L, Lemoine NR, Neoptolemos JP. Adenovirus mediated transfer of p 53 and p 16 (INK4a) results in pancreatic cancer regression in vitro and in vivo. Gene Ther 2001; 8:199-208. [PMID 11313791]

13. Hahn SA, Schutte M, Hoque AT, Moskaluk CA, da Costa LT, Rozenblum E, et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science 1996; 271:350-3. [PMID 8553070]

14. Friedman JM, Fialkow PJ. Familial carcinoma of the pancreas. Clin Genet 1976; 9:463-9. [PMID 1269168]

15. Lynch HT, Lanspa SJ, Fitzgibbons RJ Jr, Smyrk T, Fitzsimmons ML, McClellan J. Familial pancreatic cancer (Part 1): genetic pathology review. Nebr Med J 1989; 74:109-12. [PMID 2542813]

16. Hruban RH, Petersen GM, Ha PK, Kern SE. Genetics of pancreatic cancer. From genes to families. Surg Oncol Clin N Am 1998; 7:1-23. [PMID 9443984]

17. Banke MG, Mulvihill JJ, Aston CE. Inheritance of pancreatic cancer in pancreatic cancer prone-families. Med Clin North Am 2000; 84:677-90. [PMID 10872424]

18. Applebaum SE, Kant JA, Whitcomb DC, Ellis IH. Genetic testing. Counseling, laboratory, and regulatory issues and the EUROPAC protocol for ethical research in multicenter studies of inherited pancreatic diseases. Med Clin North Am 2000; 84:575-88. [PMID 10872415]

19. Bartsch DK, Sina-Frey M, Ziegler A, Hahn SA, Przypadlo E, Kress R, et al. Update of familial pancreatic cancer in Germany. Pancreatology 2001; 1:510-6. [PMID 12120230]

20. Del Chiaro M, Bertacca L, Zerbi A, Longoni B, Giovannetti A, Cipollini G, et al. An Italian study on genetic susceptibility to pancreatic cancer. Pancreatology 2004; 4:107. [PMID 15181318]

21. Vimalachandran D, Ghaneh P, Costello E, Neoptolemos JP. Genetics and prevention of pancreatic cancer. Cancer Control 2004; 11:6-14. [PMID 14749618]

22. Schenk M, Schwartz AG, O'Neal E, Kinnard M, Greenson JK, Fryzek JP, et al. Familial risk of pancreatic cancer. J Natl Cancer Inst 2001; 93:640-4. [PMID 11309441]

23. Rieder H, Bartsch DK. Familial pancreatic cancer. Fam Cancer 2004; 3:69-74. [PMID 15131409]

24. Tulinius H, Olafsdottir GH, Sigvaldason H, Tryggvadottir L, Bjarnadottir K. Neoplastic diseases in families of breast cancer patients. J Med Genet 1994; 31:618-21. [PMID 7815419]

25. Thompson D, Easton DF; Breast Cancer Linkage Consortium. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002; 94:1358-65. [PMID 12237281]

26. Phelan CM, Lancaster JM, Tonin P, Gumbs C, Cochran C, Carter R, et al. Mutation analysis of the BRCA2 gene in 49 site-specific breast cancer families. Nat Genet 1996; 13:120-2. [PMID 8673090]

27. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999; 91:1310-6. [PMID 10433620]

28. Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, et al. Germline BRCA2 mutation in patients with apparently sporadic pancreatic carcinomas. Cancer Res 1996; 56:5360-4. [PMID 8968085]

29. Murphy KM, Brune KA, Griffin C, Sollenberger JE, Petersen GM, Bansal R, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer : deleterious BRCA2 mutation in 17%. Cancer Res 2002; 62:3789-93. [PMID 12097290]

30. Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. BRCA2 germline mutation in familial pancreatic carcinoma. J Natl Cancer Inst 2003; 95:214-21. [PMID 12569143]

31. Petersen GM, Hruban RH. Familial pancreatic cancer: where are we in 2003? J Natl Cancer Inst 2003; 95:180-1. [PMID 12569133]

32. Su GH, Hruban RH, Bansal RK, Bova GS, Tang DJ, Shekher MC, et al. Germline and somatic mutations of STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers. Am J Pathol 1999; 154:1835-40. [PMID 10362809]

33. Lim W, Olschwang S, Keller JJ, Westerman AM, Menko FH, Boardman LA, et al. Relative frequency and morphology of cancers in STK11 mutation carriers. Gastroenterology 2004; 126:1788-94. [PMID 15188174]

34. Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, et al. Increased risk of cancer in Peutz-Jeghers syndrome. N Engl J Med 1987; 316:1511-4. [PMID 3587280]

35. Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zametkin DP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16NK4 mutations. N Engl J Med 1995; 333:970-4. [PMID 7666916]

36. Bartsch DK, Sina-Frey M, Lang S, Wild A, Gerdes B, Barth P, et al. CDKN2A germline mutations in familial pancreatic cancer. Ann Surg 2002; 236:730-7. [PMID 12454511]

37. Vasen HF, Gruis NA, Frants RR, van Der Velden PA, Hille ET, Bergman W. 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 Can 2000; 87:809-11. [PMID 10956390]

38. Lynch HT, Brand RE, Hogg D, Deters CA, Fusaro RM, Lynch JF, et al. Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma-pancreatic carcinoma-prone families: the familial atypical mole melanoma-pancreatic carcinoma syndrome. Cancer 2002; 94:84-96. [PMID 11815963]

39. Marra G, Boland CR. Hereditary nonpolyposis colorectal cancer: the syndrome, the genes, and historical perspectives. J Natl Cancer Inst 1995; 87:1114-25. [PMID 7674315]

40. Lynch HT, Voorhees GJ, Lanspa SJ, McGreevy PS, Lynch JF. Pancreatic carcinoma and hereditary nonpolyposis colon cancer: a family study. Br J Cancer 1985; 52:271-3. [PMID 4027169]

41. Peltomaki P, Gao X, Mecklin JP. Genotype and phenotype in hereditary nonpolyposis colon cancer: a sudy of families wih different vs. Shared predisposing mutations. Fam Cancer 2001; 1:9-15. [PMID 14574010]

42. Finch MD, Howes N, Ellis I, Mountford R, Sutton R, Raraty M, Neoptolemos JP. Hereditary pancreatitis and familial pancreatic cancer. Digestion 1997; 58:564-9. [PMID 9438603]

43. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996; 14:141-5. [PMID 8841182]

44. Pfutzer RH, Barmada MM, Brunskill AP, Finch R, Hart PS, Neoptolemos J, et al. SPINK1/PSTI polymorphisms act as disease modifiers in familil and idiopatic chronic pacreatitis. Gastroenterology 2000; 119:615-23. [PMID 10982753]

45. Lowenfels AB, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. Med Clin North Am 2000; 84:565-73. [PMID 10872414]

46. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, Whitcomb DC. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 1997; 89:442-6. [PMID 9091646]

47. Lynch HT, Brand RE, Deters CA, Shaw TG, Lynch JF. Hereditary pancreatic cancer. Pancreatology 2001; 1:466-71. [PMID 12120226]

48. Klein AP, Beaty TH, Bailey-Wilson JE, Brune KA, Hruban RH, Petersen GM. Evidence for major gene influencing risk of pancreatic cancer. Genet Epidemiol 2002; 23:133-49. [PMID 12214307]

49. Eberle MA, Pfutzer R, Pogue-Geile KL, Bronner MP, Crispin D, Kimmey MB, et al. A new susceptibility locus for autosomal dominant pancreatic cancer maps to chromosome 4q32-34. Am J Hum Genet 2002; 70:1044-1048. [PMID 11870593]

50. Tersmette AC, Petersen GM, Offerhaus GJ, Falatko FC, Brune KA, Goggins M, et al. Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. Clin Cancer Res 2001; 7:738-44. [PMID 11297271]

51. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA. Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology 2003; 124:1292-9. [PMID 12730869]

52. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004; 64:2634-38. [PMID 15059921]

53. 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. [PMID 12750283]

54. Rulyak SJ, Brentnall TA. Inherited pancreatic cancer: surveillance and treatment strategies for affected families. Pancreatology 2001; 1:477-85. [PMID 12120228]

55. Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol 2004; 2:606-21. [PMID 15224285]

56. Aretini P, D'Andrea E, Pasini B, Viel A, Costantini RM, Cortesi L, et al. Different expressivity of BRCA1 and BRCA2: analysis of 179 Italian

pedigrees with identified mutation. Breast Cancer Res Treat 2003; 81:71-9. [PMID 14531499]

57. Tanaka S, Nakaizumi A, Ioka T, Takakura R, Uehara H, Nakao M, et al. Periodic Ultrasonography checkup for the early detection of pancreatic cancer. Pancreas 2004; 28:268-72. [PMID 15084969]

58. Charpentier KP, Brentnall TA, Bronner MP, Byrd D, Marsh C. A new indication for pancreas transplantation : high grade pancreatic dysplasia. Clin Transplant 2004; 18:105-7. [PMID 15108779]