



WJG 20th Anniversary Special Issues (14): Pancreatic cancer

Screening and early detection of pancreatic cancer in high risk population

Ming-Chu Chang, Jau-Min Wong, Yu-Ting Chang

Ming-Chu Chang, Jau-Min Wong, Yu-Ting Chang, Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei 101, Taiwan

Author contributions: Chang MC, Wong JM and Chang YT designed the study; Chang MC and Chang YT wrote the manuscript.

Correspondence to: Yu-Ting Chang, MD, MS, PhD, Department of Internal Medicine, National Taiwan University Hospital, No.7, Chung Shan South Road, Taipei 101, Taiwan. yutingchang@ntu.edu.tw

Telephone: +886-2-23123456 Fax: +886-2-23633658

Received: October 26, 2013 Revised: January 5, 2014

Accepted: January 20, 2014

Published online: March 7, 2014

Abstract

Pancreatic cancer is a serious growing health issue in developed countries. For patients diagnosed with pancreatic cancer, the five year survival rate is below 5%. One major important reason leads to the poor survival rate is lack of early detection of pancreatic cancer. Over 80% of the patients are diagnosed in advanced disease stages. Screening for pancreatic cancer is a desirable option for high risk individuals to allow early detection and treatment of curable pancreatic neoplasms at a pre-invasive stage. This article highlights the need, endpoint, population, method, diagnostic yield, and the problems of current screening programs.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Pancreatic cancer screening; High risk population; Pancreatic neoplasm; Peutz-Jeghers syndrome

Core tip: Screening for pancreatic cancer is a desirable option for high risk individuals to allow early detec-

tion and treatment of curable pancreatic neoplasms at a pre-invasive stage. This article highlights the need, endpoint, population, method, diagnostic yield, and the problems of current screening programs.

Chang MC, Wong JM, Chang YT. Screening and early detection of pancreatic cancer in high risk population. *World J Gastroenterol* 2014; 20(9): 2358-2364 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i9/2358.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i9.2358>

INTRODUCTION

Pancreatic cancer is one of the most lethal diseases despite marked improvement in medical and cancer care over the past years. The number of newly diagnosed pancreatic cancer patients has increased significantly in recent years^[1]. The most common histological subtype of pancreatic cancer is adenocarcinoma, which comprises 87% of the pancreatic malignancies. Among the pancreatic cancer patients, there were only 15%-20% diagnosed as “resectable” and surgery was the only way to treat the disease. The majority of the pancreatic cancer patients were diagnosed as unresectable and chemotherapy was the standard treatment to control the incurable disease. The prognosis for patients with pancreatic cancer remains poor. The overall survival rate was 5% combining all stages, 20% for patient with localized disease and 1%-2% for those with distant metastasis. In most cases, pancreatic cancer has progressed before clinical manifestation. Many patients initially thought to have localized and resectable cancer succumb to recurrent or metastatic disease. Hence, there is an urgent need to detect small asymptomatic cancers or precursor lesions, which are potentially curable for the most devastating disease.

OPPORTUNITY AND POTENTIAL WINDOW OF SCREENING

A recent study suggested that there may be a large window and good opportunity for detecting pancreatic cancer when the disease is in earliest and most treatable stages^[2]. Quantitative analysis of the timing of the genetic evolution of sporadic pancreatic cancer indicated a time span of at least 10 years between the occurrence of cancer-initiating mutations and the formation of parental nonmetastatic founder cell^[2]. Indeed, patients with pancreatic tumors diagnosed incidentally had longer median survival^[3] than those with tumors discovered after symptoms appeared, suggesting that early detection of small asymptomatic cancers or precursors lesions may improve the outcome. Identification of high risk populations of pancreatic cancer for screening becomes essential. Distinct clinical and genetic features are thought to increase the risk of pancreatic cancers. It has been estimated about 10% of pancreatic cancer has a familial basis. Hereditary pancreatic cancer includes inherited cancer syndromes with a recognized known germline mutation associated with an increased risk of pancreatic cancer and familial pancreatic cancer with two or more cases of pancreatic cancer in their families. Screening pancreatic cancer in these high risk individuals might be recommended for early detection to improve the prognosis of pancreatic cancer. A multidisciplinary international consortium met to discuss pancreatic screening was held recently^[4] and some statements regarding to pancreatic cancer screening were made and voted to guide the pancreatic cancer screening.

DEFINITION OF "SUCCESS" OF SCREENING

A very recent effort made by international cancer of the pancreas screening (CAPS) has proposed to define "successful screening" by detection and treatment of T1N0M0 margin negative pancreatic cancer and high grade dysplastic precursor lesions, including pancreatic intraepithelial neoplasia-3 (PanIN-3), intraductal papillary mucinous neoplasm (IPMN) with high grade dysplasia, and mucinous cystic neoplasm (MCN) with high grade dysplasia^[4].

WHO TO SCREEN?

Not all populations with risk of pancreatic cancer need to be screened because there is no evidence that screening for pancreatic cancer is effective in reducing mortality and the harms of screening for pancreatic cancer exceed any potential benefits^[5]. Clinical risk factors include age, obesity, smoking, diabetes, and non-genetic chronic pancreatitis are associated with pancreatic cancer. However, the specificity of these factors to pancreatic cancer is low. For example, the risk for developing pancreatic cancer increases with age, mostly in individuals at age over 45.

Overweight and obese individuals have an increased risk (odds ratio: 1.8 and 1.22 in males and females, respectively) and earlier disease onset^[6]. Current cigarette smokers and former smokers who had quit for less than 5 years also have a higher risk of pancreatic cancer than non-smokers (odds ratio: 1.71 and 1.78 for current smokers and recent past smokers, respectively)^[7]. Patients with diabetes are at higher risk for pancreatic cancer (odds ratio: 1.76)^[8], and new onset of diabetes may be an early indicator of pancreatic cancer^[9]. Several studies have indicated that patients with (non-genetic) chronic pancreatitis had a higher incidence of pancreatic cancer over the general population (odds ratio: 2.23)^[10-12].

HIGH RISK POPULATIONS

Screening is suggested in high risk populations, including individuals with lifetime risk of pancreatic cancer over 5% or/and increased relative risk over 5 times proposed by CAPS^[4]. Table 1 listed the proposed high risk population to screen and their relatively risk and/or lifetime risk of pancreatic cancer.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers (PJ) syndrome is an autosomal dominantly inherited syndrome caused germline *STK11* gene mutations with high penetrance^[13]. It is characterized by mucocutaneous pigmentation and hamartomatous polyps of the gastrointestinal (GI) tract. Patient with PJ syndrome have a risk of multiple GI and non-GI cancers. The cumulatively lifetime risk of pancreatic cancer is 36%, with a relatively risk (RR) of 132^[14,15]. Patients with PJ syndrome whatever with family history of pancreatic cancer are suggested to be candidates for pancreatic cancer screening^[4].

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Familial atypical multiple mole melanoma syndrome is an autosomally dominant disease with variable penetrance caused by *p16/CDKN2A* gene mutation^[16]. It is characterized by familial occurrence of multiple benign melanocytic nevi, dysplastic nevi, and melanoma^[17]. Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome is associated with extrapancreatic (sarcomas, endometrial, breast and lung cancers) and pancreatic cancers. The risk of developing pancreatic cancer risk is about 13-22 folds^[18-20]. *p16* mutation carriers with one or more affected first degree relative (FDR) with pancreatic cancer should be considered for screening^[4].

FAMILIAL BREAST AND OVARIAN CANCER

Familial breast and ovarian cancer syndrome is an autosomal dominantly inherited syndrome associated

Table 1 High risk population and the estimated risk for pancreatic cancer

Syndrome	Gene	RR	Lifetime risk
Peutz-Jeghers syndrome	<i>STK11/LKB1</i>	132	36% by age 65 yr
Hereditary pancreatitis	<i>PRSS1</i>	53	Male: 11% and 49% by age 50 and 75 yr Female: 8% and 55% by age 50 and 75 yr
FAMMM	<i>p16</i>	13-22	16% lifetime risk
Familial breast and ovarian	<i>BRCA1/2</i>	3-10	5% lifetime risk
HNPCC	<i>MLH1, MSH6, MSH2, PMS2</i>	1.5-9	8.6% lifetime risk
Familial pancreatic cancer			
2 FDR	Unknown	6.4	8%-12% lifetime risk
3 FDR	Unknown	32	40% lifetime risk

FDR: First degree relative; HNPCC: Hereditary non-polyposis colorectal cancer; PRSS1: Cationic trypsinogen gene; FAMMM: Familial atypical multiple mole melanoma syndrome.

with germline mutations of *BRC A1* and *BRC A2* genes. Mutation carriers are at high risk for breast, ovarian, GI cancers (bile duct, gallbladder, stomach, pancreas) and prostate cancers^[21-24]. *BRC A2* carriers are associated with higher risk of pancreatic cancer (3-10 folds) than *BRC A1* carriers (2.3-3.6 folds)^[24,25]. *BRC A2* mutation carriers with one or more affected FDR with pancreatic cancer and those with two or more affected family members (even without a FDR) should be considered for screening^[4].

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME

The lynch syndrome is associated with mismatch repair genes (*MLH1, MSH2, MSH6* and *PMS2*). Hereditary non-polyposis colorectal cancer (HNPCC) is characterized by early-onset colorectal cancers and extra-colonic cancers including pancreas^[26]. The lifetime risk of pancreatic cancer is 3.7% by age of 70, an 8.6-fold increased risk compared to general population^[27]. Patients with Lynch syndrome and one affected FDR with PC should be considered for screening^[4].

HEREDITARY PANCREATITIS

Hereditary pancreatitis is a rare inherited disorder. It is transmitted as an autosomal dominant disorder with incomplete penetrance^[28,29]. Hereditary pancreatitis is associated with a high risk of pancreatic cancer with a lifetime risk about 40%^[30]. In those individuals with a paternal inheritance pattern, the cumulative risk is even approaching 75%^[30]. This risk of pancreatic cancer is related to the duration of inflammation^[31]. Screening of *PRSS1* (Cationic trypsinogen) mutation carriers with longstanding

chronic pancreatitis is being performed within established programs^[32].

FAMILIAL PANCREATIC CANCER

Familial pancreatic cancer (FPC) describes families with at least two first-degree relatives with confirmed exocrine pancreatic cancer that do not fulfill the criteria of other inherited tumor syndromes. FPC is also used to describe families with exocrine pancreatic cancer in two or three or more relatives of any degree^[33,34]. An indicative pattern of an autosomal dominant trait of inheritance has been identified in 58%-80% of FPC families^[35-37]. Previous studies have described an increased risk of developing pancreatic cancer in unaffected FDRs that depends on the number of relatives with pancreatic cancer^[38]. Studies of the European Registry of Hereditary Pancreatitis and FPC (EUROPAC) and German national case collection for FPC (FaPaCa) described the phenomenon that patients in younger generations develop the disease about 10 years earlier than their affected parents^[36,37]. The proportion of patients younger than 50-year-old appeared to be higher (16%) in FPC families compared to the general population^[34]. For individuals with two affected first-degree relatives and individuals with three affected first-degree relatives, the relative risk are 32^[39]. The risk of pancreatic cancer seemed to be higher among members of FPC kindred with a young age of onset (younger than 50 years of age) compared with kindred with an age of onset older than 50 years of age. The life-time risk rose to 38% for individuals with three affected first-degree relatives, if one of the affected was diagnosed under the age of 50 years^[40].

PALB2 gene was identified as a PC susceptibility gene recently^[41]. It is a partner and localizer of *BRC A2*. *PALB2* germline mutations have been detected in up to 3% of patients with familial PC^[41-43]. The risk of PC among *PALB2* gene mutation carriers is estimated to be similar to that found for *BRC A2* gene mutation carriers. *PALB2* mutation carriers with one or more affected FDR with PC should be screened^[4].

WHEN TO SCREEN?

Patients with hereditary pancreatitis has an higher risk of early onset pancreatic cancer. Screening typically begins at age 40 in *PRSS1* mutation carriers^[44]. In other high risk populations, there is no consensus as to whether to recommend initiating screening and the end of screening^[4].

SCREEN TECHNIQUES

Up to now, there is no ideal single screening method or screening program for detection of early pancreatic cancer. Serum CA19-9 levels is the most commonly used serum marker in pancreatic cancer. However, the sensitivity and specificity of serum CA19-9 as a diagnostic marker are not good for screening pancreatic



Table 2 Reported pancreatic cancer screening programs and diagnostic yield

Study	Screening modalities	Case (n)	Study population	Diagnostic yield upon imaging
Rulyak <i>et al</i> ^[46] , 2001	EUS	35	FPC	34.3%
Canto <i>et al</i> ^[56] , 2004	EUS	38	FPC, PJS	76%
Canto <i>et al</i> ^[55] , 2006	EUS	78	FPC, PJS	22%
Poley <i>et al</i> ^[47] , 2009	EUS	44	FPC, FAMMM, PJS	23%
Langer <i>et al</i> ^[48] , 2009	EUS + MRCP	76	FPC, PCMS	36%
Verna <i>et al</i> ^[49] , 2010	EUS and/or MRCP	51	FPC, FAMMM, HNPC	EUS: 65% MRI: 33%
Ludwig <i>et al</i> ^[50] , 2011	MRCP	109	FPC	8.3%
Vasen <i>et al</i> ^[51] , 2011	MRCP	79	FAMMM	20%
Canto <i>et al</i> ^[52] , 2012	MRCP, EUS, CT	216	FPC, HBOC, PJS	42.6%
Al-Sukhni <i>et al</i> ^[53] , 2012	MRCP	262	FPC, FAM- MM, PJS, hereditary pancreatitis	32%

EUS: Endoscopic ultrasonography; MRI: Magnetic resonance imaging; CT: Computed tomography; FAMMM: Familial atypical multiple mole melanoma syndrome; FPC: Familial pancreatic cancer; HBOC: Hereditary breast-ovarian cancer; HNPC: Hereditary nonpolyposis associated colorectal cancer; IPMN: Intraductal papillary mucinous neoplasia; MRCP: Magnetic resonance cholangiopancreatography; PCMS: Pancreatic carcinoma-melanoma syndrome; PJS: Peutz-Jeghers syndrome.

cancer^[45]. The most common screening imaging used for the detection of pancreatic cancer are endoscopic ultrasonography (EUS), computed tomography (CT) and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP). EUS is an invasive procedure which might detect lesions smaller than 1 cm. However, the major problem of EUS is its operator dependent. CT scanning demonstrated a low sensitivity to detection pancreatic dysplasia. MRI with MRCP is a non-invasive procedure which could detect earlier and minor changes in pancreatic parenchymal and (main) pancreatic duct compared to CT scan. Table 2 summarized the reported pancreatic cancer screening programs with the reported diagnostic yield. MRI with MRCP and EUS are considered the most accurate tools for pancreatic imaging as promising recommended tool for screening^[46-56]. The major weakness of CT is its radiation exposure and the suboptimal detection rate as a routine screening tool for asymptomatic high risk individuals^[4]. MRI with MRCP is less invasive and more objective compared to EUS. It still lacks randomized controlled studies to compare EUS and MRI with MRCP in pancreatic cancer screening in high risk individuals. Regarding to the imaging study as a screening tool, over diagnosis is a major problem which might cause over treatment of a benign lesion. The risk of incorrect diagnosis is particularly high for EUS because of it is an operator-dependent examination with only modest interobserver agreement^[57]. Abdominal ultra-

sound and endoscopic retrograde cholangiopancreatography are not recommended for screening, owing to their low diagnostic sensitivity and the risk of pancreatitis, respectively^[4].

EMERGING PROBLEMS AND FUTURE PROSPECTIVE

There are still some unresolved problems in pancreatic cancer screening. First of all, the aim of screening is to find the earliest pancreatic cancer (T1N0M0) or high grade precursor lesions in PanIN, IPMN and MCN. In fact, the high grade PanINs are actually microscopic lesions which might cause some tiny or abnormal findings in imaging. Even with fine needle aspiration, the aspirated substance could not represent the worst condition or whole picture what it is. Secondly, we still have no imaging modality or accurate criteria to differentiate benign pancreatic cystic lesions from malignant cystic tumors with dysplasia or malignancy. There are some proposed “high risk stigmata and worrisome features”^[58] to help us for picking up true meaningful or suspected malignant pancreatic cystic lesions or IPMN to avoid unnecessary operations or over-treatment. However, there is still no reliable or good method to differentiate the nature of pancreatic cystic lesions. With the advancement and frequent use of abdominal imaging, more and more incidentally found pancreatic lesions and/or IPMNs are disclosed. How to follow up the increasing numbers of patient with optimal programs to avoid under detection of pancreatic cancer and also to avoid overtreatment will be a great challenge for clinician.

CONCLUSION

Screening pancreatic cancer in high risk populations is suggested to enhance the potential early detection of curable early pancreatic cancer. It is a potential way to improve the outcome of pancreatic cancer. Although some consensus are proposed to be followed, there is still lack of ideal screening method and program at the present time. Further study and advancement for improving the sensitivity and specificity of screen methods to achieve the goal of early detection of pancreatic cancer is warranted in the near future.

REFERENCES

- 1 **Yadav D**, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; **144**: 1252-1261 [PMID: 23622135 DOI: 10.1053/j.gastro.2013.01.068]
- 2 **Yachida S**, Jones S, Bozic I, Antal T, Leary R, Fu B, Kamiyama M, Hruban RH, Eshleman JR, Nowak MA, Velculescu VE, Kinzler KW, Vogelstein B, Jacobuzio-Donahue CA. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; **467**: 1114-1117 [PMID: 20981102 DOI: 10.1038/nature09515]
- 3 **Winter JM**, Cameron JL, Lillemoe KD, Campbell KA, Chang D, Riall TS, Coleman J, Sauter PK, Canto M, Hruban RH, Schulick RD, Choti MA, Yeo CJ. Periampullary and

- pancreatic incidentaloma: a single institution's experience with an increasingly common diagnosis. *Ann Surg* 2006; **243**: 673-680; discussion 680-683 [PMID: 16633003 DOI: 10.1097/01.sla.0000216763.27673.97]
- 4 **Canto MI**, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, Nio Y, Schulick RS, Bassi C, Kluijft I, Levy MJ, Chak A, Fockens P, Goggins M, Bruno M. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 2013; **62**: 339-347 [PMID: 23135763 DOI: 10.1136/gutjnl-2012-303108]
 - 5 **U. S. Preventive Services Task Force**. Screening for family and intimate partner violence: recommendation statement. *Ann Intern Med* 2004; **140**: 382-386 [PMID: 14996680]
 - 6 **Li D**, Morris JS, Liu J, Hassan MM, Day RS, Bondy ML, Abbruzzese JL. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA* 2009; **301**: 2553-2562 [PMID: 19549972 DOI: 10.1001/jama.2009.886]
 - 7 **Boffetta P**, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. *Lancet Oncol* 2008; **9**: 667-675 [PMID: 18598931 DOI: 10.1016/S1470-2045(08)70173-6]
 - 8 **Ansary-Moghaddam A**, Huxley R, Barzi F, Lawes C, Ohkubo T, Fang X, Jee SH, Woodward M. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 2435-2440 [PMID: 17164367 DOI: 10.1158/1055-9965.EPI-06-0368]
 - 9 **Chari ST**, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 2005; **129**: 504-511 [PMID: 16083707]
 - 10 **Malka D**, Hammel P, Maire F, Rufat P, Madeira I, Pessione F, Lévy P, Ruszniewski P. Risk of pancreatic adenocarcinoma in chronic pancreatitis. *Gut* 2002; **51**: 849-852 [PMID: 12427788 DOI: 10.1136/gut.51.6.849]
 - 11 **Lowenfels AB**, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andrén-Sandberg A, Domellöf L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993; **328**: 1433-1437 [PMID: 8479461 DOI: 10.1056/NEJM199305203282001]
 - 12 **Bansal P**, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterology* 1995; **109**: 247-251 [PMID: 7797022 DOI: 10.1016/0016-5085(95)90291-0]
 - 13 **Gruber SB**, Entius MM, Petersen GM, Laken SJ, Longo PA, Boyer R, Levin AM, Mujumdar UJ, Trent JM, Kinzler KW, Vogelstein B, Hamilton SR, Polymeropoulos MH, Offerhaus GJ, Giardiello FM. Pathogenesis of adenocarcinoma in Peutz-Jeghers syndrome. *Cancer Res* 1998; **58**: 5267-5270 [PMID: 9850045]
 - 14 **Giardiello FM**, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology* 2000; **119**: 1447-1453 [PMID: 11113065 DOI: 10.1053/gast.2000.20228]
 - 15 **van Lier MG**, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol* 2010; **105**: 1258-1264; author reply 1265 [PMID: 20051941 DOI: 10.1038/ajg.2009.725]
 - 16 **Lynch HT**, Fusaro RM, Sandberg AA, Bixenman HA, Johnson LR, Lynch JF, Ramesh KH, Leppert M. Chromosome instability and the FAMMM syndrome. *Cancer Genet Cytogenet* 1993; **71**: 27-39 [PMID: 8275450 DOI: 10.1016/0165-4608(93)90199-V]
 - 17 **Haluska FG**, Hodi FS. Molecular genetics of familial cutaneous melanoma. *J Clin Oncol* 1998; **16**: 670-682 [PMID: 9469357]
 - 18 **Goldstein AM**, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT, Azizi E, Bergman W, Bianchi-Scarra G, Bruno W, Calista D, Albricht LA, Chaudru V, Chompret A, Cuellar F, Elder DE, Ghiorzo P, Gillanders EM, Gruis NA, Hansson J, Hogg D, Holland EA, Kanetsky PA, Kefford RF, Landi MT, Lang J, Leachman SA, MacKie RM, Magnusson V, Mann GJ, Bishop JN, Palmer JM, Puig S, Puig-Butille JA, Stark M, Tsao H, Tucker MA, Whitaker L, Yakobson E. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet* 2007; **44**: 99-106 [PMID: 16905682 DOI: 10.1136/jmg.2006.043802]
 - 19 **Lynch HT**, Fusaro RM, Lynch JF, Brand R. Pancreatic cancer and the FAMMM syndrome. *Fam Cancer* 2008; **7**: 103-112 [PMID: 17992582 DOI: 10.1007/s10689-007-9166-4]
 - 20 **de Snoo FA**, Bishop DT, Bergman W, van Leeuwen I, van der Drift C, van Nieuwpoort FA, Out-Luiting CJ, Vasen HF, ter Huurne JA, Frants RR, Willemze R, Breuning MH, Gruis NA. Increased risk of cancer other than melanoma in CDKN2A founder mutation (p16-Leiden)-positive melanoma families. *Clin Cancer Res* 2008; **14**: 7151-7157 [PMID: 18981015 DOI: 10.1158/1078-0432.CCR-08-0403]
 - 21 **Brose MS**, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *J Natl Cancer Inst* 2002; **94**: 1365-1372 [PMID: 12237282 DOI: 10.1093/jnci/94.18.1365]
 - 22 **Thompson D**, Easton DF. Cancer Incidence in BRCA1 mutation carriers. *J Natl Cancer Inst* 2002; **94**: 1358-1365 [PMID: 12237281 DOI: 10.1093/jnci/94.18.1358]
 - 23 **Lal G**, Liu G, Schmocker B, Kaurah P, Ozcelik H, Narod SA, Redston M, Gallinger S. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. *Cancer Res* 2000; **60**: 409-416 [PMID: 10667595]
 - 24 **Hartge P**, Struewing JP, Wacholder S, Brody LC, Tucker MA. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *Am J Hum Genet* 1999; **64**: 963-970 [PMID: 10090881 DOI: 10.1086/302320]
 - 25 **Ozcelik H**, Schmocker B, Di Nicola N, Shi XH, Langer B, Moore M, Taylor BR, Narod SA, Darlington G, Andrusis IL, Gallinger S, Redston M. Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. *Nat Genet* 1997; **16**: 17-18 [PMID: 9140390 DOI: 10.1038/ng0597-17]
 - 26 **Geary J**, Sasieni P, Houlston R, Izatt L, Eeles R, Payne SJ, Fisher S, Hodgson SV. Gene-related cancer spectrum in families with hereditary non-polyposis colorectal cancer (HNPCC). *Fam Cancer* 2008; **7**: 163-172 [PMID: 17939062 DOI: 10.1007/s10689-007-9164-6]
 - 27 **Kastrinos F**, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, Bandipalliam P, Stoffel EM, Gruber SB, Syngal S. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA* 2009; **302**: 1790-1795 [PMID: 19861671 DOI: 10.1001/jama.2009.1529]
 - 28 **Lowenfels AB**, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. *Med Clin North Am* 2000; **84**: 565-573 [PMID: 10872414 DOI: 10.1016/S0025-7125(05)70240-6]
 - 29 **Teich N**, Rosendahl J, Tóth M, Mössner J, Sahin-Tóth M. Mutations of human cationic trypsinogen (PRSS1) and chronic pancreatitis. *Hum Mutat* 2006; **27**: 721-730 [PMID: 16791840 DOI: 10.1002/humu.20343]
 - 30 **Lowenfels AB**, Maisonneuve P, DiMaggio EP, Elitsur Y, Gates LK, Perrault J, Whitcomb DC. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst* 1997; **89**: 442-446 [PMID: 9091646 DOI: 10.1093/jnci/89.6.442]
 - 31 **Whitcomb DC**. Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. *Am J Physiol Gastrointest*

- Liver Physiol* 2004; **287**: G315-G319 [PMID: 15246966 DOI: 10.1152/ajpgi.00115.2004]
- 32 **Vitone LJ**, Greenhalf W, Howes NR, Neoptolemos JP. Hereditary pancreatitis and secondary screening for early pancreatic cancer. *Rocz Akad Med Bialymst* 2005; **50**: 73-84 [PMID: 16358943]
- 33 **Lynch HT**, Brand RE, Deters CA, Shaw TG, Lynch JF. Hereditary pancreatic cancer. *Pancreatology* 2001; **1**: 466-471 [PMID: 12120226 DOI: 10.1159/000055849]
- 34 **Hruban RH**, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Falatko F, Yeo CJ, Kern SE. Familial pancreatic cancer. *Ann Oncol* 1999; **10** Suppl 4: 69-73 [PMID: 10436789 DOI: 10.1093/annonc/10.suppl_4.S69]
- 35 **Lynch HT**, Fitzsimmons ML, Smyrk TC, Lanspa SJ, Watson P, McClellan J, Lynch JF. Familial pancreatic cancer: clinicopathologic study of 18 nuclear families. *Am J Gastroenterol* 1990; **85**: 54-60 [PMID: 2296965]
- 36 **Schneider R**, Slater EP, Sina M, Habbe N, Fendrich V, Matthäi E, Langer P, Bartsch DK. German national case collection for familial pancreatic cancer (FaPaCa): ten years experience. *Fam Cancer* 2011; **10**: 323-330 [PMID: 21207249 DOI: 10.1007/s10689-010-9414-x]
- 37 **McFaul CD**, Greenhalf W, Earl J, Howes N, Neoptolemos JP, Kress R, Sina-Frey M, Rieder H, Hahn S, Bartsch DK. Anticipation in familial pancreatic cancer. *Gut* 2006; **55**: 252-258 [PMID: 15972300 DOI: 10.1136/gut.2005.065045]
- 38 **Klein AP**, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Griffin C, Cameron JL, Yeo CJ, Kern S, Hruban RH. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004; **64**: 2634-2638 [PMID: 15059921 DOI: 10.1158/0008-5472.CAN-03-3823]
- 39 **Wang L**, Brune KA, Visvanathan K, Laheru D, Herman J, Wolfgang C, Schulick R, Cameron JL, Goggins M, Hruban RH, Klein AP. Elevated cancer mortality in the relatives of patients with pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2829-2834 [PMID: 19843679 DOI: 10.1158/1055-9965.EPI-09-0557]
- 40 **Brune KA**, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, Klein AP. Importance of age of onset in pancreatic cancer kindreds. *J Natl Cancer Inst* 2010; **102**: 119-126 [PMID: 20068195 DOI: 10.1093/jnci/djp466]
- 41 **Jones S**, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, Lin JC, Palmisano E, Brune K, Jaffee EM, Iacobuzio-Donahue CA, Maitra A, Parmigiani G, Kern SE, Velculescu VE, Kinzler KW, Vogelstein B, Eshleman JR, Goggins M, Klein AP. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* 2009; **324**: 217 [PMID: 19264984 DOI: 10.1126/science.1171202]
- 42 **Slater EP**, Langer P, Niemczyk E, Strauch K, Butler J, Habbe N, Neoptolemos JP, Greenhalf W, Bartsch DK. PALB2 mutations in European familial pancreatic cancer families. *Clin Genet* 2010; **78**: 490-494 [PMID: 20412113 DOI: 10.1111/j.1399-0004.2010.01425.x]
- 43 **Harinck F**, Kluijdt I, van Mil SE, Waisfisz Q, van Os TA, Aalfs CM, Wagner A, Olderode-Berends M, Sijmons RH, Kuipers EJ, Poley JW, Fockens P, Bruno MJ. 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 [PMID: 22166947 DOI: 10.1038/ejhg.2011.226]
- 44 **Ulrich CD**. Pancreatic cancer in hereditary pancreatitis: consensus guidelines for prevention, screening and treatment. *Pancreatology* 2001; **1**: 416-422 [PMID: 12120218 DOI: 10.1159/000055841]
- 45 **Homma T**, Tsuchiya R. The study of the mass screening of persons without symptoms and of the screening of outpatients with gastrointestinal complaints or icterus for pancreatic cancer in Japan, using CA19-9 and elastase-1 or ultrasonography. *Int J Pancreatol* 1991; **9**: 119-124 [PMID: 1744437]
- 46 **Rulyak SJ**, Brentnall TA. Inherited pancreatic cancer: surveillance and treatment strategies for affected families. *Pancreatol* 2001; **1**: 477-485 [PMID: 12120228 DOI: 10.1159/000055851]
- 47 **Poley JW**, Kluijdt I, Gouma DJ, Harinck F, Wagner A, Aalfs C, van Eijck CH, Cats A, Kuipers EJ, Nio Y, Fockens P, Bruno MJ. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol* 2009; **104**: 2175-2181 [PMID: 19491823 DOI: 10.1038/ajg.2009.276]
- 48 **Langer P**, Kann PH, Fendrich V, Habbe N, Schneider M, Sina M, Slater EP, Heverhagen JT, Gress TM, Rothmund M, Bartsch DK. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut* 2009; **58**: 1410-1418 [PMID: 19470496 DOI: 10.1136/gut.2008.171611]
- 49 **Verna EC**, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, Prince MA, Chung WK, Fine RL, Chabot JA, Frucht H. 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 [PMID: 20876795 DOI: 10.1158/1078-0432.CCR-09-3209]
- 50 **Ludwig E**, Olson SH, Bayuga S, Simon J, Schattner MA, Gerdes H, Allen PJ, Jarnagin WR, Kurtz RC. Feasibility and yield of screening in relatives from familial pancreatic cancer families. *Am J Gastroenterol* 2011; **106**: 946-954 [PMID: 21468009 DOI: 10.1038/ajg.2011.65]
- 51 **Vasen HF**, Wasser M, van Mil A, Tollenaar RA, Konstantinovski M, Gruis NA, Bergman W, Hes FJ, Hommes DW, Offerhaus GJ, Morreau H, Bonsing BA, de Vos tot Nederveen Cappel WH. Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation. *Gastroenterology* 2011; **140**: 850-856 [PMID: 21129377 DOI: 10.1053/j.gastro.2010.11.048]
- 52 **Canto MI**, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, Topazian M, Takahashi N, Fletcher J, Petersen G, Klein AP, Axilbund J, Griffin C, Syngal S, Saltzman JR, Mortelet KJ, Lee J, Tamm E, Vikram R, Bhosale P, Margolis D, Farrell J, Goggins M. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology* 2012; **142**: 796-804; quiz e14-15 [PMID: 22245846]
- 53 **Al-Sukhni W**, Borgida A, Rothenmund H, Holter S, Semotiuk K, Grant R, Wilson S, Moore M, Narod S, Jhaveri K, Haider MA, Gallinger S. Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. *J Gastrointest Surg* 2012; **16**: 771-783 [PMID: 22127781 DOI: 10.1007/s11605-011-1781-6]
- 54 **Brentnall TA**. Pancreatic cancer surveillance: learning as we go. *Am J Gastroenterol* 2011; **106**: 955-956 [PMID: 21540900 DOI: 10.1038/ajg.2011.68]
- 55 **Canto MI**, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, Fishman EK, Brune K, Axilbund J, Griffin C, Ali S, Richman J, Jagannath S, Kantsevoy SV, Kalloo AN. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006; **4**: 766-781; quiz 665 [PMID: 16682259 DOI: 10.1016/j.cgh.2006.02.005]
- 56 **Canto MI**, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, Ali SZ, Jagannath S, Petersen GM, Fishman EK, Piantadosi S, Giardiello FM, Hruban RH. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol* 2004; **2**: 606-621 [PMID: 15224285 DOI: 10.1016/S1542-3565(04)00244-7]
- 57 **Topazian M**, Enders F, Kimmey M, Brand R, Chak A, Clain J, Cunningham J, Eloubeidi M, Gerdes H, Gress F, Jagannath S, Kantsevoy S, LeBlanc JK, Levy M, Lightdale C, Romagnuolo J, Saltzman JR, Savides T, Wiersema M, Woodward T, Petersen G, Canto M. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. *Gastrointest Endosc* 2007; **66**: 62-67 [PMID: 17382940 DOI: 10.1016/

j.gie.2006.09.018]

58 **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K; In-

ternational Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]

P- Reviewers: Kim SM, Ramia JM, Shen SQ
S- Editor: Wen LL **L- Editor:** A **E- Editor:** Ma S





百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045