REVIEW ARTICLES

SCREENING IN GENETICALLY INDUCED PANCREATIC CANCER: AN UPDATE

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INTRODUCTION

It is likely that hereditary factors play a role in 17% or more of pancreatic cancers. Ten percent of patients have a familial history that causes disease. Another 7% who apparently have a history of sporadic pancreatic cancer but carry a genetic mutation that causes the disease [1]. Pancreatic cancer is the fifth leading cause of cancer death in the United States [2]. Studies from Pakistan have shown that in 1989 it was 0.47% [3]. There was no significant increase over last two decades [4]. It is an aggressive disease that is uniformly fatal [5,6]. Improvements in surgical techniques have not changed the prognosis which still remains poor. As a result, much focus has been placed on the identification and detection of the specific genetic abnormalities that leads to this disease. After identifying these abnormalities, the effected individuals have a chance for curative treatment at early stage. Family history of genetic abnormality is the key to finding the susceptible individuals [7,8]. After highlighting these individuals, any molecular testing can be offered [9].

Without resection, the overall median survival is 4-6 months with an estimated 5 year survival rate of 0.4%-5% [10]. Chemotherapy has only a modest effect in improving survival by just a few weeks or months [11]. Unfortunately, due to the lack of specific symptoms and current limitations in imaging, only 10%-15% of patients are suitable for a potentially curative resection on presentation. Genetic factors not only play an individual role in cancer formation but this is further augmented many times under the effect of environmental factors like tobacco smoking [12,13]. Molecular analysis is allowing us to detect the specific genetic mutations which can be detected at an early stage so that an effective treatment can be offered to these patients [14]. The aim of this update has been to present a discussion on the genetic factors involved in pancreatic cancer and their clinical use.

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Background of Genetic Disorders

Malignant growth results from mutations in several genes involved in cell cycle control [15]. These genes are of two types, tumor suppressor genes and an oncogene (K-ras). In pancreatic cancers, K-ras mutations have been found frequently (80%-100%), and they could be a good marker to detect tumor DNA in the plasma. BRCA2 mutations are the commonest inherited disorder [16,17]. Evidence for genetic alterations in pancreatic cancer has been obtained. Loss of chromosomal arms 1p, 9p (p16), 17p (p53), and 18q (DPC4) has been seen. This leads to inactivation or mutation of tumor suppressor genes in pancreatic cancer which leads to failure of normal growth [18]. Various genes effect at different stages of tumor development. Pancreatic cancer is associated with a high rate of inactivation of tumor suppressor genes. Potential loss of function of these genes has been reported in more than 50% of cases. As a result up regulation of vascular endothelial growth factor (VEGF) occurs. VEGF promotes angiogenesis in solid tumors.

Progression of Disease

A progression model for pancreatic cancer like that for many other cancers is also established [19]. The term pancreatic intraepithelial neoplasia (PanIN) now

describes the various changes seen in the pancreatic duct system, and is graded as 1 to 3 according to the degree of structural dysplasia and cytological atypia. Cell proliferation rates increase with advancing PanIN lesions, consistent with the theory that these are progressive lesions. PanIN-3, previously referred to as carcinoma in situ lesions, demonstrates severe atypia and are likely to progress to invasive carcinoma [20]. The genetic mutations that take place in these precursor lesions appear to occur in a temporal fashion. These appear one after the other and are cumulative; progressing from 9% in normal ducts to 85% in invasive carcinoma and may signify a poorer prognosis [21].

Genetic Risk Factors

Up to 5%-10% of pancreatic cancer cases are due to a primary genetic factor. In certain families, this is associated with an autosomal dominant pattern of inheritance [12]. These can be divided into three groups. First group is genetic syndrome associated with pancreatic cancer. The second group is familial clusters of pancreatic cancer without obvious genetic syndrome. The third one is those with pancreatic cancer, in primary relatives of patients with a nonpancreatic cancer. Several of these hereditary disorders predispose persons to both endocrine and exocrine pancreatic cancer. These include the multiple endocrine neoplasia type 1 syndrome, hereditary pancreatitis, hereditary nonpolyposis colon cancer/Lynch syndrome-II, von Hippel Lindau syndrome, ataxia-telangiectasia, and the familial atypical multiple mole melanoma syndrome. Case reports and formal epidemiologic studies have suggested the possibility of familial aggregations of pancreatic cancer outside the context of these rare familial syndromes.

Familial pancreatic cancer (FPC) was first described in 1987. The causative mutation remains unknown, although recent work has identified a subset of patients with BRCA2 germline mutation [22]. The BRCA2 protein product plays a diverse role through its interaction with proteins involved in cell cycle regulation, transcriptional regulation, and DNA repair [23]. Loss of function is thought to lead to chromosomal instability, and carriers of the defective gene have a 26%-86% increased risk of developing breast cancer [24]. The penetrance for pancreatic cancer appears to be lower; in recent studies. It was found in approximately 5% of patients with pancreatic cancer who had no family history of pancreatic cancer and in up to 17% in FPC families. More recently, in one study 19% families were found to harbor significant BRCA2 germ line mutations and suggested that BRCA2 testing may be appropriate in pancreatic cancer screening [22].

The familial atypical multiple mole melanoma (FAMMM) syndrome is an autosomal dominant inherited syndrome with incomplete penetrance. Its pathogenesis has been linked to inactivation of tumor suppresser gene, and carriers have a 2-fold increased risk of pancreatic cancer [25]. Hereditary pancreatitis is an autosomal dominant condition characterized by recurrent childhood attacks of acute pancreatitis resulting in the development of chronic pancreatitis in teenage years. Any form of pancreatitis is thought to pose a risk for pancreatic cancer development, ranging from a 15-25 time risk in sporadic chronic pancreatitis to a 70-100 time risk in hereditary pancreatitis [26].

Peutz-Jeghers syndrome consists of multiple oromucosal and intestinal hamartomas. It is associated with the development of cancer at multiple sites and has an autosomal dominant pattern of inheritance with a high risk of pancreatic cancer [27]. Hereditary nonpolyposis colorectal carcinoma has an increased risk of pancreatic cancer. Affected individuals of this autosomal dominant condition also have an increased risk of colonic and extra-colonic cancers. These are caused by mutations in the DNA repair genes but the exact risk of pancreatic cancer is unknown [28]. Ataxia

telangiectasia is an autosomal recessive condition that is associated with the loss of the ataxia telangiectasia mutated gene. Carriers of the mutated gene have an approximately 3 times relative risk of pancreatic cancer [29].

Li-Fraumeni syndrome is an autosomal dominant inherited condition, which predisposes to several neoplasms. Pancreatic neoplasms however are rare and the exact risk is unknown due to limited data [30]. Familial adenomatous polyposis is an autosomal dominant condition with near complete penetrance. There is an approximately 4.5 times increased risk of pancreatic cancer [31]. Patients with Fanconi anemia (FA), the pancreatic cancers that arise have low penetrance for the pancreatic cancer phenotype [32]. In patients with multiple endocrine neoplasia type 1 (MEN1), the most common functional pancreatic endocrine tumor (PET) syndrome is Zollinger Ellison syndrome (ZES). Some progress in its early diagnosis and management have been appreciated [33]. Physician knowledge about pancreatic cancer's natural history and syndrome identification is important for these lesions to be picked up early [34].

Prevention and Screening

Clinicians should be aware of the tumour syndromes that are associated with an increased risk of PC. Screening tests are only recommended in high risk patients. BRCA2 mutational testing in FPC and p16 testing in patients with FAMMM have shown the most promising results to date but have yet to reach widespread clinical application [22,35]. Patients considered to be high risk should be offered participation in screening programs in a specialist research environment [36]. Individuals who test positive should undergo secondary screening to detect the cancer at a potentially preneoplastic stage, which may be up to a year before a neoplasm is clinically apparent [37]. If genetic analysis is suggestive of dysplasia and there is evidence to support this, then it would be reasonable to proceed to total pancreatectomy since the multifocal nature of these dysplastic lesions in high risk groups precludes any form of pancreas preserving procedure [38]. Indeed, reports now suggest that high risk individuals benefit from intensive screening.

Biological Markers for Screening

It is possible to detect specific K-ras mutations in the pancreatic juice, fine-needle aspirates, duodenal fluid, bile, and stool samples of patients with pancreatic cancer [39,40]. Serum screening for K-ras mutations in combination with measurement of the tumor marker CA19-9 is very helpful in diagnosis [41]. Detection of p53 mutations appears to be more promising, with a greater specificity for pancreatic cancer, even in cases with chronic pancreatitis. In conjunction with mutant K-ras analysis, p53 detection in both stool and pancreatic juice offers enhanced detection of pancreatic cancer. Telomerase activity that is highly specific for malignancy can be detected in small cellular samples such as pancreatic juice and bile as well as in fine-needle aspirates [42,43]. Serial analysis of gene expression (SAGE) and microarray technology can analyze hundreds and thousands of genes at a time and thus making them useful in screening programs. Serum glycophosphoprotein osteopontin (OPN) may have utility as a diagnostic marker in patients with pancreatic cancer [44].

Secondary Screening

If molecular analysis of either serum or pancreatic juice reveals a mutation, secondary screening using tests such as endoscopic luminal ultrasound (EUS) and multislice computed tomography (CT) are used [45,46]. A more aggressive screening approaches such as endoscopic retrograde cholangiopancreatography (ERCP) may be used. Both CT and magnetic resonance imaging (MRI) can be used to image the pancreas. However, they have limitations. ERCP can detect subtle changes in the pancreatic ducts. Currently, pancreatic juice is

probably the most suitable sample for the genetic analysis of early pancreatic cancer. However, ERCP has a 5%-10% complication rate, and these effects can sometimes be severe.

Alternatively, an intraluminal ultrasound may be used to obtain detailed images of the pancreas and also the parenchymal tissue. Inflammation and fibrosis are common in pancreatitis. However, the parenchyma is often normal in other cancer conditions such as FPC or Peutz-Jeghers syndrome. Hahn SA et al reported their experience of screening high risk individuals from three families with FPC.30 Both ERCP and EUS may have a role in screening examinations; however, in the presence of background pathology, the power of these modalities to identify early pancreatic neoplasia remains to be established. For a number of solid tumors, including pancreatic cancer, efforts aimed at disease prevention may be more successful than currently available anticancer treatments. However, preclinical and epidemiologic studies suggest that several drugs may have chemopreventive potential in pancreatic cancer [47].

CONCLUSION

Although these genetic diseases leading to pancreatic cancer are not so common but these individuals need counseling and should be considered for germline mutation analysis as an initial step to secondary screening [48]. Screening of these individuals is justifiable both scientifically and economically [49]. In the future, risk stratification will improve with the identification of more genetic alterations responsible for developing an increased risk to pancreatic cancer and with advances in radiological techniques.

New developments in molecular genetics may contribute to the identification of cancer prone families. Appropriate screening and management protocols may be initiated in order to prevent cancer and/or to detect cancer at an early stage, thereby complete cure in these cases [50].

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