Review

An overview of preventive strategies for pancreatic cancer

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Summary

Cancer chemoprevention is defined as the use of specific chemical compounds to prevent, inhibit or reverse carcinogenesis. Chemopreventive intervention can occur throughout carcinogenesis. Many specific food components (e.g. calcium, selenium, folic acid) may also be suitable for chemopreventive use. Chemopreventive drugs are usually administered chronically and are expected to have low toxicity. A variety of mechanisms explain the actions of chemopreventive compounds including modification of carcinogen activation and cellular uptake, inhibition of aberrant signal transduction, induction of apoptosis and inhibition of angiogenesis. As our understanding of carcinogenesis has developed, more specific pharmacologic targets are being selected, e.g. retinoid receptors or cyclo-oxygenases.

Introduction

Cancer of the pancreas is responsible for 168,000 deaths per year and is the ninth most common cause of death from cancer in both sexes combined. The mortality to incidence ratio is 98% and the sex ratio is close to 1. Most cases and most deaths occur in developed countries (approximately two thirds). For men, the incidence and mortality rates are between 6 and 10 per 100,000 and for women between 4 and 6.5 per 100,000, respectively [1]. Epidemiologic studies have identified groups at increased risk (Table 1). Inherited disorders with an increased risk of pancreatic cancer are summarized in Table 2. It is estimated that 5-10% of patients with pancreatic cancers may have an inherited predisposition to this disease.

Hereditary pancreatitis is one of the most well-studied of these inherited conditions. It is an autosomal-dominant disease, with a variable expression and an estimated penetrance of 80%. The gene for this condition has recently been mapped to chromosome 7q35 [2] and the disease is believed to be caused by a mutation in the cationic trypsinogen gene [3]. Acute attacks of abdominal pain begin early in life (mean age ± SD: 13.7 ± 12.3 years). The mean age of development of pancreatic cancer is 56.9 ± 11.2 years, and the mean number of years from onset of symptoms of pancreatitis until diagnosis of pancreatic cancer is 39.6 ± 9.7 years. The standardized incidence ratio (expected/observed) is 53 (CI-23=105); and the cumulative risk of pancreatic cancer to age 70 years is 40%, which increases to 75% with a paternal inheritance pattern [4].

In familial melanoma, persons inheriting a mutant allele of p16 are at increased risk of developing pancreatic carcinoma. Germline mutations of the von Hippel-Lindau gene and germline defects in mismatch repair genes are also thought to account for a minute proportion of familial pancreatic adenocarcinoma. A recent paper demonstrated the presence of germline mutations in the BRCA2 gene in 4 of 41 (9.8%) and a specific mutation (6174 del T) in 2 of 245 (0.8%) pancreatic cancer patients [5]. Insights gained from an understanding of the molecular pathogenesis of these rare disorders may enable us to develop better approaches to preventive strategies.

Molecular pathogenesis of pancreatic cancer

The genetic lesions in infiltrating pancreatic adenocarcinoma have been well characterized and these include frequent mutations of the K-ras (90%) and p16 genes (80%) and less frequently the p53 (50%) and DPC4 (50%) genes [6, 7]. K-ras mutations have also been detected in the "pancreatic intraductal lesions (PIL)" a term used to describe a
noninvasive neoplastic precursor of pancreatic cancer. Investigators have found that alterations of the p16 gene affect a subset of PDLs that contain mutations of the K-ras gene and that these mutations might identify high-risk precursors of the invasive malignancy [8]. Knowledge of the molecular biology of pancreatic cancer may be useful in the development of screening tests, e.g. detection of K-ras gene mutations in pancreatic juice, bile, or stool.

Primary Prevention involves the identification and eradication of carcinogenic factors. Three examples will be discussed, viz. tobacco usage, diet and occupation. The most consistent risk factor for pancreatic cancer is cigarette smoking [9]. The conclusion was based on the evaluation of findings from nine cohort studies and eight case control studies summarized by Anderson et al [10]. Relative risk estimates are approximately 2-fold. Subsequent studies [11] have combined these conclusions. Fuchs et al [12] found a significant increase in risk with increasing pack-years of smoking as well as 49% reduction in pancreatic cancer risk within 2 years of smoking. Despite the strong epidemiological association of smoking as a causative factor in pancreatic cancer, there has not been developed a clear biochemical mechanism to explain this finding. Several studies have reported carcinogen-DNA adduct levels to be higher in the pancreas of smokers compared to nonsmokers [13]. Nitrosamines [14] and aromatic amines [15] may both play a role. About 30 arylamines including 2-naphthylamine and 4 amino-biphenyl are present in cigarette smoke [16]. In a recent paper, Anderson et al [17] demonstrated in about one quarter of human pancreas tissues the presence of an ABP-DNA adduct, (N-deoxyguanosin-8-yl ABP). Molecular epidemiological studies may shed further light on these associations. The N-acetylation polymorphism segregates individuals into rapid, intermediate and slow acetylate or phenotypes. The rapid acetylator genotype (NAT 10) has been associated with an increased risk of bladder cancer among smokers [18]. NAT1 activity has been identified in human pancreatic tissue [17] and there may be a significant role for NAT1 in metabolic activation in the human pancreas.

Dietary factors
An excellent survey of dietary constituents has recently been published [19]. Associated with a "probable reduction in risk" included diets high in vegetables and fruit while diets high in non-starch polysaccharides and fiber as well as high in vitamin C were regarded as possibly protective. High intakes of energy, cholesterol and meat were associated with a "possibly increased" risk of pancreatic cancer. Alcohol, coffee, tea intake bore no relationship to risk of pancreatic cancer.

A variety of protective mechanisms have been postulated by which vegetables and fruit may reduce the risk of cancer. They include the induction of detoxification mechanisms, antioxidant effects, alterations in hormone metabolism and inhibition of nitrosamine formation [20]. The associations between meat consumption and cancer may involve ingestion of genotoxic chemical carcinogens such as N-nitrosocompounds and heterocyclic amines which are present in food as a result of pickling, curing or cooking. In cooked meat and fish, a variety of mutagenic heterocyclic amines have been identified that are formed as pyrolysis products of proteins [17].

Occupational exposures
In Table 3 information reviewed by Anderson et al [19] is summarized. In general, it is difficult to pinpoint specific occupational exposures associated with a definite increase in risk.

Table 3. Occupational exposures (Anderson et al [19])

<table>
<thead>
<tr>
<th>Occupational exposure</th>
<th>Increased risk</th>
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<tbody>
<tr>
<td>Asbestos</td>
<td>inconsistent</td>
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<tr>
<td>Ionizing radiation</td>
<td>inconsistent</td>
</tr>
<tr>
<td>Fossil fuel products</td>
<td>possible</td>
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<tr>
<td>Rubber manufacturing</td>
<td>slight increase</td>
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<tr>
<td>Tanning; chromate exposure</td>
<td>slight increase</td>
</tr>
<tr>
<td>Chemical industry</td>
<td>inconsistent</td>
</tr>
<tr>
<td>Pesticides</td>
<td>possible</td>
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</tbody>
</table>

Chemoprevention
This term refers to the use of chemical agents that suppress or reverse carcinogenesis [21]. Chemoprevention is to be distinguished from chemotherapy that employs agents to treat cancer. However, the distinction between chemoprevention and chemotherapy may be indistinct since some agents such as Cox-2 inhibitors may inhibit angiogenesis as well as modulate a key enzyme involved in early neoplastic transformation [22]. Another example is tamoxifen which has been shown to reduce risk of developing breast cancer and also is used in the management of established cancer. The development of chemopreventive agents for use in pancreatic cancer will induce not only the identification with some precision of those at high risk, but also an understanding of potential sites for molecular targeting. The relative inaccessibility of the pancreas makes it rather problematic to try and measure effects on intermediate biomarkers such as have been studied in the colon, cervix and aerodigestive tract [23].

Perhaps the most promising area lies in the area of farnesyl transferase inhibitors (FT1). K-ras mutations are highly common in pancreatic cancers and also occur in some pre-invasive lesions. Ras proteins serve as connectors between signals generated at the plasma membrane and nuclear effectors. Disruption of the ras signaling pathway could have significant potential as a chemopreventive strategy. Ras proteins require post translational modification with a farnesyl moiety for both normal and oncogenic activity. Two substrates may be targets, viz. farnesyl PPI and the COOH-terminal CAAX motif of ras tetrapeptides. Several isoprenoid compounds have been studied including farnesol, geraniol and perillyl alcohol. In an animal model, these compounds suppress pancreatic tumor growth [24]. Perillyl alcohol may preferentially stimulate Bak-induced apoptosis in malignant versus normal cells [25].
Secondary Prevention

Secondary prevention involves the early detection and eradication of premalignant lesions or the detection of early stage cancer by screening. Screening involves testing asymptomatic individuals for a specific disease. Procedures for screening are based on two principles: they must effectively detect early cancer and a treatment must be available to ensure that if administered early, it results in an outcome that is better than no treatment [26]. Grades of evidence have been adopted by several organizations including the National Cancer Institute. These grades are a hierarchical listing of study designs and provide a useful scale for determining the efficacy of preventive interventions [27].

Grade I: Evidence obtained from at least one properly randomized controlled trial.

Grade II-1: Evidence obtained from well-designed controlled trials without randomization.

Grade II-2: Evidence obtained from well-designed cohort or case-control analytical studies preferably from more than one group.

Grade II-3: Evidence obtained from comparisons between time or places with or without the intervention.

Grade III: Evidence suggested by respected authorities based on clinical experience, descriptive studies or expert committees.

At present, it is evident that no information exists that would lead to a recommendation for screening for pancreatic cancer in the general population. At issue is the question of whether strategies exist now or are likely to be developed that could detect cancer of the pancreas at an early curable stage in those at increased risk. While at present, the only curative form of therapy is surgical resection, there is hope that other means such as chemoprevention may be developed in the future to interdict carcinogenesis if premalignant lesions were detectable.

Possible approaches to screening of high risk individuals

Although there is currently no effective strategy applicable to the general population or even those at increased risk, individuals who are in hereditary pancreatic cancer families may be interested in undergoing screening. Listed in Table 4 are possible techniques for screening for high risk individuals.

Table 4. Possible techniques for screening of high risk individuals.

<table>
<thead>
<tr>
<th>Non-Invasive</th>
<th>K-ras gene mutation</th>
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<tr>
<td>Stool or blood analysis for K-ras gene mutations</td>
<td>K-ras gene mutation can be identified in the bile, stool and blood of patients with advanced pancreatic cancer [28, 29] by the use of the PCR technique. In a recent study of K-ras mutations in pancreatic juice obtained at ERCP, all patients without pancreatic cancer had normal sequences for the K-ras 12th codon. Seventeen of 22 patients with pancreatic carcinoma had a mutation of the ras 12 codon. Two patients (one with chronic pancreatitis and one with idiopathic pancreatitis) with no evidence of pancreatic cancer at first examination but found to have a mutation on the K-ras codon, subsequently developed pancreatic tumors many months later [30]. Other studies have shown that benign inflammatory tissue of the pancreas associated with chronic pancreatitis may contain K-ras mutations [31]. In a recent case report, the authors described the detection of K-ras mutations at codon 12 in the pancreatic juice of a patient 3.5 years before the clinical diagnosis of pancreatic cancer [32]. The sensitivity and specificity of this test require further definition.</td>
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<tr>
<td>Computed tomography</td>
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<td>Position emission tomography</td>
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<td>Magnetic resonance imaging</td>
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<td>Endoscopic ultrasonography</td>
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<td>Endoscopic retrograde cholangiography for brush cytology or collection of pancreatic juice or bile for cytology and K-ras mutation analysis</td>
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<td>Endoscopic ultrasonography for brush cytology or collection of pancreatic juice or bile for cytology and K-ras mutation analysis</td>
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<td>Duodenal/pancreatic juice collection (Dreiling tube) for K-ras analysis</td>
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References


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