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Research review

High-risk population in sporadic pancreatic adenocarcinoma: guidelines for screening

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ARTICLE INFO

Article history:
Received 24 March 2014
Received in revised form
24 May 2014
Accepted 24 June 2014
Available online 13 October 2014

Keywords:
Pancreatic cancer
Screening
Sporadic
Genetic predisposition

ABSTRACT

Background: Pancreatic cancer (PC) is one of the most deadly forms of cancer in the United States, with an annual incidence to death ratio of 0.92 because of the late stage at diagnosis. Identification of high-risk individuals (HRIs) that would be ideal for screening is needed to identify precursor lesions and small early stage disease. Those with a genetic predisposition have largely been identified, but little is known about those at high-risk for sporadic PC. This study asserts that a high-risk population does exist in sporadic pancreatic adenocarcinoma and proposes simple guidelines for screening.

Methods: A systematic review was conducted of the literature regarding identification of and screening in high-risk groups.

Results: Those with the highest genetic risk of developing PC include those with hereditary pancreatitis (87 times more likely at age 55), Peutz–Jehgers syndrome (132 times more likely at age 50), *p16-Leiden* mutations (48 times more likely), and familial pancreatic cancer (FPC) kindreds (32 times more likely). Those with the highest risk of developing sporadic PC include those with new-onset diabetes older than 50 y and smoking history.

Conclusions: Given that sporadic PC is the single largest patient population effected with this devastating disease, some form of screening should be initiated. Currently, the medical community does nothing to attempt early detection of PC. However, sufficient evidence now exists to begin a screening protocol in a high-risk cohort, which would be patients with new-onset diabetes older than 50 y and a smoking history.

1. Introduction

Pancreatic cancer (PC) is projected to be the 10th most common cancer in the United States in 2013, yet it will be the fourth leading cause of cancer death [1]. Because more than 95% of PC is diagnosed at a later stage, the 5-y survival rate remains only 6% [1]. Resection of PC at an early stage represents the greatest potential for long-term survival. A screening program to detect PC at a resectable stage is needed. However, with a low incidence rate of about 1%, a screening program would be beneficial only for HRIs [2].

Many risk factors for PC have been suggested and quantified [3], but no true high-risk sporadic PC population has been definitively identified for a screening program. This is particularly true for sporadic pancreatic adenocarcinoma patients, which make up 90%–95% of PC sufferers [4]. Chronic pancreatitis, diabetes, smoking, and other lifestyle risk factors have been linked to the development of PC [5,6], but currently there

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http://dx.doi.org/10.1016/j.jss.2014.06.046

is no accepted standard on how to evaluate, screen, or risk stratify these types of high-risk patients. This large patient population of possible sporadic PCs is known, but currently there are no standards to begin to screen and or prevent this carcinogenetic pathway from occurring. One of the reasons for the lack of any screening is that one-third of United Statesadults (34.9%) are obese, an estimated 42.1 million people, or 18.1% of all adults (aged ≥18 y) smoke (i.e., >20 pack year history), and 25.8 million Americans, 8.3% of the population, have diabetes. This denominator of possible patients, estimated to be 80 million people is significantly greater than the 46,420 estimated new cases of sporadic PCs in 2014. However, the argument for screening is based on the fact that a cumulative risk of two out of three of these factors could be more predictive, and if we do not start with some form of screening then we will not see any overall survival improvement in the next decade.

This study asserts that a true higher risk population does exist in sporadic pancreatic adenocarcinoma.

2. Methods

A literature search was conducted using Medline via Ovid (National Institute of Health - National Library of Medicine). Search parameters included: "pancreatic neoplasms and diagnosis and prevention and control" and "pancreatic neoplasms and diagnosis and epidemiology." A second literature search was conducted using PubMed, Library of Congress, and EBSCO, all via EndNote. Several search parameters were used, including "title" search terms of "PC," "pancreatic adenocarcinoma," "high-risk," and "diabetes," and "abstract" search terms of "screening," "high-risk," and "new-onset" (Fig. 1).

All searches were further restricted to include only English language articles, human studies, and publish dates between 2005 and 2013, to include only current-screening methods and therapies. Further filtering retained only articles that discussed screening methods and/or protocols and/or risk factors for PC.

Articles pertaining to screening were included only if they discussed presumed validated screening methods, with a focus on defining a high-risk population ideal for screening. Articles discussing non-validated or potential screening methods were removed because non-validated methods would not yet be useful for a screening protocol.

Articles pertaining to risk factors were included only if they discussed presumed validated risk factors for PC because many risk factors have been speculated, but not proven, to be significant. Articles that did not include risk ratios (RR), or an equivalent measure, were removed. To reduce the possibility of missed diagnoses, studies pertaining to diabetes were considered only if they stratified risk based on new-onset *versus* longstanding and used established guidelines (A1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, or oral glucose tolerance test ≥200 mg/dL) or prescription diabetic medication use to determine diabetes status [7].

3. Results

This study defines three separate at-risk groups of the approximately 45,000 patients diagnosed with PC each year: (1) those with known hereditary conditions that predispose an individual to PC, (2) those with familial clustering of PC caused by an unknown genetic mutation (groups 1 and 2 totaling approximately 4500 [8]), and (3) those with clinical predisposition for PC (approximately 19,000 [9,10]).

3.1. *Known hereditary conditions causing PC*

It is well known that there are several hereditary conditions that predispose an individual to PC. Some confer a greater risk than others (Fig. 2).

An inherited form of chronic pancreatitis, known as hereditary pancreatitis, is one such condition. Hereditary pancreatitis is most frequently caused by a mutation in either the *PRSS1*/cationic trypsinogen gene or the *SPINK1*/serine protease inhibitor gene [8]. This condition has been shown to confer an RR of up to 87 (95% confidence interval [CI] 42–114) [11], with a mean diagnostic age of approximately 55 [11,12]. Presenting symptoms of hereditary pancreatitis include

Search Engine	Search Parameters	Filter 1: English language, Human studies, Published 2005-2013	Filter 2: Main topic is presumed validated risk factors for PC with RRs (or equiv) given OR Main topic is screening program with focus on defining high-risk population.	Filter 3: Differentiates new-onset vs. longstanding AND Uses established guidelines/diabetic medication use for diabetes dx
Medline via Ovid	Pancreatic Neoplasms AND Diagnosis AND Prevention and Control →27 articles	→10 articles	→ 5 Articles	
	Pancreatic Neoplasms AND Diagnosis AND Epidemiology →332 articles	→127 articles	→21 articles	
Pubmed, Library of Congress, EBSCO via EndNote	Title: Pancreatic Cancer Title: High-Risk →36 articles	→26 articles	→14 articles	
	Title: Pancreatic Adenocarcinoma Title: High-Risk →6 articles	→3 articles	→1 articles	
	Title: Pancreatic cancer Abstract: Screening Abstract: High-Risk →121 articles	→83 articles	→42 articles	
	Title: Pancreatic Cancer Title: Diabetes Abstract: New-Onset →23 articles	→21 articles	→14 articles	→10 articles

Fig. 1 – Current reported literature for screening PC.