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Mini-review

Modifiable and non-modifiable risk factors for pancreatic cancer: A review

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ABSTRACT

Pancreatic ductal adenocarcinoma is associated with a poor prognosis and a high case-fatality rate. The reasons for poor prognosis are low rates of curative resection due to local infiltration and distant metastasis. To increase survival rates of patients with pancreatic cancer, early detection through surveillance and screening is important. However, screening could only be cost-effective in high-risk populations. Identification of significant risk factors therefore assumes significance. Risk factors could be non-modifiable or modifiable. Non-modifiable risk factors include increasing age, familial cancer syndromes, Afro-American race, hereditary and other forms of chronic pancreatitis, diabetes, and non-O blood group. Important modifiable risk factors include smoking, obesity, dietary factors such as non-vegetarian diet, and toxins. Preventive strategies at the population level and an effective screening program targeted at high-risk people may help in prevention and early detection of pancreatic ductal adenocarcinoma.

Introduction

Cancer is among the leading causes of death worldwide with 14 million new cases and 8.2 million cancer-related deaths having been reported in 2012. The annual cancer cases and mortality are expected to increase to 22 million of new cases and 11.2 million cancer-related deaths by 2025 [1]. Cancer of the pancreas, although relatively uncommon, ranks seventh for cancer mortality globally, and fourth in the United States [2,3].

Pancreatic ductal adenocarcinoma with its associated variants accounts for 85–90% of all pancreatic neoplasms and is therefore referred to as the pancreatic cancer. Ductal adenocarcinoma may vary from well differentiated to poorly differentiated, with the most common being moderately differentiated cancers [4]. Other cancers that might arise from the ductal cells are adenosquamous carcinoma, squamous cell carcinoma and giant cells carcinoma which constitute about 2% of all pancreatic cancer cases [5,6]. Unlike the declining trends in incidence and mortality from other leading cancers in the United States (lung, breast, colorectal and prostate) the incidence and mortality of pancreatic cancer has been increasing over the past two decades [7,8]. Based on 2009–2013 data, the age-adjusted incidence and mortality of pancreatic cancer in USA has been reported as 12.4 and 10.9 per 100,000 per year, respectively [9]. It is now predicted that pancreatic cancer may become the second leading cause of cancer mortality in the United States by 2030 [10].

The prognosis of pancreatic cancer is poor with 1-year and 5-year survival rates being <25% and 5%, respectively [11]. Most patients with pancreatic cancer are diagnosed at an advanced stage when the disease is unresectable and therefore have a median survival of <1 year; thus, the case fatality ratio of pancreatic cancer is about 0.99 [12]. Understandably, the survival is higher (16.6%) for localized tumors but only <10% of tumors are detected early [13]. Even in patients with localized and resectable tumors, the long-term prognosis remains dismal due to high rates of local recurrence and distal metastases.

The diagnosis of pancreatic cancer may be delayed by up to 2 years after initial presentation to a physician. The positive predictive value (PPV) of most of the symptoms amount individually to <1%. The presence of jaundice, on the other hand is more alarming, prompts an immediate workup raising its PPV to 22% and thus may lead to the diagnosis of the malignancy at an earlier stage [14].

Therefore, there remains an urgent need for earlier diagnosis of pancreatic cancer. Large population based cohorts have now identified certain modifiable and non-modifiable risk factors which may predict increased odds of developing pancreatic cancer which will be discussed further in this review.

Risk factors for pancreatic cancer

The risk factors can be grouped as either host and environmental factors, or as non-modifiable and modifiable risk factors [15,16].

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Most host factors are non-modifiable while the environmental factors may be modifiable to some extent.

Host or non-modifiable factors

Age

Pancreatic cancer is predominately a disease of older individuals. Pancreatic cancer is rare in the 1st three decades of life. After age 30, however, incidence rates increase exponentially and peaks in the 7th and 8th decades [6,12]. In the US, majority of the patients with pancreatic cancer are diagnosed between the ages of 40 and 80 years with the median age at diagnosis of pancreatic cancer being 71 years. The mean age of patients with early stage cancer is about 2.3 years younger than those with advanced stage cancer, suggesting that progression of cancer takes about 1–2 years to advance from early to late stage [17]. In India, the incidence of pancreatic cancer starts to rise in the 5th decade and peaks in the 6th decade [18].

Gender

Pancreatic cancer is 30% more common in men than women. The overall age adjusted incidence rate for pancreatic cancer is 13.9/100,000 for men and 10.9/100,000 for women. The incidence rates differ sharply among men and women between highly developed and less developed countries. Incidence rates of 8.5/1,00,000 for men and 5.6/1,00,000 for women are observed in developed countries, while incidence rate of 3.3/1,00,000 in men vs. 2.4/1,00,000 in women are reported in less developed or developing countries (Fig. 2) [19]. In India, males are 1.5–2 times more affected than females [17]. Several studies have evaluated gender-specific hormonal risk factors for a causal role in susceptibility to the pancreatic cancer [20,21]. A recent systematic review [20] has concluded that reproductive factors are not associated with the development of pancreatic cancer in women. This suggests that the differences in pancreatic cancer rates between men and women may be due to environmental factors like smoking,. although it is possible that there may yet be undiscovered genetic factors influencing cancer incidence and mortality in males and females.

Ethnicity

Race is a recognized risk factor for pancreatic cancer. Significant differences in the incidence of pancreatic cancer have been reported between races. In the United States, African-Americans have a higher incidence than Caucasians while the incidence is lowest in Asian Americans and Pacific Islanders [10]. African-Americans are also more likely to be diagnosed with advanced disease and less likely to receive surgery for pancreatic cancer [22]. The higher incidence in African-Americans has been attributed to differences in modifiable risk factors such as diet, alcohol, smoking, and vitamin D insufficiency. However, recent population based studies have shown that the increased incidence of pancreatic cancer is not completely explained by the known and suspected risk factors listed above, suggesting other factors that may contribute to the increased risk [23]. These factors may include race-specific genetic differences which result in an increased risk of acquired mutations from known toxins e.g. in the ability to detoxify tobacco products [24,25]. In a study comparing the oncogene mutations and biomarker immunoexpression between African-Americans and Caucasians, the investigators found that African-Americans had significantly higher rates of *K-ras* mutations to valine and lower rates of *K-ras* mutations to cysteine. There was also lower expression of Fas and a trend towards higher immunoexpression to HER2 on immunohistochemistry amongst the African-Americans [26]. Chinese patients with pancreatic cancer have also been found to have different expressions of *K-ras* and *p53* than Western or Japanese patients with pancreatic cancer [27,28]. These findings suggest that there may be genetic and molecular differences related to race and ethnicity, which may influence the incidence and biological behavior in pancreatic cancer similar to those seen in other tumors [29]. These differences may also explain the difference in survival rates after treatment of pancreatic cancer in different racial groups. In particular, Asian patients appear to have a better survival rate than non-Asian patients. Longnecker et al. [30] studied over 10,000 patients with pancreatic cancer through the USA SEER cancer registry from 1973 to 1995. Asian patients were found to have less aggressive tumors than either white or black patients.

Blood group

Large epidemiological studies have found an association between ABO blood groups and the risk of developing pancreatic cancer [31]. People with blood groups A, AB, or B have a higher risk of developing pancreatic cancer than people with blood group O (the ORs for pancreatic cancer in subjects with types A, AB, and B were 1.38 [95% confidence interval (95% CI), 1.18–1.62], 1.47 (95% CI, 1.07–2.02), and 1.53 (95% CI, 1.21–1.92), respectively) [32]. In support of these findings, a recent genome wide association study has identified a common genetic variant at the ABO locus of 9q34 to be associated with increased pancreatic cancer risk [33]. The pathogenetic mechanism behind this association between the ABO locus and pancreatic cancer is, however, yet to be elucidated. Non-O blood groups may potentiate the risk of other factors like smoking as was reported in a joint model [31] where current smokers with non-O blood type had an adjusted OR of 2.68 (95% CI, 2.03–3.54) compared with nonsmokers of blood type O.

Genetic risk factors

Pancreatic cancer, like all other cancers, is a fundamentally genetic disease caused by both inherited and acquired genetic mutations. Genetic variation/mutations plays an important role in both the familial and non-familial (sporadic) occurrences of pancreatic cancer. More than 80% of pancreatic cancer develops due to sporadically occurring mutations. A small proportion of pancreatic cancer cases are due to inherited germline mutations.

(i) **Inherited Genetic mutations (Germline Mutations)**

Recently, some germline mutations have been recognized which have been associated with increased risk of pancreatic cancer in some genetic syndromes and certain familial pancreatic cancer kindreds, accounting for 5–10% of all patients (Table 1). This has also led to an interest in identifying high-risk individuals who can then be screened cost effectively to detect premalignant (PanIN, IPMN) or early stage tumors.

- ❖ Familial Pancreatic Cancer:

Familial pancreatic cancer is defined as at least two first-degree relatives with pancreatic cancer. The risk of pancreatic cancer increases exponentially with the number of first-degree relatives involved, ranging from three-fold when two first-degree relatives have pancreatic cancer to 57 fold increased risk with three affected first-degree relatives [37]. *BRCA2* mutations are the most common inherited mutations in familial pancreatic cancer though other mutations like PALB2 have also been reported.

- ❖ Familial Cancer Syndromes: Increased risk of pancreatic cancer is also found to be associated with a number of familial cancer syndromes. These include FAMMM syndrome, hereditary pancreatitis, Peutz–Jeghers syndrome, cystic fibrosis, hereditary breast and ovarian cancer, Fanconi anemia, familial adenomatous polyposis, Li-Fraumeni syndrome, and Lynch syndrome. These syndromes are associated with germline mutations in certain genes like BRCA2, p16, ATM, STK11, PRSS1,

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