

# Epidemiology and Inherited Predisposition for Sporadic Pancreatic Adenocarcinoma



Rachael Z. Stolzenberg-Solomon, PhD, MPH, RD<sup>a,\*</sup>,  
Laufey T. Amundadottir, PhD<sup>b,\*</sup>

## KEYWORDS

• Pancreatic cancer • Diabetes • Etiology • Genome-wide association studies

## KEY POINTS

- Given the changing demographics of Western populations, the numbers of pancreatic cancer cases are projected to increase during the next decade.
- Diabetes, recent cigarette smoking, and excess body weight are the most consistent risk factors of pancreatic cancer.
- The search for common and rare germline variants that influence risk of pancreatic cancer through genome-wide association studies (GWAS) and high-throughput-sequencing-based studies is underway and holds the promise of increasing the knowledge of variants and genes that play a role in inherited susceptibility of this devastating disease.
- Although research gaps remain, research reported in this review has advanced the understanding of pancreatic cancer.

## EPIDEMIOLOGY FOR PANCREATIC ADENOCARCINOMA

### *Descriptive Epidemiology*

Although pancreatic cancer accounts for less than 3% of cancer incidence, it ranks seventh for cancer mortality globally<sup>1</sup> and fourth in the United States.<sup>2</sup> Annually an

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Both authors contributed equally to this review.

This work was supported by the Intramural Research Program of the National Institutes of Health, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services.

<sup>a</sup> Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Room 6E420, Rockville, MD 20850, USA; <sup>b</sup> Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 8717 Grovemont Circle, Bethesda, MD 20892, USA

\* Corresponding authors. Nutritional Epidemiology Branch and Laboratory of Translational Genomics, National Cancer Institute, National Institutes of Health, Bethesda, MD.

*E-mail addresses:* [rs221z@nih.gov](mailto:rs221z@nih.gov); [amundadottir@mail.nih.gov](mailto:amundadottir@mail.nih.gov)

Hematol Oncol Clin N Am 29 (2015) 619–640

<http://dx.doi.org/10.1016/j.hoc.2015.04.009>

0889-8588/15/\$ – see front matter Published by Elsevier Inc.

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estimated 338,000 and 46,420 people will be diagnosed with pancreatic cancer and 331,000 and 39,590 will die from the disease, worldwide and in the United States, respectively.<sup>1,2</sup> There is no effective screening test for the malignancy; therefore, it is most often diagnosed at advanced stages with metastatic disease, which contributes to its high fatality with a mortality to incidence ratio of 0.98.<sup>1</sup> The 5-year survival rate is 6.7%, which is poorer than that of other cancers.<sup>2</sup> Only 9% of pancreatic cancer cases are diagnosed with localized disease when surgical resection may be an option for a cure.<sup>3</sup> Those with localized disease have a 5-year survival of 25.8%.<sup>3</sup> More than 90% of pancreatic cancers are ductal adenocarcinomas, with neuroendocrine tumors constituting about 5%.<sup>4</sup>

Internationally, rates of pancreatic cancer vary by 7-fold, with higher rates in developed than in developing countries.<sup>1</sup> In part the variation in incidence and mortality patterns worldwide may be explained by underascertainment of the disease and imperfect mortality data.<sup>1</sup> Pancreatic cancer occurs slightly more often in men than in women and in African Americans than in Caucasians and other ethnicities in the United States.<sup>2</sup> Its incidence and mortality rates increase with age. More than 88% of pancreatic cancer is diagnosed among people aged 55 years or older, with the median age at diagnosis of 71 years.<sup>3</sup> In the United States, incidence and mortality rates for pancreatic cancer either decreased or remained stable during the latter part of the twentieth century but increased slightly since 2000 (Figs. 1 and 2).<sup>2,5</sup> Given the changing demographics in the United States, namely, the aging population and minority distribution, one recent study has projected that the number of pancreatic cancer deaths will surpass that of breast and colorectal cancer by the year 2030.<sup>6</sup>

## **Risk Factors**

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### **Diabetes**

Diabetes is associated with approximately a 2-fold risk for pancreatic cancer overall.<sup>7-9</sup> Excess risks tend to be particularly high (2.5- to 10-fold) for diabetes diagnosed within 5 years of pancreatic cancer diagnosis and become attenuated with long duration of diabetes.<sup>7-9</sup> A large pooled case-control study showed that the association with pancreatic cancer remained significant among those having diabetes for 20 years or more; however, the excess risk was diminished to 30%.<sup>9</sup>

**Biomarkers for diabetes and insulin resistance** Although diabetes as defined by fasting glucose, glucose intolerance,<sup>7</sup> or hemoglobin A(1c),<sup>10,11</sup> a marker for glucose control, has consistently been associated with pancreatic cancer in prospective epidemiologic studies, studies of other biomarkers hypothesized to mediate the diabetes-pancreatic cancer relationship have shown no association or inconsistent results (Table 1).<sup>10-17</sup> Insulin is a mitogen and has growth-promoting activity on pancreatic cancer cells, and patients with type 2 diabetes exhibit hyperinsulinemia during the early stages of the disease.<sup>18</sup> Two studies that examined insulin and subsequent risk of pancreatic cancer showed significant elevated risks that were graded with significant trends across increasing categories of insulin. In both studies, the associations were stronger among cases occurring 10 years or more after their blood collection.<sup>11,12</sup> These findings support that the positive associations observed among the later occurring cases are not the consequence of subclinical pancreatic cancer and that insulin resistance may play a role in pancreatic cancer etiology.

A nested case-control study of 4 cohorts examined the association between 83 metabolites and pancreatic cancer.<sup>19</sup> The investigators observed significant positive associations between plasma branched-chain amino acids (ie, isoleucine, leucine, and valine) and subsequent risk of pancreatic cancer in both humans and in a mutant

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