

# Special Section: Pancreatic Cancer

Cancer of the pancreas is one of the deadliest cancer types. Most pancreatic cancer patients will die within the first year of diagnosis, and just 6% will survive five years. Over the past decade, pancreatic cancer death rates have been slowly increasing among US men and women, in contrast to the downward trend in rates for most other major cancer sites, such as lung, colorectum, female breast, and prostate. The lack of progress in primary prevention, early diagnosis, and treatment underscores the need for additional efforts in pancreatic cancer research and has motivated us to address this disease in the current edition of *Cancer Facts & Figures*. Specifically, this special section provides updated information on occurrence, prevention, early detection, diagnosis, and treatment of pancreatic cancer. This information is intended to inform anyone interested in learning more about pancreatic cancer, including policy makers, researchers, clinicians, cancer control advocates, patients, and caregivers.

The pancreas contains two types of glands that each perform very different functions. The exocrine glands produce enzymes that help digest food; the endocrine glands produce important hormones such as insulin, which regulates blood sugar levels. Exocrine and endocrine cells form completely different types of tumors with distinct risk factors, symptoms, diagnostic tests, treatment, and survival rates. Exocrine tumors are the focus of this special section because they are by far the most common type of pancreatic cancer, representing about 95% of cases.

## How Many Cases and Deaths Are Estimated to Occur in 2013?

Pancreatic cancer is the 10th most common cancer diagnosis among men and the 9th most common among women in the US. In 2013, an estimated 45,220 new cases of pancreatic cancer will be diagnosed nationwide.

Pancreatic cancer accounts for about 7% of all cancer deaths and ranks fourth as a cause of cancer death among both men and women in the US. In 2013, approximately 38,460 people are expected to die from pancreatic cancer nationwide.

## Who Gets Pancreatic Cancer?

### Sex

- Pancreatic cancer is about 30% more common in men than in women. During 2005-2009, the age-adjusted incidence rate (per 100,000 persons) of pancreatic cancer was 13.6 for men and 10.5 for women.
- The lifetime risk of developing pancreatic cancer is about 1.5% for both men and women (Table 1).

- Men are more likely than women to develop pancreatic cancer at every age after 35 years (Figure 1a, page 26).
- During 2005-2009, the age-adjusted death rate (per 100,000 persons) for pancreatic cancer was 12.5 for men and 9.5 for women.

### Age

- Pancreatic cancer incidence and death rates increase with advancing age, with a steep increase after about age 50.
- During 2005-2009, the incidence rate (per 100,000) in men was 1.2 among those 35 to 39 years of age compared to 100.5 among those 85 years and older; in women the rate was 1.0 among those 35 to 39 years of age compared to 87.7 among those 85 years and older (Figure 1a, page 26).
- During 2005-2009, the median age at diagnosis of pancreatic cancer was 71 years of age. This means that about half of all patients developed this disease when they were older than age 71.
- The likelihood of developing pancreatic cancer in the next 10 years is about four times higher at age 70 than at age 50 (Table 1).

### Race/Ethnicity

- Pancreatic cancer incidence and mortality rates vary across different racial/ethnic groups, with the highest rates in African Americans and the lowest rates in Asian Americans/Pacific Islanders (Figure 2, page 27).
- Incidence rates are higher in African Americans than in whites at every age (Figure 1b, page 26).
- During 2005-2009, the incidence rate (per 100,000 persons) was 15.3 for African Americans, 11.6 for whites, and 8.8 for Asian Americans/Pacific Islanders.

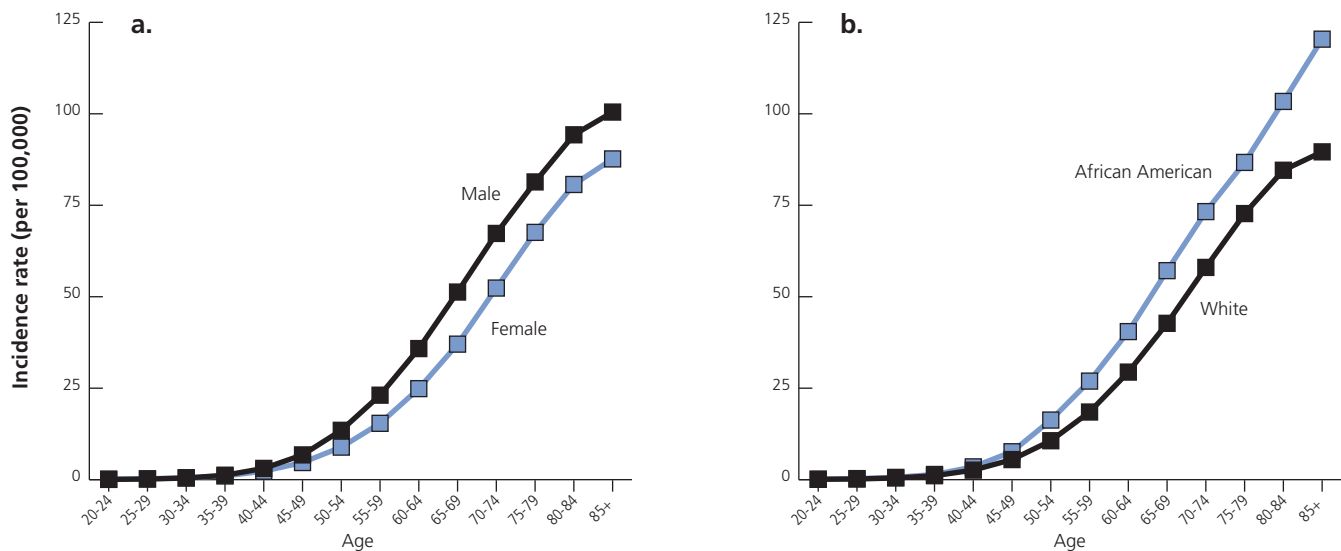
**Table 1. Probability (%) of Developing Pancreatic Cancer over Selected Age Intervals by Sex, US, 2007-2009\***

Age	Male	Female
0 to 39	0.01 (1 in 9,746)	0.01 (1 in 9,479)
40-49	0.05 (1 in 2,063)	0.04 (1 in 2,674)
50-59	0.18 (1 in 563)	0.12 (1 in 843)
60-69	0.41 (1 in 241)	0.30 (1 in 335)
70-79	0.65 (1 in 155)	0.56 (1 in 179)
Lifetime risk	1.48 (1 in 67)	1.45 (1 in 69)

\*For people free of cancer at beginning of age interval. Percentages and "1 in" numbers may not be equivalent due to rounding.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.6.1. Statistical Research and Applications Branch, National Cancer Institute, 2012.srab.cancer.gov/devcan.

**Figure 1. Pancreatic Cancer Incidence Rates\* by Age and Sex (a) and Age and Race (b), US, 2005-2009.**



\*Age adjusted to the 2000 US standard population.

**Source:** North American Association of Central Cancer Registries (NAACCR). Data are collected by cancer registries participating in NCI's SEER program and CDC's National Program of Cancer Registries.

American Cancer Society, Surveillance Research, 2013

- Mortality rates (per 100,000 persons) during the corresponding time interval were 13.8, 10.7, and 7.5 for African Americans, whites, and Asian American/Pacific Islanders, respectively.
- Racial differences in pancreatic cancer rates are largely explained by established risk factors, such as cigarette smoking, obesity, and diabetes.<sup>1</sup>

### Socioeconomic status

Number of years of education is one measure of socioeconomic status used by researchers to study health disparities.

- Pancreatic cancer death rates are higher among those with fewer years of education.
- One study found that in 2007, the pancreatic cancer death rate among non-Hispanic white men 25 to 64 years of age was about 80% higher for those with 12 or fewer years of education than for those with 16 or more years of education; among non-Hispanic white women, the death rate for the less-educated group was double that of the most educated.<sup>2</sup>
- This study also found that from 1993 to 2007, pancreatic cancer death rates among non-Hispanic white men and women 25 to 64 years of age increased among those with the least education, but remained stable among those with the most education.<sup>2</sup>
- Another study found that low income was associated with an 80% increased risk of pancreatic cancer in white men and a 170% increased risk in African American men after accounting for differences in smoking, dietary factors, and heavy alcohol drinking.<sup>1</sup>

### Are There Geographic Differences in Pancreatic Cancer in the US?

- Despite substantial international variation, within the US, pancreatic cancer incidence and mortality rates vary only slightly between states.
- Among whites, pancreatic cancer death rates are highest in the Northeast, and range from 8.4 (per 100,000) in the District of Columbia to 12.1 in Connecticut (Figure 3, page 28).
- Among African Americans, death rates are highest in the Midwest, and range from 7.8 (per 100,000) in West Virginia to 18.9 in Iowa (Figure 3, page 28).

### How Has the Occurrence of Pancreatic Cancer Changed over Time?

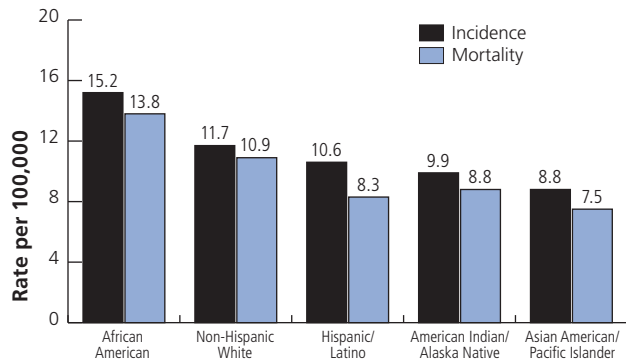
#### Incidence trends

During the past 10 years of data (2000-2009), for which we have coverage for almost the entire US, pancreatic cancer incidence rates increased by 0.9% per year among white men, white women, and African American men, while rates remained stable for African American women and men and women of all other major racial and ethnic groups.<sup>3</sup>

#### Mortality trends

Although the pancreatic cancer death rate increased for the overall US over the past 10 years of data (2000-2009), this increase was confined to white men and women (by 0.5% per year) and Asian American and Pacific Islander men (by 1.0% per year).<sup>3</sup>

**Figure 2. Pancreatic Cancer Incidence and Mortality Rates\* by Race and Ethnicity†, US, 2005-2009.**



\*Per 100,000, age adjusted to the 2000 US standard population. †Persons of Hispanic/Latino origin may be of any race.

**Sources:** Incidence: North American Association of Central Cancer Registries (NAACCR) data; Mortality: US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention. Data for American Indians/Alaska Natives are based on Contract Health Service Delivery Area (CHSDA) counties.

American Cancer Society, Surveillance Research, 2013

## Can Pancreatic Cancer Be Prevented?

The causes of pancreatic cancer are not well understood, though there are several factors known to increase risk. Known modifiable risk factors include obesity, cigarette smoking, and other forms of tobacco use. Risk factors that are not modifiable include a family history of pancreatic cancer and certain inherited syndromes. Strategies for preventing pancreatic cancer include not smoking and maintaining normal body weight. Consuming adequate quantities of fruits and vegetables may also have a preventive effect, although strong evidence for this association is lacking.

### Modifiable Risk Factors

#### Tobacco use

Tobacco use is the most important known risk factor for pancreatic cancer; approximately 20% of pancreatic cancers are attributable to cigarette smoking.<sup>4</sup> The risk of developing pancreatic cancer is about twice as high among smokers as among never smokers;<sup>5</sup> risk increases with greater tobacco use and longer duration of smoking.<sup>6,7</sup> Cigar and pipe smoking also increase risk.<sup>8,9</sup> Quitting smoking rapidly reduces the risk of pancreatic cancer; after 5-10 years of cessation, the risk among former smokers returns to that of never smokers.<sup>4,10</sup> Use of smokeless tobacco products also increases the risk of pancreatic cancer.<sup>11</sup> Evidence on secondhand smoke exposure and pancreatic cancer is inconsistent.<sup>12</sup>

#### Obesity and physical activity

Obesity has also been fairly consistently linked to increased risk of pancreatic cancer. Obese individuals have a 20% higher risk of developing pancreatic cancer than those who are normal weight.<sup>13-15</sup> Being obese during early adulthood may be associated

with an even greater risk of pancreatic cancer and a younger age of disease onset.<sup>16</sup> Abdominal obesity may increase risk independent of general obesity, especially in women.<sup>15,17</sup>

Results regarding the association between physical activity and pancreatic cancer risk are mixed.<sup>14,18-21</sup> A slightly decreased risk of pancreatic cancer was linked to total and occupational physical activity in a recent literature review<sup>22</sup> but not in a previous one.<sup>23</sup> There is currently limited evidence to support a protective effect of recreational physical activity on risk of pancreatic cancer.<sup>22</sup>

#### Alcohol use

Whether alcohol use causes pancreatic cancer remains to be determined. A positive association between alcohol use and pancreatic cancer was found in several but not all studies.<sup>24</sup> Accumulating evidence suggests that a moderate increased risk is limited to heavy alcohol users.<sup>25</sup> A recent meta-analysis showed that consumption of three or more drinks of alcohol per day is associated with a 20% to 30% increased risk of pancreatic cancer.<sup>25</sup> However, due to the strong relationship between alcohol consumption and tobacco use, it is difficult to eliminate the effect of smoking when studying the association between alcohol drinking and pancreatic cancer risk.

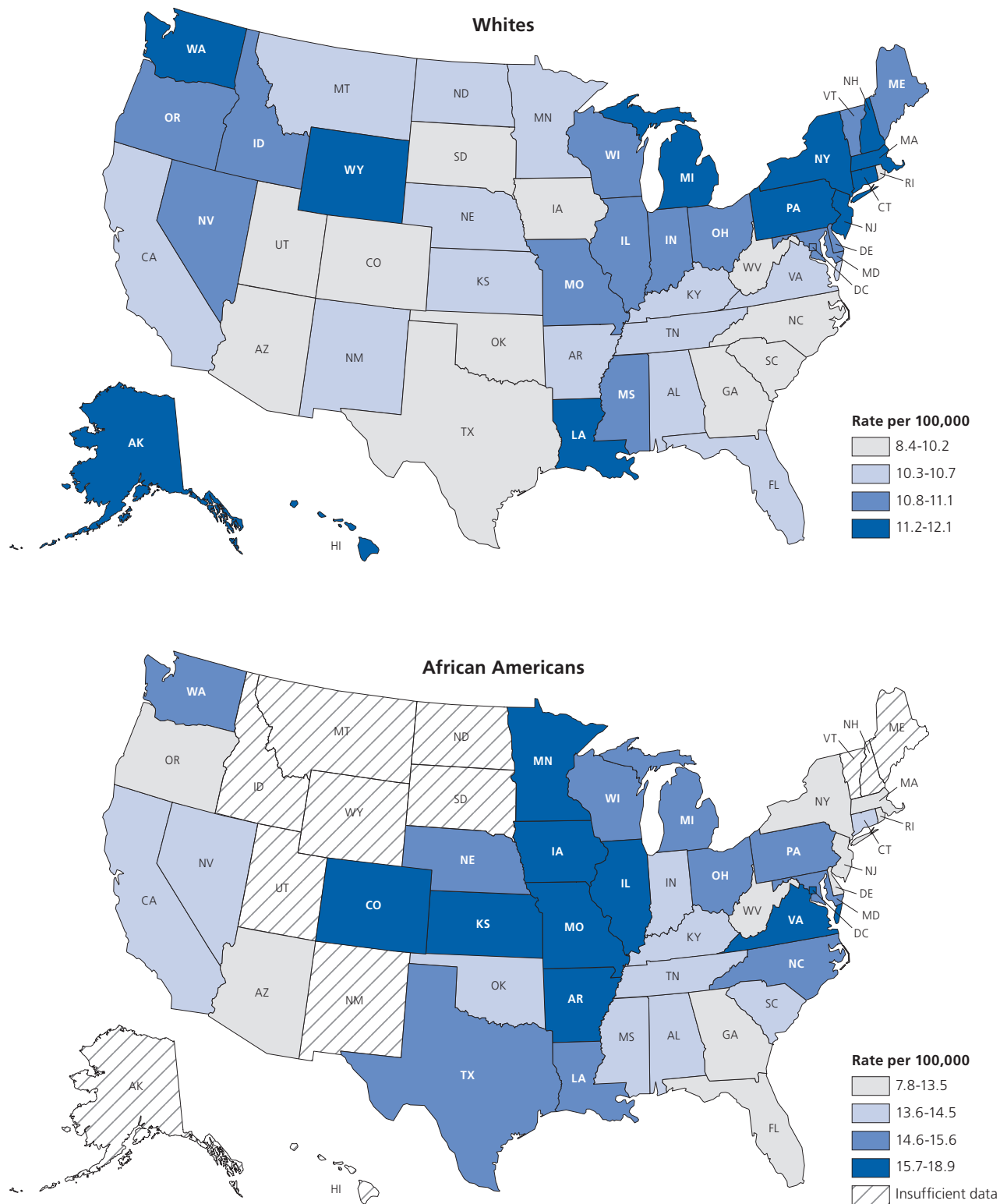
#### Dietary factors

A number of dietary factors have been assessed regarding their association with pancreatic cancer risk. There is some evidence that the consumption of red and processed meat may slightly increase risk.<sup>26</sup> Investigators have also found some evidence for increased risk among those who consume meat that has been cooked at very high temperatures.<sup>27</sup> A protective effect of folate intake on pancreatic cancer risk has been reported in several studies;<sup>28</sup> however, a recent large analysis found no association.<sup>29</sup> At present, there is limited evidence supporting a protective effect of fruit and vegetable consumption on the risk of pancreatic cancer.<sup>30-33</sup> No association between coffee consumption and pancreatic cancer was found in a recent analysis that combined many studies.<sup>34</sup>

#### Sunlight and vitamin D

Studies are conflicting about the relationship between sunlight, vitamin D, and pancreatic cancer. Several studies have found that sun exposure is associated with lower pancreatic cancer death rates, suggesting that vitamin D, acquired primarily through sun exposure to the skin, may be protective against pancreatic cancer.<sup>35-37</sup> However, results from epidemiological studies that assessed individual-level vitamin D intake and pancreatic cancer risk have been inconsistent. Two large studies found that both dietary vitamin D and vitamin D derived from both diet and sunlight exposure are protective.<sup>38,39</sup> Conversely, a recently published analysis found that while there was no association between low levels of vitamin D and pancreatic cancer, high vitamin D levels were associated with an increased risk of pancreatic cancer.<sup>40</sup>

**Figure 3. Geographic Patterns in Pancreatic Cancer Death Rates\* by State and Race, US, 2005-2009.**



\*Age adjusted to the 2000 US standard population. Insufficient data indicates states with fewer than 20 deaths.

Source: US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention.

American Cancer Society, Surveillance Research, 2013



## Non-modifiable Factors and Medical Conditions

### Family history

A number of studies have linked family history to an increased risk of pancreatic cancer. Generally, individuals with a family history of pancreatic cancer have a nearly 2-fold increased risk for developing pancreatic cancer, compared to those without such a history.<sup>41</sup> The risk increases to 7- to 9-fold for individuals with at least 1 first-degree relative (a parent or sibling) with pancreatic cancer and 17- to 32-fold for individuals with 3 or more first-degree relatives with pancreatic cancer.<sup>42,43</sup> Risk is also increased if a first-degree relative was diagnosed with pancreatic cancer before age 50.<sup>43</sup>

### Genetic factors

Genetic factors (factors related to gene variations or alterations) account for approximately 5% to 10% of all pancreatic cancer cases.<sup>44,45</sup> There are several gene mutations that are associated with an increased risk of pancreatic cancer, though these are extremely rare in the general population.<sup>46,47</sup> Mutations in the *BRCA2* gene are associated with a 3- to 10-fold increased risk of pancreatic cancer and account for the highest proportion (5% to 17%) of known causes of inherited pancreatic cancer.<sup>48-50</sup> Mutations in the *CDKN2A* gene, which are linked to the familial atypical multiple mole-melanoma (FAMMM) syndrome, are associated with an approximately 13- to 22-fold increased risk of pancreatic cancer.<sup>51</sup> Patients with Peutz-Jeghers Syndrome (PJS), which is usually caused by *STK11* mutations, have an 11% to 36% chance of developing pancreatic cancer during their lifetime.<sup>52,53</sup> The risk among people with hereditary pancreatitis (inflammation of the pancreas) linked to *PRSS1* mutations is approximately 70 times greater than that expected in the normal population, with lifetime risk of developing pancreatic cancer approximately 40% to 55%.<sup>54</sup> Patients with hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome), which is most often caused by *MLH1* or *MSH2* mutations, have about a 9-fold increased risk of developing pancreatic cancer.<sup>45,55</sup> Recent studies have found that people with non-O blood groups (i.e., blood groups A, AB, and B) have a slightly increased risk of pancreatic cancer, though the mechanisms of this association are still unclear.<sup>56-58</sup>

### Chronic pancreatitis (inflammation of the pancreas)

Accumulating evidence suggests that long-standing chronic pancreatitis is a strong risk factor for pancreatic cancer, though pancreatitis may also be an early indicator of pancreatic cancer.<sup>54,59,60</sup> After excluding the pancreatic cancer cases diagnosed within 2 years from chronic pancreatitis diagnosis, a review study reported a 6-fold increased risk of pancreatic cancer among patients with chronic pancreatitis.<sup>54</sup> The risk is especially strong in patients with rare types of pancreatitis, such as hereditary pancreatitis and tropical pancreatitis. The lag period between pancreatitis diagnosis and pancreatic cancer onset is usually about 10 to 20 years. Despite the strong association between

chronic pancreatitis and pancreatic cancer, chronic pancreatitis is uncommon; moreover, only about 4% of these patients will develop pancreatic cancer within 20 years of diagnosis.<sup>59</sup>

### Diabetes

About 25% of patients with pancreatic cancer have diabetes mellitus at diagnosis, and roughly another 40% have pre-diabetes (higher than normal blood glucose levels).<sup>61,62</sup> Compared with non-diabetic individuals, patients with long-term ( $\geq 5$  years) type-II diabetes have a 50% increased risk of pancreatic cancer.<sup>63</sup> Pancreatic cancer can cause diabetes, and sometimes diabetes is an early sign of the tumor.<sup>62</sup> Elevated pancreatic cancer risk has also been reported among individuals with type-I diabetes.<sup>64</sup> Recent reports also suggest that hyperglycemia (high blood glucose), abnormal glucose metabolism, and insulin resistance are associated with increased risk of pancreatic cancer.<sup>65-69</sup>

### Infection and other medical conditions

Several studies have detected an increased risk of pancreatic cancer among people with chronic infections with hepatitis B virus, hepatitis C virus,<sup>70,71</sup> and *Helicobacter pylori*.<sup>72</sup> Individuals with a history of cholecystectomy (surgical removal of the gallbladder)<sup>73</sup> or partial gastrectomy (partial surgical removal of the stomach)<sup>74</sup> have also been found to be at increased risk of developing pancreatic cancer. Other medical conditions that may increase risk include cystic fibrosis<sup>75</sup> and periodontal disease.<sup>76</sup>

## Can Pancreatic Cancer Be Detected Early?

Early stage pancreatic cancer usually has no symptoms. When symptoms do occur, the tumor has usually spread to surrounding tissues or distant organs. Common symptoms of pancreatic cancer include mild abdominal discomfort, mid-back pain, jaundice (yellowing of the skin or whites of the eyes), and weight loss. Nausea and vomiting may occur among patients with more advanced disease. In the US, only about 15% to 20% of pancreatic cancer cases are diagnosed early enough to be eligible for surgery.

To date, there is no single, reliable test for the early detection of pancreatic cancer; therefore, screening the general population is not recommended by any health agency.<sup>77</sup> Existing screening programs have been limited to research settings with a focus on detecting precancerous lesions among high-risk individuals.<sup>78</sup>

The most frequently tested techniques for pancreatic cancer screening include endoscopic ultrasound (EUS), helical computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic retrograde cholangiopancreatography (ERCP). Single use of EUS or various combinations of these imaging techniques are capable of detecting early pancreatic cancer or precancer in high-risk patients, such as those with chronic, hereditary, or tropical pancreatitis; Peutz-Jeghers syndrome; cystic fibrosis; or familial atypical multiple mole-melanoma.<sup>79-81</sup> However, it remains unclear whether screening high-risk populations is effective in

**Table 2. Median Pancreatic Cancer Survival by Stage at Diagnosis**

Stage	Median Survival*
IA	24.1 Months
IB	20.6 Months
IIA	15.4 Months
IIB	12.7 Months
III	10.6 Months
IV	4.5 Months

\*Data from Bilimoria et al.<sup>84</sup>

reducing pancreatic cancer mortality. Therefore, pancreatic cancer screening should currently be limited to high-risk populations within a research setting.<sup>78</sup> Recent advances in understanding the molecular basis of cancer offer promise for the discovery of new methods for detecting pancreatic cancer early.

## How Is Pancreatic Cancer Diagnosed?

When pancreatic cancer is suspected, patients will be asked to provide a full medical history and be given a physical exam mainly focused on the abdomen, but also of the skin and eyes for indications of jaundice (yellow coloring). Pancreatic cancer is typically diagnosed with the use of an imaging test, usually a CT scan, often with a contrast dye, given by mouth or through injection, to better outline abnormal areas.<sup>46,82</sup> This procedure is also often used to stage the tumor, with 70% to 85% accuracy for predicting whether or not the tumor can be surgically removed. If pancreatic cancer is highly suspected but a CT scan appears normal, additional diagnostic tests, such as endoscopic ultrasound or ERCP, may be performed. The ERCP technique is especially useful in patients with bile duct tumors<sup>83</sup> and endoscopic ultrasound can often detect small tumors missed by CT scan. A cancer diagnosis is typically confirmed with a biopsy – a procedure in which a small sample of the tumor is removed and viewed under a microscope. The most common type of biopsy to confirm pancreatic cancer is called a fine needle aspiration biopsy. The needle is inserted into the pancreas guided by an endoscopic ultrasound or CT scan images to obtain tissues for evaluation. However, a tissue diagnosis is not needed for patients who are scheduled for surgery. Due to the deep location of the pancreas and the medical complications of biopsy, pancreatic cancer is the least likely of all major cancers to be microscopically confirmed.

## What Factors Influence Pancreatic Cancer Survival?

The prognosis (disease course and expected outcome) of pancreatic cancer is largely determined by the stage of disease at diagnosis, which is based on the tumor's size, whether there is lymph node involvement, and the extent of spread locally and to distant organs. Table 2 presents the characteristics and median survival time for each stage of invasive pancreatic cancer. The median survival ranges from 4.5 months for the most advanced stage to 24.1 months for the earliest stage.<sup>84</sup>

At present, surgery provides the only chance of prolonged survival for pancreatic cancer patients. Even for patients with a tumor that has been surgically removed (generally Stages I or II), the 5-year survival is only about 20% to 25%. Indications of a poor survival outcome include positive resection margins (cancer cells at the outer edge of the removed tissue), poor tumor differentiation (the tumor does not resemble pancreatic tissue), a large tumor size, lymph node involvement, high levels of preoperative carbohydrate (or cancer) antigen 19-9 (CA19-9), and persistently elevated levels of postoperative CA 19-9.<sup>46,85-89</sup> In addition, several molecular markers have been associated with poor outcome after surgery.<sup>90,91</sup> As these molecular markers were mainly evaluated in small studies, their value requires further validation in larger studies, and thus none have been routinely used in clinical practice.

## How Is Pancreatic Cancer Treated?

### Treatment

Patients with pancreatic cancer are best managed by a multidisciplinary team, including surgeons, medical and radiation oncologists, radiologists, gastroenterologists, pain management experts, nutritionists, social workers, and others. The treatment choice is largely determined by whether the tumor can be surgically removed. Surgery remains the only treatment that offers a chance of cure for pancreatic cancer patients.<sup>92</sup>

For those patients who are candidates for surgery (approximately 20% of all pancreatic cancer patients), the operative approaches include cephalic pancreatoduodenectomy (the Whipple procedure), distal pancreatectomy, or total pancreatectomy, depending on the location of the tumor (see sidebar on page 31). Postoperative (adjuvant) chemotherapy either alone or in combination with radiation has been proven to improve progression-free and overall survival in both randomized controlled trials and observational studies.<sup>93,94</sup> The role of radiation therapy by itself in the adjuvant setting remains unclear.<sup>95</sup> Treatment with chemotherapy or chemoradiotherapy prior to surgery (neoadjuvant) is an emerging strategy. The goal of neoadjuvant treatment is to increase the ability to successfully remove all of the tumor.<sup>96</sup> However, there is no evidence that neoadjuvant therapy is superior to adjuvant therapy, especially among those patients who clearly have resectable disease.<sup>97</sup> For this reason,

## Pancreatic Cancer Treatment Options

### Surgery

- Cephalic pancreatoduodenectomy (Whipple procedure) is the removal of the head of the pancreas, the gallbladder, part of the stomach, part of the small intestine, and the bile duct, retaining enough of the pancreas to produce digestive juices and insulin.
- Distal pancreatectomy is the removal of the body and the tail of the pancreas as well as the spleen.
- Total pancreatectomy is the removal of the whole pancreas, part of the stomach, part of the small intestine, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes.

**Chemotherapy** is the use of drugs to kill cancer cells by preventing them from growing and dividing. Gemcitabine is usually the recommended first-line drug for pancreatic cancer patients. It can be given alone or in combination with other drugs.

**Radiation therapy** is the use of high-energy radiation to control or kill cancer cells. Radiation can be delivered by a machine outside the body (external beam radiation) or can come from a radioactive substance implanted in or near the cancer (internal radiation or brachytherapy). Brachytherapy is rarely used in treating pancreatic cancer.

**Chemoradiation therapy** combines chemotherapy and radiation therapy to increase the effects of both. The side effects of this combination therapy are more severe than either therapy alone.

**Targeted therapy** is the use of drugs or other substances to inhibit the growth of cancer cells by interfering with specific molecules involved in tumor progression. Erlotinib, which targets the epidermal growth factor receptor (EGFR), may be used with gemcitabine among pancreatic cancer patients with advanced disease.

neoadjuvant treatment is considered more relevant for patients with locally advanced or borderline resectable disease.<sup>97-99</sup>

The treatment for patients with advanced disease focuses on managing symptoms and relieving pain and suffering (palliative care). Treatment options include chemotherapy alone or in combination with radiation. The combination of 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) can help prolong life in patients with advanced disease, though many patients are too ill to tolerate this regimen. Other treatment options include gemcitabine alone or in combination with a platinum agent, erlotinib (Tarceva), or fluoropyrimidine.<sup>82</sup>

### Supportive care

Given the poor survival and persistent symptoms experienced by many pancreatic cancer patients who do not respond to treatment, care focusing on relieving and preventing suffering represents an important aspect of managing this disease. Palliative care should be offered at the initiation of any treatment regimen in order to relieve symptoms and side effects, which include pain, bile duct or gastric outlet obstruction, and loss of appetite. Palliative efforts may also include psychological support to relieve patients' stresses associated with pancreatic cancer diagnosis and treatment.

Opioid analgesics (morphine and similar drugs) are often needed to help reduce pain. Radiation may be given to help relieve pain from locally advanced disease. Another pain management approach is nerve block, whereby a pain specialist injects either an anesthetic or a medication to block or destroy the nerves. For example, abdominal pain can sometimes be treated effectively by endoscopic ultrasound or CT guided celiac plexus block.

If the tumor is blocking the bile duct, a stent (a thin tube) can be placed to relieve the blockage using nonsurgical approaches, such as ERCP and percutaneous transhepatic cholangiogram (PTC). If a patient develops gastric-outlet obstruction, treatment may include duodenal wall stents or PEG (percutaneous endoscopic gastrostomy) placement for decompression. Sometimes, a patient may need surgery to create a bypass (biliary bypass or gastric bypass) to manage obstructive jaundice and gastric outlet obstruction.

If the pancreas is not working well or has been partially or entirely removed, a special diet and specially prescribed enzymes may help the patient's digestion. Meeting with a nutritionist is also often very helpful for patients who are losing weight and have a poor appetite because of their disease.

## What Is the American Cancer Society Doing about Pancreatic Cancer?

### Research

The American Cancer Society, through its Extramural Grants program, funds individual investigators in medical schools, universities, research institutes, and hospitals throughout the United States. Currently, this program is funding \$8,077,500 in pancreatic cancer research through 32 research grants. Ongoing research includes:

- Identifying new avenues of early detection and treatment through better understanding of the biological mechanisms of pancreatic cancer development, progression, and metastasis
- Determining the optimal sequencing strategy for pancreatic cancer treatment through mathematical decision analysis



- Examining new biomarkers for drug response to optimize the effectiveness of common chemotherapeutic agents, such as gemcitabine
- Testing new therapeutic agents for targeted therapy, such as PARP inhibitors and glutaminase inhibitors
- Exploring targeted delivery of pro-apoptotic therapeutics into pancreatic cancer cells
- Integrating immunotherapy into pancreatic cancer treatment regimens

The Society's intramural research program also conducts a wide range of research on pancreatic cancer. For example, researchers from the surveillance research program monitor trends in pancreatic cancer incidence and mortality, and recently published a study showing that socioeconomic disparities in pancreatic cancer death rates widened among working-age US populations during 1993-2007. Using data collected in the Society's Cancer Prevention Study II (CPS-II), Society epidemiologists have also examined the relationship between pancreatic cancer death and various factors, including alcohol consumption, carbohydrate intake, aspirin use, and reproductive patterns. In addition, the CPS-II Nutrition Cohort is part of a large international Pancreatic Cancer Cohort Consortium (PanScan), which aims to identify genetic factors, environmental exposures, and gene-environment interactions that contribute to the development of pancreatic cancer. To date, PanScan researchers have discovered four novel regions in the genome associated with risk for pancreatic cancer. In addition, many other epidemiological studies on environmental risk factors (including lifestyle factors) have been published.

## Advocacy

The American Cancer Society Cancer Action Network<sup>SM</sup> (ACS CAN), the nonprofit nonpartisan advocacy affiliate of the American Cancer Society, recognizes that cancer research is the engine behind our ongoing progress in the fight against cancer. Research offers hope to the millions of people who face cancer – for better treatments, for more opportunities to prevent and detect the disease early, and for improved quality of life for those already diagnosed. The National Cancer Institute (NCI) – one of the 27 institutes and centers that comprise the National Institutes of Health (NIH) – is the foundation of the nation's cancer research efforts. As a federal agency, NCI-funded research has played a role in every major advance in the fight against cancer over the past 70 years. That's why it is so important that the NCI continues to receive the government investment that it needs to support lifesaving research projects. Funding for pancreatic cancer research at NCI has increased from \$73 million in 2007 to \$100 million in 2011. Billions of dollars exist in the federal budget for medical research purposes, and ACS CAN is leading the effort to lobby our government for the crucial funds necessary for the clinical research that could lead to the prevention, early detection, and effective treatment of pancreatic cancer.

## Resources outside the American Cancer Society

- **National Cancer Institute:** [cancer.gov/cancertopics/types/pancreatic/](http://cancer.gov/cancertopics/types/pancreatic/)
- **Pancreatic Cancer Action Network:** [pancan.org/](http://pancan.org/)
- **The Lustgarten Foundation:** [lustgarten.org/](http://lustgarten.org/)
- **Hirshberg Foundation for Pancreatic Cancer Research:** [pancreatic.org/](http://pancreatic.org/)
- **National Pancreas Foundation:** [pancreasfoundation.org/](http://pancreasfoundation.org/)
- **Pancreatica Initiative:** [pancreatica.org/](http://pancreatica.org/)

## References

1. Silverman DT, Hoover RN, Brown LM, et al. Why do Black Americans have a higher risk of pancreatic cancer than White Americans? *Epidemiology* 2003;14(1): 45-54.
2. Jemal A, Simard EP, Xu J, Ma J, Anderson RN. Selected cancers with increasing mortality rates by educational attainment in 26 states in the United States, 1993-2007. *Cancer Causes Control* 2012.
3. Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975-2009, Featuring the Burden and Trends in HPV-Associated Cancers and HPV Vaccination Coverage Levels. *JNCI* (in press).
4. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 2008;393(4): 535-45.
5. Anderson K, Potter JD, Mack TM. Pancreatic cancer. In: Schottenfeld D, Fraumeni JF, editors. *Cancer Epidemiology and Prevention*. New York: Oxford University Press, 2006:721-62.
6. Lynch SM, Vrieling A, Lubin JH, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Am J Epidemiol* 2009;170(4): 403-13.
7. Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol* 2012;23(7):1880-8.
8. Henley SJ, Thun MJ, Chao A, Calle EE. Association between exclusive pipe smoking and mortality from cancer and other diseases. *J Natl Cancer Inst* 2004;96(11): 853-61.
9. Bertuccio P, La Vecchia C, Silverman DT, et al. Cigar and pipe smoking, smokeless tobacco use and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol* 2011;22(6): 1420-6.
10. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010;126(10): 2394-403.
11. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Smokeless Tobacco and some Tobacco-specific N-Nitrosamines*. Lyon, France: IARC, 2007.
12. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *A review of human carcinogens. Part E: Personal habits and indoor combustions*. Lyon, France: IARC, 2009.
13. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer* 2003;89(3): 519-23.
14. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* 2001;286(8): 921-9.



15. Arslan AA, Helzlsouer KJ, Kooperberg C, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Arch Intern Med* 2010;170(9): 791-802.
16. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA* 2009;301(24): 2553-62.
17. Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. *Br J Cancer* 2005;93(11): 1310-5.
18. Heinen MM, Verhage BA, Goldbohm RA, Lumey LH, van den Brandt PA. Physical activity, energy restriction, and the risk of pancreatic cancer: a prospective study in the Netherlands. *Am J Clin Nutr* 2011;94(5): 1314-23.
19. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Cancer Causes Control* 2007;18(2): 165-75.
20. Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. *Cancer Epidemiol Biomarkers Prev* 2005;14(2): 459-66.
21. Hanley AJ, Johnson KC, Villeneuve PJ, Mao Y. Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system. *Int J Cancer* 2001;94(1): 140-7.
22. O'Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ. Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis. *Int J Cancer* 2010;126(12): 2957-68.
23. Bao Y, Michaud DS. Physical activity and pancreatic cancer risk: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2008;17(10): 2671-82.
24. Genkinger JM, Spiegelman D, Anderson KE, et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. *Cancer Epidemiol Biomarkers Prev* 2009;18(3): 765-76.
25. Tramacere I, Scotti L, Jenab M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. *Int J Cancer* 2010;126(6): 1474-86.
26. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. *Br J Cancer* 2012;106(3): 603-7.
27. Anderson KE, Mongin SJ, Sinha R, et al. Pancreatic cancer risk: associations with meat-derived carcinogen intake in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. *Mol Carcinog* 2012;51(1):128-37.
28. Larsson SC, Giovannucci E, Wolk A. Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis. *Gastroenterology* 2006;131(4): 1271-83.
29. Bao Y, Michaud DS, Spiegelman D, et al. Folate intake and risk of pancreatic cancer: pooled analysis of prospective cohort studies. *J Natl Cancer Inst* 2011;103(24): 1840-50.
30. Jansen RJ, Robinson DP, Stolzenberg-Solomon RZ, et al. Fruit and vegetable consumption is inversely associated with having pancreatic cancer. *Cancer Causes Control* 2011;22(12): 1613-25.
31. Vrieling A, Verhage BA, van Duijnhoven FJ, et al. Fruit and vegetable consumption and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2009;124(8): 1926-34.
32. Larsson SC, Hakansson N, Naslund I, Bergkvist L, Wolk A. Fruit and vegetable consumption in relation to pancreatic cancer risk: a prospective study. *Cancer Epidemiol Biomarkers Prev* 2006;15(2): 301-5.
33. Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. *Cancer Epidemiol Biomarkers Prev* 2005;14(9): 2093-7.
34. Turati F, Galeone C, Edefonti V, et al. A meta-analysis of coffee consumption and pancreatic cancer. *Ann Oncol* 2012;23(2): 311-8.
35. Grant WB. An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking. *Int J Cancer* 2007;120(5): 1123-8.
36. Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC. Ultraviolet B irradiance and vitamin D status are inversely associated with incidence rates of pancreatic cancer worldwide. *Pancreas* 2010;39(5): 669-74.
37. Boscoe FP, Schymura MJ. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993-2002. *BMC Cancer* 2006;6: 264.
38. Bao Y, Ng K, Wolpin BM, Michaud DS, Giovannucci E, Fuchs CS. Predicted vitamin D status and pancreatic cancer risk in two prospective cohort studies. *Br J Cancer* 2010;102(9): 1422-7.
39. Giovannucci E. Vitamin D and cancer incidence in the Harvard cohorts. *Ann Epidemiol* 2009;19(2): 84-8.
40. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, et al. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010;172(1): 81-93.
41. Permutth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. *Fam Cancer* 2009;8(2): 109-17.
42. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004;64(7): 2634-8.
43. Brune KA, Lau B, Palmisano E, et al. Importance of age of onset in pancreatic cancer kindreds. *J Natl Cancer Inst* 2010;102(2): 119-26.
44. Petersen GM, de Andrade M, Goggins M, et al. Pancreatic cancer genetic epidemiology consortium. *Cancer Epidemiol Biomarkers Prev* 2006;15(4): 704-10.
45. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. *Arch Pathol Lab Med* 2009;133(3): 365-74.
46. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet* 2011;378(9791): 607-20.
47. Landi S. Genetic predisposition and environmental risk factors to pancreatic cancer: A review of the literature. *Mutat Res* 2009;681(2-3): 299-307.
48. Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2007;16(2): 342-6.
49. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst* 2003;95(3): 214-21.
50. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. *Cancer Res* 2002;62(13): 3789-93.
51. Lynch HT, Fusaro RM, Lynch JF, Brand R. Pancreatic cancer and the FAMMM syndrome. *Fam Cancer* 2008;7(1): 103-12.
52. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology* 2000;119(6): 1447-53.
53. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol* 2010;105(6): 1258-64; author reply 65.

54. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol* 2010;24(3): 349-58.
55. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA* 2009;302(16): 1790-5.
56. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nat Genet* 2009;41(9): 986-90.
57. Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and the risk of pancreatic cancer. *J Natl Cancer Inst* 2009;101(6): 424-31.
58. Wolpin BM, Kraft P, Gross M, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. *Cancer Res* 2010;70(3): 1015-23.
59. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993;328(20): 1433-7.
60. Malka D, Hammel P, Maire F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. *Gut* 2002;51(6): 849-52.
61. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology* 2008;134(4): 981-7.
62. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology* 2008;134(1): 95-101.
63. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005;92(11): 2076-83.
64. Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. *Br J Cancer* 2007;96(3): 507-9.
65. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000;283(19): 2552-8.
66. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005;293(2): 194-202.
67. Stolzenberg-Solomon RZ, Graubard BI, Chari S, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA* 2005;294(22): 2872-8.
68. Stattin P, Bjor O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007;30(3): 561-7.
69. Stocks T, Rapp K, Borge T, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. *PLoS Med* 2009;6(12): e1000201.
70. El-Serag HB, Engels EA, Landgren O, et al. Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. *Hepatology* 2009;49(1): 116-23.
71. Hassan MM, Li D, El-Deeb AS, et al. Association between hepatitis B virus and pancreatic cancer. *J Clin Oncol* 2008;26(28): 4557-62.
72. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. *J Natl Cancer Inst* 2010;102(7): 502-5.
73. Lin G, Zeng Z, Wang X, et al. Cholecystectomy and risk of pancreatic cancer: a meta-analysis of observational studies. *Cancer Causes Control* 2012;23(1): 59-67.
74. Gong Y, Zhou Q, Zhou Y, et al. Gastrectomy and risk of pancreatic cancer: systematic review and meta-analysis of observational studies. *Cancer Causes Control* 2012;23(8): 1279-88.
75. Maisonneuve P, Marshall BC, Lowenfels AB. Risk of pancreatic cancer in patients with cystic fibrosis. *Gut* 2007;56(9): 1327-8.
76. Fitzpatrick SG, Katz J. The association between periodontal disease and cancer: a review of the literature. *J Dent* 2010;38(2): 83-95.
77. Greenhalf W, Grocock C, Harcus M, Neoptolemos J. Screening of high-risk families for pancreatic cancer. *Pancreatology* 2009;9(3): 215-22.
78. Shin EJ, Canto MI. Pancreatic cancer screening. *Gastroenterol Clin North Am* 2012;41(1): 143-57.
79. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol* 2004;2(7): 606-21.
80. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006;4(6): 766-81; quiz 665.
81. Gemmel C, Eickhoff A, Helmstadter L, Riemann JF. Pancreatic cancer screening: state of the art. *Expert Rev Gastroenterol Hepatol* 2009;3(1): 89-96.
82. Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010;362(17): 1605-17.
83. Dumonceau JM, Vonlaufen A. Pancreatic endoscopic retrograde cholangiopancreatography (ERCP). *Endoscopy* 2007;39(2): 124-30.
84. Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer* 2007;110(4): 738-44.
85. Berger AC, Garcia M, Jr., Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol* 2008;26(36): 5918-22.
86. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-Castillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. *J Clin Oncol* 2006;24(18): 2897-902.
87. Hernandez JM, Cowgill SM, Al-Saadi S, et al. CA 19-9 velocity predicts disease-free survival and overall survival after pancreatectomy of curative intent. *J Gastrointest Surg* 2009;13(2): 349-53.
88. Slidell MB, Chang DC, Cameron JL, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. *Ann Surg Oncol* 2008;15(1): 165-74.
89. Maithel SK, Maloney S, Winston C, et al. Preoperative CA 19-9 and the yield of staging laparoscopy in patients with radiographically resectable pancreatic adenocarcinoma. *Ann Surg Oncol* 2008;15(12): 3512-20.
90. Blackford A, Serrano OK, Wolfgang CL, et al. SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer. *Clin Cancer Res* 2009;15(14): 4674-9.
91. Infante JR, Matsubayashi H, Sato N, et al. Peritumoral fibroblast SPARC expression and patient outcome with resectable pancreatic adenocarcinoma. *J Clin Oncol* 2007;25(3): 319-25.
92. Shaib Y, Davila J, Naumann C, El-Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. *Am J Gastroenterol* 2007;102(7): 1377-82.
93. O'Reilly EM. Refinement of adjuvant therapy for pancreatic cancer. *JAMA* 2010;304(10): 1124-5.
94. Neoptolemos JP. Adjuvant treatment of pancreatic cancer. *Eur J Cancer* 2011;47 Suppl 3: S378-80.
95. Abrams RA. Radiotherapy in the adjuvant management of pancreatic adenocarcinoma: is it helpful? *Expert Rev Gastroenterol Hepatol* 2012;6(2): 149-61.

96. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26(21): 3496-502.

97. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7(4): e1000267.

98. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008;206(5): 833-46; discussion 46-8.

99. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009;16(7): 1727-33.