Estrogen and Bisphosphonate Use and Pancreatic Cancer

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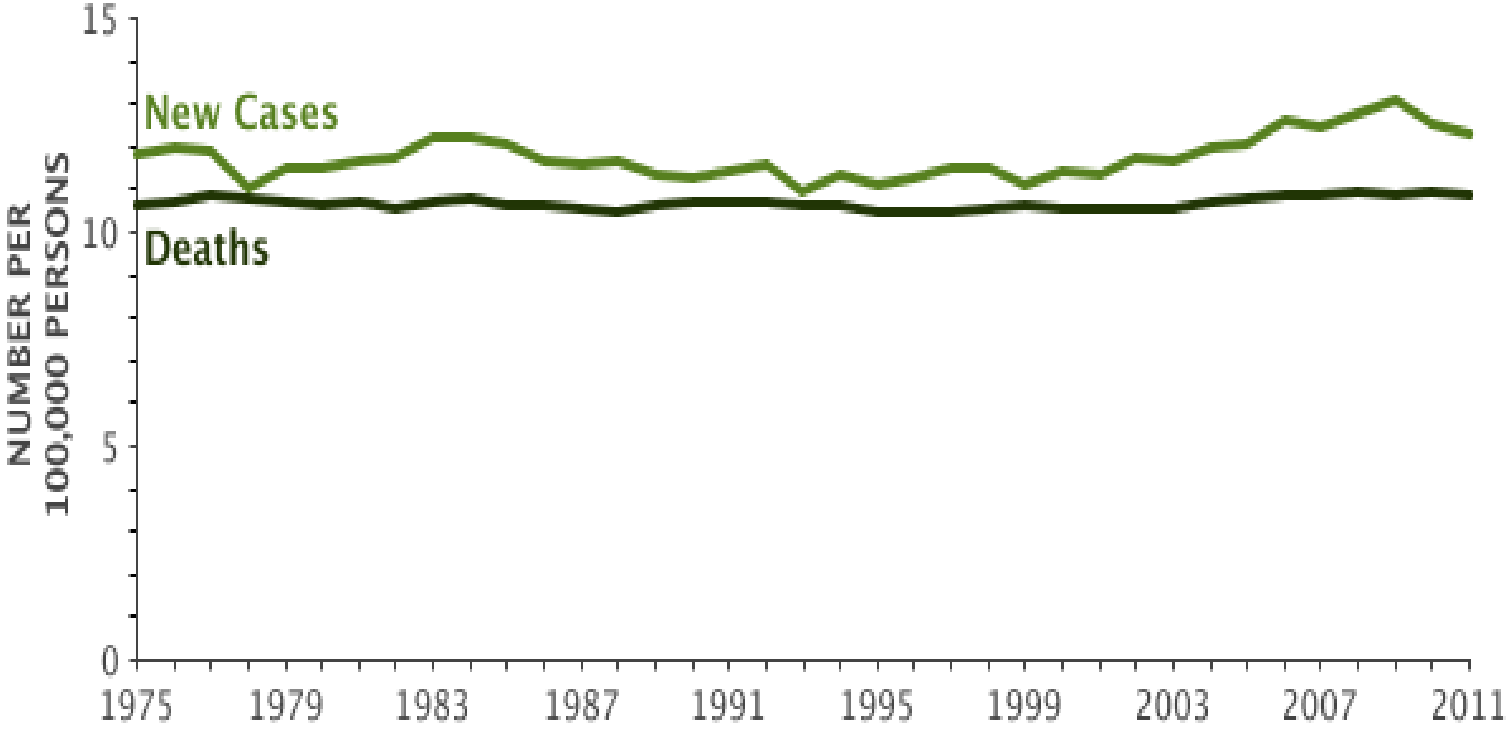
Pancreatic Cancer

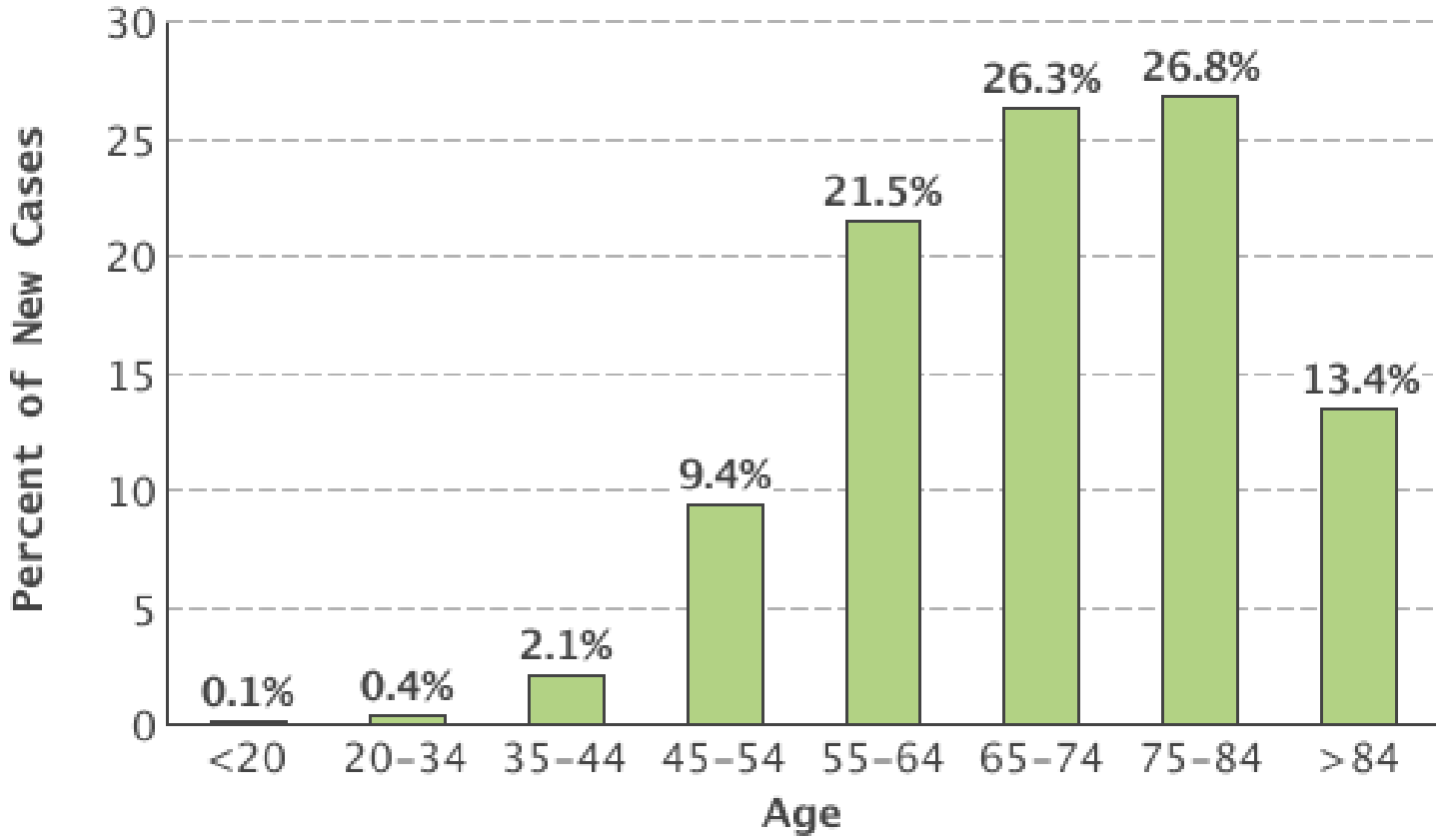
- Fourth most common cause of cancer death in the U.S.
- Few early symptoms
- Typically diagnosed at a late stage
- High case-fatality
- Unknown etiology

Incidence and Death Rate per 100,000 Persons, U.S., 1975-2011



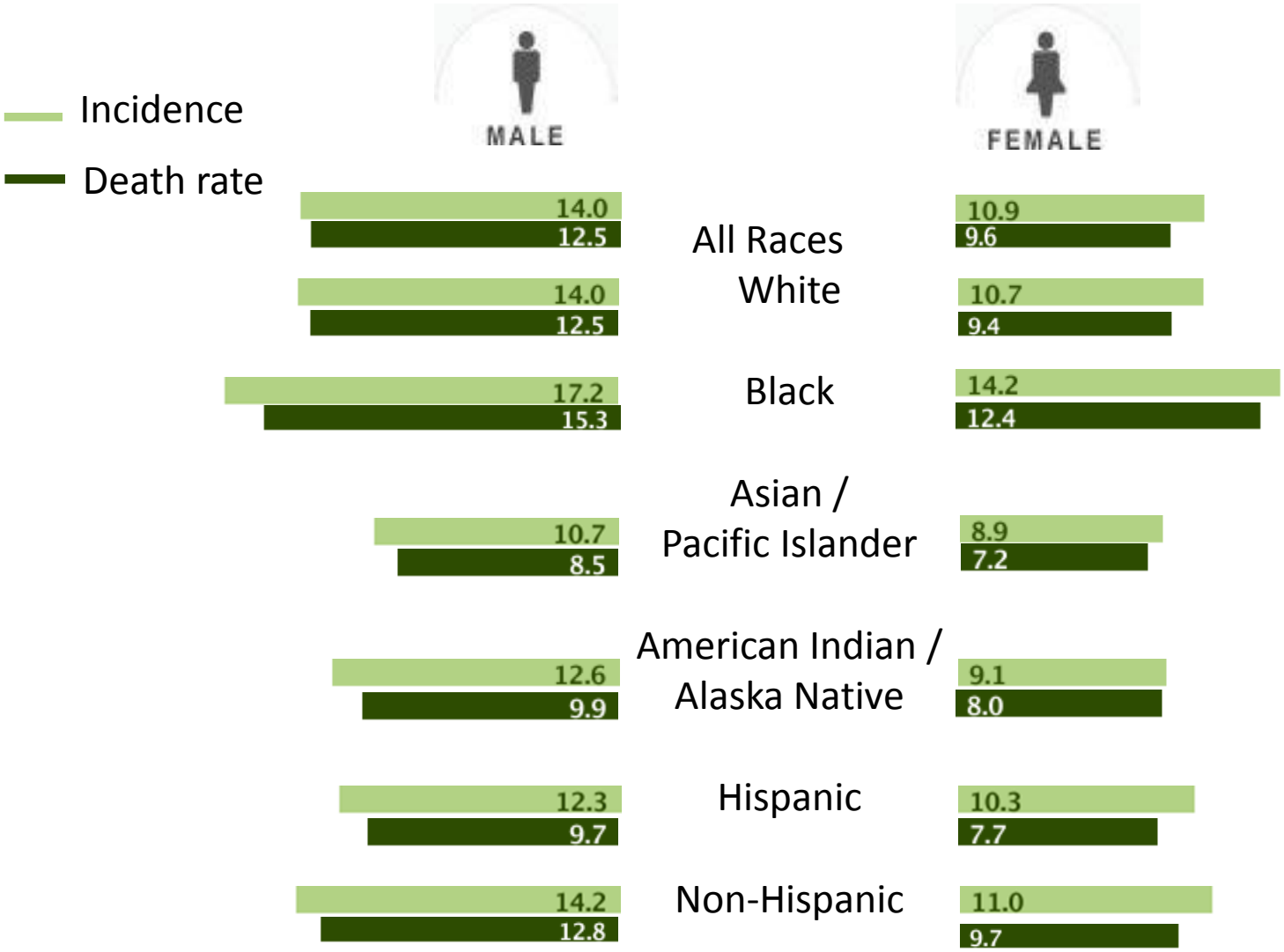
Source: SEER 9 Incidence & U.S. Mortality 1975-2011, All Races, Both Sexes. Rates are age-adjusted, based on 2007-2011 cases and deaths..

Percent of New Cases by Age Group



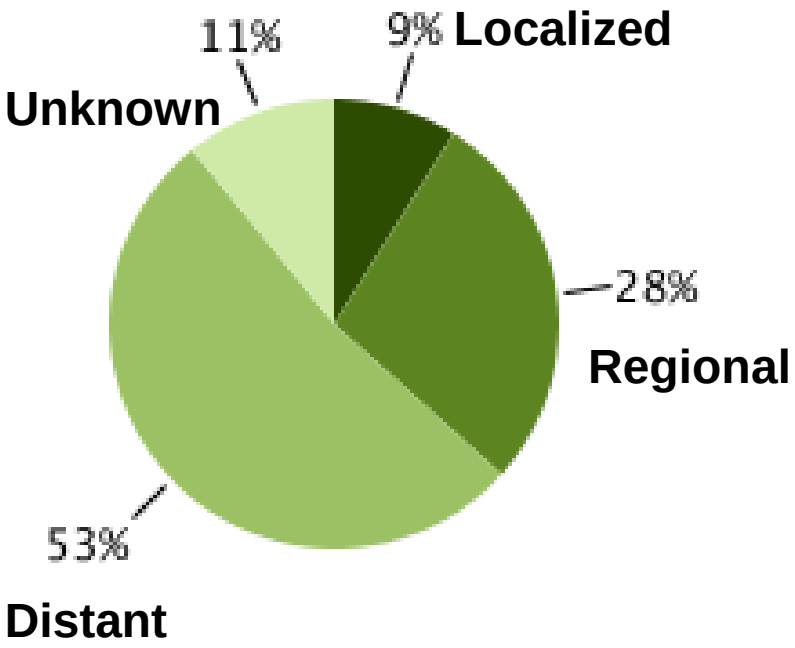
Source: SEER 18 2007-2011, All Races, Both Sexes.

Incidence and Death Rate per 100,000 Persons by Race/Ethnicity and Sex



Source: SEER 18 2007-2011, Age-Adjusted

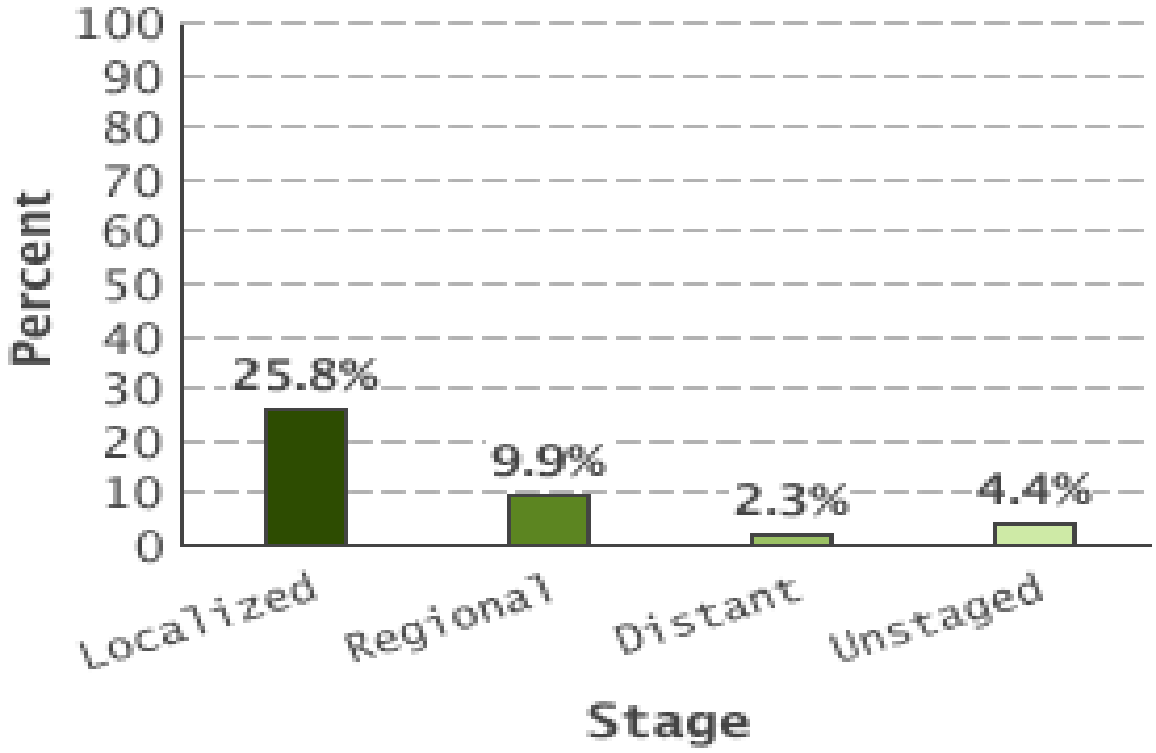
Percent of Cases by Stage



Localized: Confined to Primary Site: Stage IA ,IB
Regional: Spread to Regional Lymph Nodes: Stage IIA , IIB, III
Distant: Cancer Has Metastasized: Stage IV

SEER Cancer Statistics Factsheets: Pancreas Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/pancreas.html

Percent of Cases by 5-Year Survival



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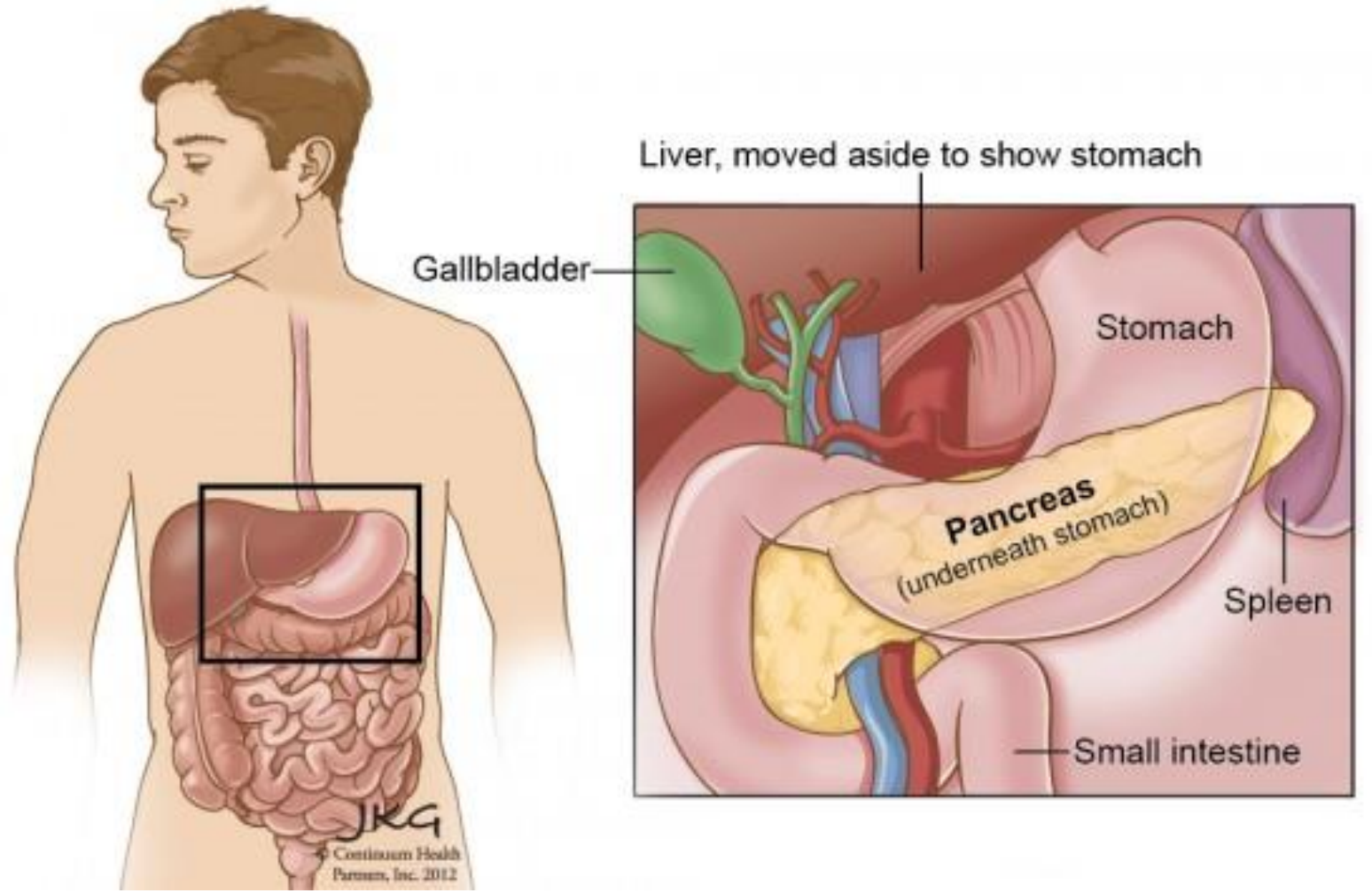
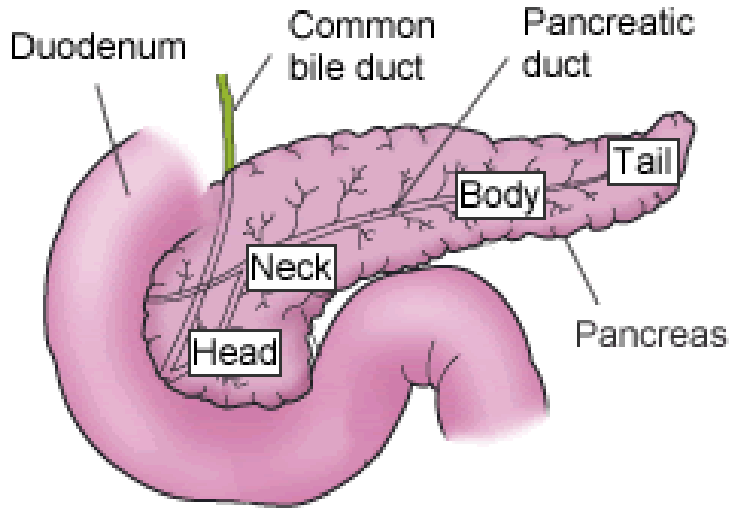
Anatomy of the Pancreas



Types of Pancreatic Cancers

- Ductal adenocarcinoma, ~ 95%
- Neuroendocrine tumors, ~ 5% (Islet-cell tumors)
- Cystic neoplasms, <1%

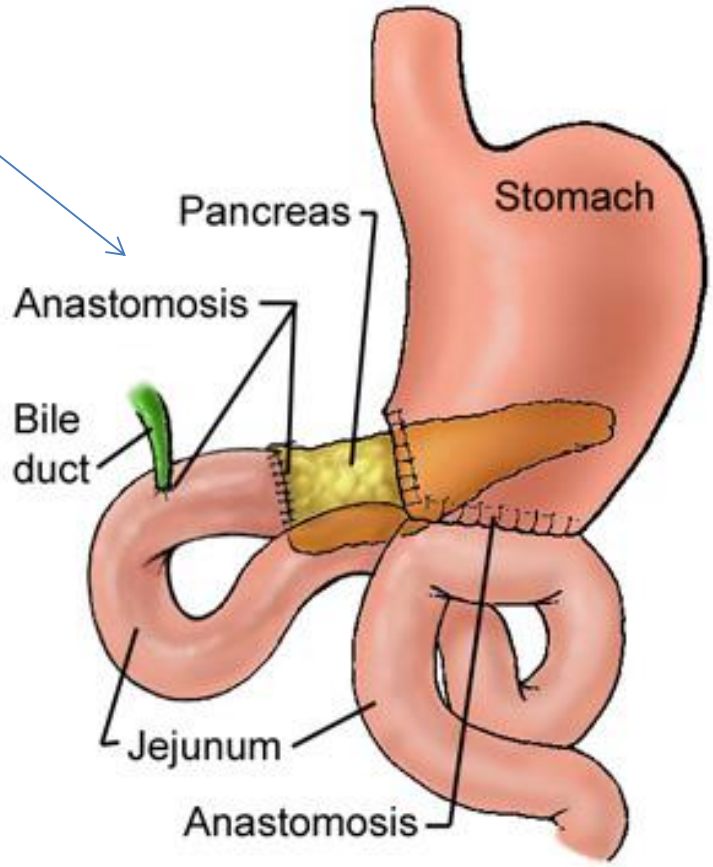


Signs and symptoms

- Jaundice
- Fatigue
- Dark urine
- Loss of appetite
- Light-colored stool
- Unexplained weight loss
- Abdominal and/or back pain
- New onset of type II diabetes

Treatment

- Surgery (whipple procedure)
- Radiation therapy
- Chemotherapy
- Targeted therapy



Risk Factors for Pancreatic Cancer

Risk factor	RR or OR (95% CI)
Smoking[1]	1.77 (1.38, 2.26)
Type II diabetes[2]	1.94 (1.66, 2.27)
BMI[3]	1.12 (1.06, 1.17)
Chronic pancreatitis[4]	2.71 (1.96, 3.74)
Hereditary pancreatitis*[5]	53 (23, 105)
Family history of pancreatic cancer^[6]	1.80 (1.48, 2.12)
Occupational exposures[7]	1.4 (1.0 , 1.8)
Genetic conditions (5-10% of cases)**[8]	5 – 10% of cases
Alcohol consumption	No confirmed link
Physical activity	No confirmed link

*Standardized incidence ratio reported

^ Two or more first-degree relatives diagnosed with pancreatic cancer

**Familial syndromes include: familial Atypical Multiple Mole Melanoma (p16), HNPCC, BRCA2, Peutz-Jeghers, Ataxia-telangiectasia

Estrogen

- Women have a persistently lower incidence of pancreatic cancer compared to men[9, 10]
- Estrogen receptors and binding proteins have been detected in pancreatic tissue in laboratory studies[11-13]
- Animal studies have found that estrogen may inhibit the progression of some pancreatic carcinomas[14, 15]

Research Question of Interest

I. Is estrogen use associated with a reduced risk of pancreatic cancer among postmenopausal women?

II. Is bisphosphonate use associated with a reduced risk of pancreatic cancer among postmenopausal women?

Epidemiologic Evidence

- Observational studies on reproductive and hormone-related factors and pancreatic cancer risk in women are mixed[16-22]
- Many of these studies examined estrogen use as dichotomous variable
- The relationship between estrogen and cancer is complicated

Estrogen Use

- Background and history[24]
  - 1941 FDA approves marketing of DES for menopausal symptoms
  - 1965- 74 sales doubled and tripled
  - 1975 increase endometrial cancer risk reported in estrogen users
  - 1982 evidence that progestins are protective against estrogen-induced endometrial changes
  - 1984 - 86 conflicting evidence on estrogen use and CVD risk; NIH states that estrogens prevent bone loss, FDA deems estrogens as an effective therapy for osteoporosis
  - 1995 - 98 PEPI trial suggests a reduced CHD risk, HERS trial reports no benefit
  - 2001 15 million women using estrogens
  - 2002 WHI reports an increase CHD risk, breast cancer risk, pulmonary embolism risk

DES: Diethylstilbestrol, CVD: Cardiovascular disease, PEPI: Postmenopausal Estrogen/Progestin Interventions, HERS: Heart and Estrogen/Progestin Replacement Study, CHD: Coronary heart disease

Bisphosphonate Use and Pancreatic Cancer

- Oral bisphosphonates are often prescribed for post-menopausal osteoporosis[25]

- Laboratory research has demonstrated that bisphosphonates can promote apoptosis and suppress cellular growth and angiogenic factors in pancreatic cancer cells in vitro and in vivo[26-28]

Research Question of Interest

I. Is estrogen use associated with a reduced risk of pancreatic cancer among postmenopausal women?

II. Is bisphosphonate use associated with a reduced risk of pancreatic cancer among postmenopausal women?

Epidemiologic Evidence

- Epidemiologic studies have demonstrated that bisphosphonate use is associated with a reduced risk of incident invasive breast cancer[29-31]

- Two observational studies have found a modest reduction in the risk of pancreatic cancer[32, 33]

- The relationship between bisphosphonates and pancreatic cancer is unclear

Specific Aims

I. To test whether estrogen use is associated with a reduced risk of pancreatic cancer among postmenopausal women.

II. To test whether bisphosphonate use is associated with a reduced risk of pancreatic cancer among postmenopausal women.

Methods

- Design: Women's Health Initiative clinical trial (CT) and observational study (OS) combined; 12-year prospective cohort
- Population: 161,808 postmenopausal women 50-79 years old
- Outcome: 885 verified pancreatic cancer cases (N = 383 CT, N = 502, OS)

Exposure Assessment

- Estrogen use
  - Type (estrogen, estrogen plus progestin)
  - Duration (time – varying dichotomous variable)
  - Prior use
  - Interval between menopause and use of HT

Exposure Assessment

- Bisphosphonate use
  - Duration (time-varying dichotomous variable)
  - Type

Analysis

- Cox regression models: HR (HR) and 95% confidence intervals (CI)
  - Date of enrollment or randomization with censoring at the end of the study period, loss of the follow-up, or death

- Models
  - Estrogen
    - Model 1: age, race/ethnicity, education, insurance, smoking status, type II diabetes, WHI study section and hormone trial assignment
      Model 2: family history of PC in $\geq$2 1st degree relatives, BMI , chronic pancreatitis, and the risk factors listed above
  - Bisphosphonate
    - Model 1: age, race/ethnicity, education, insurance, smoking status, type II diabetes, WHI study section and hormone trial assignment
    - Model 2: family history of PC in $\geq$2 1st degree relatives, BMI, chronic pancreatitis, and the risk factors listed above

PANCREATIC CANCER RESEARCH OPPORTUNITIES

Pancreatic Cancer Surveillance Program

- Familial Pancreatic Cancer (FPC)
  - Familial cancer syndromes can recapitulate the sporadic form of the disease but in a reduced time frame
  - Risk factors can be exaggerated in FPC because of the underlying susceptibility to cancer, thereby making the risk factor easier to spot than in sporadic disease
  - FPC patients share many of the same risk factors as those seen in sporadic pancreatic cancer, including smoking and diabetes
  - FPC cohorts may be ideal to study additional new risk factors for PDAC

PDAC: Pancreatic ductal adenocarcinoma

Gastrointestinal Cancer Prevention Program

- Goal
  - Provide cancer risk assessment, screening, and prevention for patients at high risk of developing gastrointestinal cancer (colon, small intestine, stomach, pancreas, and esophagus)
- Population
  - Two or more close relatives on the same side of the family with a GI cancer, especially if cancer was diagnosed before the age of 50), OR
  - GI cancer before the age of 50, OR
  - More than one primary cancer, one of which was a GI cancer, at any age, OR
  - A pre-cancerous GI polyp before age 40, OR
  - More than 10 pre-cancerous GI polyps at any age.

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