Estrogen and Bisphosphonate Use and Pancreatic Cancer

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Bio-behavioral Cancer Prevention and Control Training Program
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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

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

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Incidence</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Races</td>
<td>14.0</td>
<td>12.5</td>
</tr>
<tr>
<td>White</td>
<td>14.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Black</td>
<td>17.2</td>
<td>15.3</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>10.7</td>
<td>8.5</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>12.6</td>
<td>9.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.3</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Races</td>
<td>10.9</td>
<td>9.6</td>
</tr>
<tr>
<td>White</td>
<td>10.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Black</td>
<td>14.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>8.9</td>
<td>7.2</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>9.1</td>
<td>8.0</td>
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<tr>
<td>Hispanic</td>
<td>10.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>14.2</td>
<td>12.8</td>
</tr>
</tbody>
</table>

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

Percent of Cases by 5-Year Survival

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

Anatomy of the Pancreas

- Gallbladder
- Liver, moved aside to show stomach
- Stomach
- Pancreas (underneath stomach)
- Spleen
- Small intestine
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

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

*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\textsuperscript{[9, 10]}

• Estrogen receptors and binding proteins have been detected in pancreatic tissue in laboratory studies\textsuperscript{[11-13]}

• Animal studies have found that estrogen may inhibit the progression of some pancreatic carcinomas\textsuperscript{[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\cite{29-31}

• Two observational studies have found a modest reduction in the risk of pancreatic cancer\cite{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 >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 >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.
References

References


