Smoke Like a Man, Survive Like a Woman

Sex-Specific Differences in Lung Cancer

Pulmonary Grand Rounds
Philippe R. Montgrain, M.D.
May 1, 2008
Objectives

2. Present research on parathyroid hormone-related protein (PTHrP), a sex-dependent protein that slows lung carcinoma growth and prolongs survival.
Impact of Lung Cancer

- Kills more men and women each year than any other cancer.
- 5-year survival remains dismally low, only 15%.
THE DEADLIEST CANCER
LUNG CANCER KILLS MORE AMERICANS THAN ANY OTHER TYPE OF MALIGNANCY--AND SOME OF THE VICTIMS NEVER SMOKE. BUT DESPITE GRIM STATISTICS THERE IS SOME GOOD NEWS: FRESH RESEARCH OFFERS HOPE FOR EARLIER DIAGNOSIS AND MORE-EFFECTIVE TREATMENTS.
BY GEOFFREY COWLEY AND CLAUDIA KALB
NEWSWEEK
Updated: 6:01 PM ET Oct 17, 2007

With the news last week that former smoker Peter Jennings had succumbed to lung cancer at age 67 and Dana Reeve, who never smoked, was diagnosed with the disease at 44, millions of Americans grasped a terrible truth--the deadliest form of cancer doesn't strike just the pack-a-day crowd. Suddenly lung cancer was everyone's concern. And rightly so. Lung cancer may not inspire walkathons or pink-ribbon awareness campaigns, but after three decades of the War on Cancer and four decades of surgeon generals' reports, it remains the most devastating of all malignancies. The disease kills some 160,000 Americans a year--more than breast cancer, colon cancer and prostate cancer combined. The burden has grown steadily in recent decades, thanks to the rising incidence among women, and survival rates have scarcely budged. Nearly 60 percent of patients still die within a year of diagnosis, and 85 percent die within five.
Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths, by Sex, United States, 2008

### Estimated New Cases*

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>25%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>114,690</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>77,250</td>
<td>10%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>51,230</td>
<td>7%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,450</td>
<td>5%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>34,950</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>33,130</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,310</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,180</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>745,180</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>182,460</td>
<td>26%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>100,330</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>71,560</td>
<td>10%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>40,100</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>30,670</td>
<td>4%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>28,410</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>27,530</td>
<td>4%</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,650</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>21,260</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>19,090</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>692,000</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>90,810</td>
<td>31%</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,660</td>
<td>10%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>24,260</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17,500</td>
<td>6%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,570</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,460</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,250</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>9,950</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,790</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,100</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>294,120</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>71,030</td>
<td>26%</td>
</tr>
<tr>
<td>Breast</td>
<td>40,480</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>25,700</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>16,790</td>
<td>6%</td>
</tr>
<tr>
<td>Ovary</td>
<td>15,520</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,370</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>9,250</td>
<td>3%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>7,470</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5,840</td>
<td>2%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>5,650</td>
<td>2%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>271,530</td>
<td>100%</td>
</tr>
</tbody>
</table>

From Jemal, A. et al.
Annual Age-adjusted Cancer Death Rates* Among Males for Selected Cancers, United States, 1930 to 2004

Annual Age-adjusted Cancer Death Rates* Among Females for Selected Cancers, United States, 1930 to 2004

From Jemal, A. et al.
Equal Opportunity Killer

The New Face of LUNG CANCER
Recent Media Attention

Non-smokers can get lung cancer, too
For people like Dana Reeve, genetic factors likely fuel the disease

Associated Press
updated 9:14 a.m. PT, Wed., Aug. 10, 2005

Most lung cancers occur in smokers, but non-smoker Dana Reeve’s situation isn’t as uncommon as it appears.

Like Reeve, widow of “Superman” star Christopher Reeve, 1 in 5 women diagnosed with the disease never lit a cigarette, doctors say. Yet they share an unfortunate stigma with cancer patients who smoked.

Dana Reeve, 44, announced on Aug. 9 that she had been diagnosed with lung cancer. Reeve said in a brief statement that she was undergoing treatment for the disease and was optimistic about the prognosis.
Shock As Dana Reeve Dies At 44
Widow Of Christopher Reeve Admired For Her Spirit & Advocacy Of Medical Research

SHORT HILLS, N.J., March 7, 2006

(CBS/AP) "How could this happen?" For many, that was the inevitable question Tuesday in response to the news that Dana Reeve, the sunny and vibrant widow of Christopher Reeve, had died of lung cancer at the stunningly young age of 44.

Robin Williams said in reaction to Dana Reeve's death, "The brightest light has gone out." Williams and Christopher Reeve were roommates at The Juilliard School.

On the Senate floor Tuesday, Democrat John Kerry said he'll "never forget the grace and the strength" Reeve showed shortly after the "Superman" actor died in October 2004.

An official at the Christopher Reeve Foundation says the Reeve, 43-year-old son in his living room of...
The Main Culprit

PETER JENNINGS
1938-2005

DARYL CAGLE
MSNBC.COM
Smoke Like a Man, Die Like a Man

Figure 1. Smoking prevalence for US men and women, 1950 to 2000.4-8

Baldini and Strauss, CHEST 1997
It is not that simple…

There is mounting interest in sex-specific differences in lung cancer.

- Does histology vary with sex?
- Does the risk for lung cancer differ between men and women?
- Are there genetic or molecular differences?
- Does response to therapy differ?
- Are outcomes different between men and women?
Histology Varies with Sex

Table 1. Distribution of lung cancer by histology and gender

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Males $n = 1156$</th>
<th>Females $n = 831$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous/epidermoid</td>
<td>397 (34%)</td>
<td>165 (20%)</td>
</tr>
<tr>
<td>Small-cell</td>
<td>182 (16%)</td>
<td>142 (17%)</td>
</tr>
<tr>
<td>Large-cell</td>
<td>111 (10%)</td>
<td>90 (11%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>418 (36%)</td>
<td>384 (46%)</td>
</tr>
<tr>
<td>Brocho-alveolar</td>
<td>17 (1.5%)</td>
<td>30 (3.6%)</td>
</tr>
</tbody>
</table>

Novello and Baldini, Ann Oncol 2006
Histology Varies with Sex

The diagram shows the incidence of squamous and adenocarcinoma tumors over different years for men and women. The x-axis represents the year, ranging from 1950 to 1990, and the y-axis represents the number of cases per 100,000. The data indicates a higher incidence of adenocarcinoma compared to squamous in both genders, with a noticeable trend of increasing cases over time.
Lung Adenocarcinoma

- Association with smoking is less strong.
- Most common type of lung cancer in young persons.
- Most common in women of all ages.
- Most common in never smokers.
- Estrogens may play a role in lung adenocarcinoma tumorigenesis.
A case-control study showed that early age at menopause is associated with a reduced risk of adenocarcinoma of the lung.

The use of estrogen therapy is associated with a higher risk of adenocarcinoma.

A positive interaction exists between estrogen therapy, smoking, and the development of lung adenocarcinoma.
Women appear to be at higher risk for lung cancer:

- A case-control study of 800 patients with lung cancer found that the OR of lung cancer for those with a 40 pack-year history was 27.9 in women vs. 9.6 in men.

- Another case-control study of nearly 15,000 lung cancer patients demonstrated a higher OR for women (12.7) than for men (9.1).

Risch, Am J Epidemiol 1993
Brownson, Epidemiology 1992
Lung Cancer Risk Varies with Sex

- An American Health Foundation case-control study including 1108 men and 781 women with lung cancer found that, given the same exposure to cigarette smoke, women had 1.5-fold higher RR of developing lung cancer than men.

- In contrast, several cohort studies have not shown a higher RR of lung cancer in female smokers (studies may have suffered from lack of adjustment for duration of cigarette smoke exposure).

Zhang, JNCI 1996

US Department of Health and Human Services, 2001
Latest Data from Early Lung Cancer Action Project

Relative risk, women vs. men, corrected for age and smoking history

developing lung cancer
Genetic and Molecular Differences

- DNA repair capacity
- DNA adducts
- p53 mutations
- K-ras mutations
- Cytochrome P450 enzyme CYP1A1
- Gastrin-releasing peptide receptor
- Estrogen
Women Have Less DNA Repair Capacity

- Wei et al studied lymphocytes from patients with lung cancer.
- Lymphocytes were transfected with a plasmid containing a reporter gene that is not expressed if plasmid DNA is damaged.
- Lymphocytes were then exposed to the carcinogen benzo(a)pyrene diolepoxide.
- Females had a lower DNA repair capacity compared to males.

Wei, JNCI 2000
Women Have More DNA Adducts

- Pro-carcinogens from tobacco smoke are activated to reactive intermediates by cytochrome P450 enzymes CYP1A1 and CYP1B1.
- These reactive intermediates bind to DNA in lung epithelial cells forming DNA adducts.
- Attempts to repair these adducts can lead to mutations and cancer.
- Women have higher levels of these DNA adducts when compared to men.

Cheng, Environ Mol Mutagen 2001
Kure, Carcinogenesis 2001
Mollerup, Cancer Res 1999
<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking history (pack-years)</td>
<td>22.9</td>
<td>35</td>
<td>9.4 x 10^{-5}</td>
</tr>
<tr>
<td>Age</td>
<td>56.2</td>
<td>62.2</td>
<td>0.034</td>
</tr>
<tr>
<td>DNA adducts (per 10^8 DNA bases)</td>
<td>15.39</td>
<td>12.08</td>
<td>0.047</td>
</tr>
<tr>
<td>CYP1A1 mRNA/10^6 GAPDH mRNA</td>
<td>494</td>
<td>210</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Women Have More p53 and K-ras Mutations

- p53 is a tumor suppressor that causes arrest in both $G_1$ and $G_2$ in response to DNA damage, allowing for DNA repair or apoptosis. Female smokers have more p53 mutations than male smokers.

- K-ras is an proto-oncogene often associated with adenocarcinoma. Women are three times more likely to carry K-ras mutations than men.

Kure, Carcinogenesis 1996
Nelson, JNCI 1999
Gastrin-releasing peptide stimulates cell proliferation and has been implicated in lung cancer.

Its receptor, GRPR, is encoded on chromosome X and escapes X inactivation.

Women express more GRPR than men.

Shriver, JNCI 2000
Estrogen May Not Help Either…

- Estradiol increases proliferation of lung cancer cell lines in vitro (Stabile, Cancer Res 2002).

Response to Therapy Can Vary with Sex

- Women have better responses to platinum-based chemotherapy. Paradoxically, this may be due to decreased DNA repair capacity since these agents work by causing DNA damage in rapidly dividing cells.
- Women have better responses to the tyrosine kinase inhibitors, erlotinib and gefitinib. This could be due to the fact that women more often have activating mutations in the tyrosine kinase domain of EGFR.
No matter the stage:

<table>
<thead>
<tr>
<th>Stage</th>
<th>NSCLC Men (%)</th>
<th>NSCLC Women (%)</th>
<th>SCLC Men (%)</th>
<th>SCLC Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stages</td>
<td>14.9</td>
<td>19.6</td>
<td>5.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Local disease</td>
<td>46.6</td>
<td>56.0</td>
<td>20.7</td>
<td>21.6</td>
</tr>
<tr>
<td>Regional disease</td>
<td>15.9</td>
<td>18.5</td>
<td>9.9</td>
<td>11.7</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>2.0</td>
<td>2.3</td>
<td>1.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Surveillance, epidemiology and end results (SEER) data base
Women Are Survivors

No matter the treatment:

Table 2. Treatment in NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Female %</th>
<th>Stage of disease</th>
<th>Therapy</th>
<th>MST female:male</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Connell</td>
<td>378</td>
<td>30</td>
<td>III-IV</td>
<td>Chemot.</td>
<td>12.4:8.8</td>
<td>0.71</td>
<td>0.001</td>
</tr>
<tr>
<td>Mitsudomi</td>
<td>492</td>
<td>27</td>
<td>I-IV</td>
<td>Surg</td>
<td>60:38</td>
<td>0.63</td>
<td>0.00036</td>
</tr>
<tr>
<td>Ferguson</td>
<td>299</td>
<td>45</td>
<td>I-IV</td>
<td>All modalit.</td>
<td>12.1:9.1</td>
<td>0.75</td>
<td>0.044</td>
</tr>
<tr>
<td>Sorensen</td>
<td>259</td>
<td>46</td>
<td>III-IV</td>
<td>Chemot.</td>
<td>6.8:6.8</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Albain</td>
<td>2531</td>
<td>23</td>
<td>III-IV</td>
<td>Chemot.</td>
<td>NS:NS</td>
<td>0.77</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Paesmans</td>
<td>1052</td>
<td>10</td>
<td>III-IV</td>
<td>Chemot.</td>
<td>NS:NS</td>
<td>0.70</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 3. Treatment in SCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Female %</th>
<th>Stage of disease</th>
<th>Therapy</th>
<th>MST female:male</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson</td>
<td>378</td>
<td>28</td>
<td>LD &amp; ED</td>
<td>Ch/RT</td>
<td>13:10</td>
<td>0.77</td>
<td>0.002</td>
</tr>
<tr>
<td>Albain</td>
<td>1363</td>
<td>32</td>
<td>LD</td>
<td>Ch/RT</td>
<td>NS:NS</td>
<td>0.77</td>
<td>0.00001</td>
</tr>
<tr>
<td>Paesmans</td>
<td>763</td>
<td>11</td>
<td>LD &amp; ED</td>
<td>Chemot.</td>
<td>11.1:10.2</td>
<td>0.91</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Women Survive Longer After Surgery

Lung Cancer 47:173-181, 2005
Women Develop Cancer More Readily, but Have Better Outcomes than Men

Relative Risk women vs. men, matching other factors

- Developing lung cancer
- Dying with lung cancer

JAMA 2006; 296:180-184
The reason why women with lung cancer have better outcomes than men with lung cancer is unknown.

Research from our laboratory suggests that parathyroid hormone-related protein may play a role.
Parathyroid hormone related protein (PTHrP) was discovered as the tumor-derived product associated with humoral hypercalcemia of malignancy (HHM).

It is expressed in a wide variety of malignant and normal tissues.

Named for homology between its amino terminus, PTHrP 1-34, and the comparable portion of parathyroid hormone (PTH).

PTHrP binds the same receptor as PTH, with equal affinity.
PTHrP and Lung Cancer

- PTHrP is expressed by about 66% of non-small cell lung carcinomas (NSCLC) (Clin Cancer Res 2006; 12:499-506).

- It has effects on cell growth and differentiation, apoptosis sensitivity and matrix interactions, actions that could affect cancer progression.
PTHrP Decreases Lung Cancer Cell Proliferation

Cell number

% of initial ± SEM

[PTHrP], nM

0 0.01 0.10 1.00

100 140 180
Does PTHrP Regulate Lung Carcinoma Growth?

Animal model:

- We implanted 3 million human lung cancer cells into the lungs of athymic mice
- Cancer cells expressed the fluorescent protein DsRed
- Treated mice with neutralizing antibody to PTHrP or isotype control
- Estimated tumor burden based on tumor DsRed fluorescence
Orthotopic Lung Cancer Model
Endogenous PTHrP Slows Lung Carcinoma Growth

Hastings, Cancer 92:1402-1410, 2001
Does PTHrP Impact Survival?

- Patients undergoing surgery for non-small cell lung carcinoma
- Stain lung carcinomas for PTHrP
- Analyze survival based on PTHrP status, demographic data and cancer specifics
<table>
<thead>
<tr>
<th></th>
<th>PTHrP-positive</th>
<th>PTHrP-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>adenocarcinoma</td>
<td><img src="#" alt="Image" /></td>
<td><img src="#" alt="Image" /></td>
</tr>
<tr>
<td>squamous carcinoma</td>
<td><img src="#" alt="Image" /></td>
<td><img src="#" alt="Image" /></td>
</tr>
<tr>
<td>large cell carcinoma</td>
<td><img src="#" alt="Image" /></td>
<td><img src="#" alt="Image" /></td>
</tr>
</tbody>
</table>
PTHrP Survival Benefit in Women

Tumors in Females Make More PTHrP than in Males

Montgrain et al, Cancer 2007
Sex Steroid Receptors in Lung Cancer Cells

The differential expression of PTHrP between males and females could be due to effects of sex steroids.

Lung tumors are known to express the receptors for androgens and estrogens.
Androgens Inhibit PTHrP in Cultured Lung Cancer Cells

Montgrain et al, Cancer 2007
Androgens Decrease Lung Tumor PTHrP in vivo

Montgrain et al, Cancer 2007
PTHrP Varies with Sex

- PTHrP is associated with prolonged survival in females but not males.
- Lung carcinoma PTHrP levels are higher in females than in males.
- Androgens decrease tumor PTHrP *in vitro* and *in vivo*.

- What about effects of sex steroids on PTHrP receptor?
Estradiol Increases PTHrP Receptor

**Placebo Treatment**
- PTHrP receptor levels in mouse 1, 2, 3, and 4:
  - Mouse 1: Low levels in both tumor and lung tissues.
  - Mouse 2: Equal levels in tumor and lung tissues.
  - Mouse 3: Higher levels in tumor tissue compared to lung.
  - Mouse 4: Lower levels in lung tissue compared to tumor.
- Actin levels remain consistent across tissues.

**Estradiol Treatment**
- PTHrP receptor levels in mouse 5, 6, 7, and 8:
  - Mouse 5: Similar levels in tumor and lung tissues.
  - Mouse 6: Increased levels in tumor tissue compared to lung.
  - Mouse 7: No significant change in receptor levels between tissues.
  - Mouse 8: Increased levels in lung tissue compared to tumor.
- Actin levels remain consistent across tissues.

**Graphical Representation**
- **Y-axis**: PTHrP receptor/actin
- **X-axis**: Tumor and Lung
- **Legend**:
  - Placebo
  - Estradiol

**Statistical Significance**
- **Placebo**: No significant difference
- **Estradiol**: Significant increase in lung tissue compared to tumor (indicated by ** and *).
Testosterone Decreases PTHrP Receptor
Endothelial cells express PTHrP receptor

PTHrP is associated with decreased angiogenesis during endochondral bone development

Bakre and Varner (2002) demonstrated that PTHrP regulated angiogenesis
PTHRP Reduces Angiogenesis in Prostate Cancer

Bakre, Nature Med 2002
PTHrP Reduces Angiogenesis in Orthotopic Lung Carcinomas
PTHrP and Survival

- PTHrP slows lung cancer growth, possibly by inhibiting angiogenesis.
- PTHrP is associated with prolonged survival in women with lung cancer, but not men. Androgens decrease PTHrP and PTHrP receptor levels in males, which may result in the loss of a survival benefit.

- Does treatment with exogenous PTHrP slow lung carcinoma growth in male mice?
Exogenous PTHrP Slows Tumor Growth in Males

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Sex</th>
<th>Treatment</th>
<th>Tumor Mass (g)</th>
<th>Tumor Total Protein (mg/ml)</th>
<th>Tumor Fluorescence (RFU)</th>
<th>Tumor Image Area (pixels)</th>
<th>Tumor Image Sum Intensity (kilovoxels)</th>
<th>Tumor IL-8 (pg/ml)</th>
<th>Serum IL-8 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEN</td>
<td>Male</td>
<td>PBS (n = 6)</td>
<td>0.25 ± 0.04</td>
<td>49 ± 5</td>
<td>938 ± 133</td>
<td>27 ± 5</td>
<td>604 ± 138</td>
<td>14681 ± 2085</td>
<td>213 ± 57</td>
</tr>
<tr>
<td>PTHrP 1-34 (n = 6)</td>
<td>0.10 ± 0.03</td>
<td>33 ± 5</td>
<td>338 ± 89</td>
<td>12 ± 3</td>
<td>220 ± 67</td>
<td>10871 ± 2208</td>
<td>64 ± 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.03</td>
<td>0.004</td>
<td>0.03</td>
<td>0.02</td>
<td>0.24</td>
<td>0.03</td>
</tr>
</tbody>
</table>

P value 0.01 0.03 0.004 0.03 0.02 0.24 0.03
Conclusions

- Numerous sex-specific differences exist in lung cancer.
- Women appear to be at higher risk of developing lung cancer, but then have better outcomes regardless of stage or treatment modality.
- The cause of women’s survival advantage in lung cancer is currently unknown.
- PTHrP may play a role. The protein slows lung carcinoma growth and inhibits angiogenesis, and women make more PTHrP and PTHrP receptor due to the effects of sex steroids.
Acknowledgements

Hastings Research Group

Randolph Hastings, M.D., Ph.D.
Rick Quintana
Yvette Rascon
Erin Healy