### 2007 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>766,860</td>
<td>678,060</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>19%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Includes basal and squamous cell skin cancers and in-situ carcinomas except urinary bladder.

### 2007 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>289,550</td>
<td>270,100</td>
</tr>
<tr>
<td>Prostate</td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>23%</td>
</tr>
</tbody>
</table>

*Includes basal and squamous cell skin cancers and in-situ carcinomas except urinary bladder.

### Five-year Cancer Survival Rates (%)

#### US 1974-1998

![Five-year Cancer Survival Rates Graph](image)

Source: CA Cancer J Clin 2000;50:7-33

### Lung Cancer Risks

- Cigarette Smoking
  - Environmental Tobacco Smoke
- Other Carcinogens
  - Asbestos, Arsenic, Radon,
  - Bis(chloromethyl) ether, Chromium, Foundry fumes, nickel, mustard gas, coke oven emissions
- Air Pollution (foundries, diesel exhaust)
- Family History
- Diet (Vitamins A,C, E and selenium "protective")


![Cancer Death Rates Graph](image)

Source: SEER
**Smoking Prevalence Rates, US**

![Graph showing smoking prevalence rates for US males and females from 1955 to 1995.](image)

Garfinkel, Prev Med 26:447

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**Percentage of High School Students Who Reported Current Cigarette Smoking**

![Graph showing percentage of high school students who reported current cigarette smoking from 1991 to 1999.](image)

Youth Behavior Survey, MMWR 2000; 49

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**Risk of lung cancer, men vs. women**

<table>
<thead>
<tr>
<th>Pack-years</th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1-19</td>
<td>2.4 (1.4-4.1)</td>
<td>6.8 (4.1-11.4)</td>
</tr>
<tr>
<td>20-39</td>
<td>5.6 (3.6-8.7)</td>
<td>11.2 (7.5-16.8)</td>
</tr>
<tr>
<td>40-49</td>
<td>11.6 (7.7-17.6)</td>
<td>21.4 (14.3-32.3)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>13.8 (9.2-20.9)</td>
<td>32.7 (19.0-56.2)</td>
</tr>
</tbody>
</table>

Relative risk for developing lung cancer is 1.25 for women for any “dose” of tobacco

Zang, JNCI 88:183, 1996

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**Presentation of Lung Cancer**

- **Local Symptoms**
  - Cough
  - Dyspnea
  - Hemoptysis
  - Chest Pain
  - SVC Syndrome
  - Wheezing

- **Systemic Symptoms**
  - Constitutional
  - Skeletal
    - Clubbing
    - Hypertrophic Pulmonary Osteoarthropathy
  - Endocrine
    - SIADH (sclc)
    - Hypercalcemia (squamous)
    - Cushings Syndrome (sclc)
  - Neurologic
    - Horner Syndrome
    - Eaton-Lambert syndrome (sclc)
  - Vascular
    - Thrombopilebitis, DIC

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**Differential Diagnosis**

- **Benign**
  - Granuloma
  - Hamartoma

- **Malignant**
  - Metastasis
  - Primary Lung Ca
    - Small Cell
    - Carcinoid
    - Non-small Cell
      - Adenocarcinoma
      - Squamous
      - Large Cell

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**Pathologic diagnosis:**

- Transbronchial biopsy
- Transthoracic needle biopsy
- Cytology
  - Bronchial brushing
  - Lavage
  - Aspiration (transthoracic or transbronchial)
- Thoracotomy/VATS
**Lung tumors - Benign**

- The majority of pulmonary neoplasms are malignant
- Benign tumors/lesions
  - Hamartoma (most common)
  - Mesenchymal- leiomyoma, lipoma, chondroma (all unusual)
  - Alveolar adenoma (rare)

**Hamartoma**

Likely a misnomer as these are probably true benign neoplasms, with common chromosomal abnormality (6p21 or 12q14-15).

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**Malignant tumors - classification**

<table>
<thead>
<tr>
<th>Lung Tumor Classification</th>
<th>Small cell carcinoma</th>
<th>Non small cell carcinoma</th>
<th>Carcinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant epithelial tumors</td>
<td>Adenocarcinoma</td>
<td>Squamous Ca</td>
<td>Atypical carcinoids</td>
</tr>
<tr>
<td>Bronchioalveolar</td>
<td>Various subtypes</td>
<td>Various subtypes</td>
<td>Various subtypes</td>
</tr>
</tbody>
</table>

**Small cell carcinoma**

- Usually hilar/ central tumor
- The majority have extrapulmonary spread at time of presentation.
- Only 5% present as early stage disease.
- Critical divide between small cell and non-small cell carcinoma
  - Small cell carcinoma staged differently, treated with chemoradiation not surgery.

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**Small cell carcinoma**

- High grade tumor
- Small cells with high nuclear to cytoplasmic ratio
- Nuclear molding with stippled, salt and pepper chromatin
- Frequent mitosis and apoptosis
- “Crush” artifact - very fragile cells
- Neuroendocrine differentiation can be demonstrated by electron microscopy and immunohistochemistry (few neurosecretory granules due to poor differentiation)
**Small Cell**

Atypical adenomatous hyperplasia - adenocarcinoma precursor

- Focal, 5.0 mm or less, with defined borders
- Alveoli lined by cuboidal to low columnar cells with variable atypia
- Alveolar walls may be slightly thickened
- Non-mucinous
- Clinical significance unclear (?time to progression to carcinoma)

**Adenocarcinoma**

- Most often a peripheral tumor
- Many are near pleura and cause pleural puckering.
- Cut surface can be mucoid or firm, depending on degree of fibrosis and mucin production
- Small tumors can be associated with lymph node and distant metastasis.
Adenocarcinoma

- Histologic varieties are multiple, including solid, acinar, papillary, mucinous types even within the same tumor
- Rarer types include signet ring morphology
- Differentiation can recapitulate goblet cell, Clara cell or type II pneumocyte differentiation
- Bronchial glands can produce a distinct subtype mimicking salivary gland type tumors
  - These unusual tumors are central and in younger patients

Adenocarcinoma - Bronchioloalveolar

- Distinct morphologic and clinical variant
- Grows along pre-existing alveoli and terminal bronchioles without stromal invasion
- Grossly can form a nodule, but can also produce diffuse disease mimicking pneumonia
- Can be mucinous or non-mucinous.
- Often multifocal

[Images of adenocarcinoma and adenocarcinoma-BAC features]
Are these observations relevant?

- EGFR mutation and amplification correlates with response to EGFR targeted agents (tyrosine kinase inhibitors gefitinib and erlotinib).
  - This subgroup of patients are also more likely to be women, non-smokers, and of Asian descent but not exclusively so.
- Activating K-ras mutations indicate resistance to these agents (about 30% of lung adenocarcinomas)
- Few, if any, lung adenocarcinomas have both activating K-ras and EGFR mutations in the same tumor.
Squamous precursors

• Squamous metaplasia, dysplasia and carcinoma in situ in lung progresses in a sequence similar to the changes described in the head and neck and cervix.
• Koilocytosis is not common; this HPV viral cytopathic change is seen in papillomatosis of larynx and trachea (HPV 6/11)

Squamous carcinoma

• Usually of bronchogenic origin; however can also arise from peripheral areas of squamous metaplasia
• Frequently have central necrosis
• Faster doubling time than adenocarcinoma; often larger at presentation
• Metastasis in relation to tumor size may occur later than adenocarcinoma

Large cell carcinoma

• This subtype shows no differentiation towards either squamous or adenocarcinoma
• Aggressive tumors with poor prognosis
• If subjected to ultrastructural examination, many of these tumors show either glandular or squamous differentiation.
• Nevertheless, these tumors are separated out because of their high grade and poor prognosis
Carcinoids

- Malignant neoplasm of neuroendocrine cell origin
- Can be central or peripheral; central lesions can cause bronchial obstruction
- Project into bronchial lumen but often have intact mucosa above them (grow under the mucosa)
- Typical carcinoids are low grade malignancies; atypical carcinoids (mitoses and necrosis) are intermediate grade when compared to non-small cell carcinomas

Endobronchial carcinoid

Carcinoids

- Histologic features
  - Nest and cords surrounded by delicate stroma
  - Uniform cells with salt and pepper chromatin
  - Neurosecretory granules are abundant and easily demonstrated by electron microscopy or immunohistochemistry (well differentiated tumors)

Metastatic Carcinoma

- The lung is a frequent site of metastatic tumor, both from extrapulmonary and intrapulmonary primaries.
- In autopsy series, between 20 and 50% of patients that expire from extra-pulmonary primaries have lung metastasis.
- Melanoma, sarcomas, renal cell carcinoma, germ cell tumors, breast carcinoma as well as carcinomas of bladder, larynx, thyroid and prostate
Lung Cancer Staging

- Small Cell Carcinoma
  - Limited: confined to hemithorax
  - Extensive
- Non-small Cell Carcinoma
  - T, N, M: Clinical Stage 1-4

Therapy - Non-small Cell Lung Cancer

- Stage I, II
  - Lobectomy + adjuvant chemotherapy
- Stage IIIa
  - Neoadjuvant chemotherapy, radiation, surgery
- Stage IIIb
  - Chemotherapy + radiation
- Stage IV
  - Chemotherapy

Therapy - small cell

- Limited
  - Chemotherapy + Radiation
- Extensive
  - Chemotherapy

CT Screening
Assessment of Interval Growth

Benign or Malignant?
**Gene Expression Signatures in Biopsy Specimens of Lung Cancer**

Gene expression signatures can be used to predict the risk of cancer death. High-risk gene expression profiles include MYC (gene transcription regulation), TGFβ1 (growth factor binding), FHL2 (oncogenesis-β-catenin), CCNB1 (G2/M transition), and LOXL2 (scavenger receptor). Low-risk gene expression profiles include HLADPB1 (class II MHC) and SELENBP1 (selenium binding).

### Biopsy: Prognosis

<table>
<thead>
<tr>
<th>High Risk for Cancer Death</th>
<th>Low Risk</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC</td>
<td>HLADPB1</td>
<td>Gene transcription regulation</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>SELENBP1</td>
<td>Growth factor binding</td>
</tr>
<tr>
<td>FHL2</td>
<td></td>
<td>Oncogenesis-β-catenin</td>
</tr>
<tr>
<td>CCNB1</td>
<td></td>
<td>G2/M transition</td>
</tr>
<tr>
<td>LOXL2</td>
<td></td>
<td>Scavenger receptor</td>
</tr>
</tbody>
</table>

*Images of gene expression profiles are shown.*

*Am J Respiratory and Critical Care Medicine 170: 167*