2007 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men 766,860</th>
<th>Women 678,060</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All Other Sites</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

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

*ONS=Other nervous system.
The Scheme:
From Nicotine Addiction to Lung Cancer

Cigarette smoking → Metabolic Activation (eg. Cytochrome P450) → Field Carcinogenesis

NICOTINE ADDICTION → CARCINOGENS (Ba-P, NNK) → MUTATIONS, etc (p53, k-ras) → LUNG CANCER

Metabolic Detoxification (eg. Glutathione S-Transferase) → Excretion → Repair (Normal DNA), Apoptosis

Modified from Hecht JNCI; 1999

Five-year Cancer Survival Rates (%)
US 1974-1998

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”)


Source: SEER
Smoking Prevalence Rates, US

Percentage of High School Students Who Reported Current Cigarette Smoking

Garfinkel, Prev Med 26:447

Youth Behavior Survey, MMWR 2000; 49
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

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
    - Horners Syndrome
    - Eaton-Lambert syndrome (sclc)

Vascular
  - Thrombophlebitis, DIC
Differential Diagnosis

- Benign
  - Granuloma
  - Hamartoma

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

Pathologic diagnosis:

specimen types

- 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).
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.
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

Malignant tumors - classification

Lung Tumor Classification

- Malignant epithelial tumors
- Small cell carcinoma
- Non small cell carcinoma
- Carcinoids
  - Atypical carcinoids
  - Adenocarcinoma
  - Squamous Ca
  - Large cell CA
  - Bronchioloalveolar
  - Various subtypes
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
Adenocarcinoma/”BAC features”

Combined non-invasive and invasive carcinoma
Is there a meaning to the histologic diversity of adenocarcinoma?

- Studies examining response to gefitinib (EGFR targeting tyrosine kinase inhibitor) found activating EGFR mutations in patients with favorable response.
- Gene profiling studies found distinct subclasses of adenocarcinoma.

BAC
Mixed invasive and Poor differentiation/
Takeuchi et al, 2005
BAC features
No BAC pattern
Borczuk and Powell, 2005

Gene expression profiling in lung adenocarcinoma
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.

Malignant tumors - classification
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

Squamous carcinoma
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
Large cell/ Giant cell carcinoma

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
Carcinoids

- Histologic features
  - Nests 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
Gene Expression Signatures in Biopsy Specimens of Lung Cancer

Am J Respiratory and Critical Care Medicine 170: 167

Biopsy: Prognosis

<table>
<thead>
<tr>
<th>High Risk for</th>
<th>Cancer Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC</td>
<td>Gene transcription regulation</td>
</tr>
<tr>
<td>TGFB1</td>
<td>Growth factor binding</td>
</tr>
<tr>
<td>FHL2</td>
<td>Oncogenesis-β-catenin</td>
</tr>
<tr>
<td>CCNB1</td>
<td>G2/M transition</td>
</tr>
<tr>
<td>LOXL2</td>
<td>Scavenger receptor</td>
</tr>
</tbody>
</table>

Low Risk

<table>
<thead>
<tr>
<th>HLADPB1</th>
<th>Class II MHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SELENBP1</td>
<td>Selenium binding</td>
</tr>
</tbody>
</table>

![Graphs of Cyclin B1, FHL2, and HLA-DRB1 survival probability over time to event in days with low and high expression]