Causes of death, 2001:

<table>
<thead>
<tr>
<th></th>
<th>1. Infectious and parasitic diseases: 14.9 million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Heart diseases: 11.1 million</td>
</tr>
<tr>
<td></td>
<td>3. Cancers: 7.3 million</td>
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<td>4. Stroke: 5.5 million</td>
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<tr>
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<td>5. Respiratory diseases: 3.6 million</td>
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<tr>
<td></td>
<td>6. Accidents, fires, drowning, etc.: 3.5 million</td>
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<tr>
<td></td>
<td>7. Maternal and perinatal: 3.0 million</td>
</tr>
<tr>
<td></td>
<td>8. Violence (war, homicide, suicide): 1.6 million</td>
</tr>
</tbody>
</table>

Population: 6,122,210,000  
Deaths: 56,554,000

USA

World Health Organization  
World Health Report 2002
Cancer Incidence

### Cancers of epithelia: carcinomas

- oral cavity and pharynx
- digestive organs
- respiratory system
- breast
- reproductive tract
- urinary organs
- skin melanoma
- leukemias and lymphomas
- central nervous system
- connective tissue, muscles and vasculature
- other

**KEY:**
- new cases per year (total = 1,220,000)
- deaths per year (total = 552,200)

<table>
<thead>
<tr>
<th>Year</th>
<th>colorectal</th>
<th>lung and bronchus</th>
<th>stomach</th>
<th>breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930</td>
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<td>1940</td>
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<td>1950</td>
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<td>1960</td>
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<td>1970</td>
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<td>1980</td>
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<tr>
<td>1990</td>
<td></td>
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</tr>
</tbody>
</table>
Essential Characteristics of Cancer Cells

1. Rapid/dysregulated cell division
2. Avoid apoptosis/differentiation
3. Avoid senesence by telomere shortening
4. Genomically unstable (Mut L/S HNPCC vs. FAP)
5. Invasive
6. Survive Elsewhere (10^{-3} to 10^{-6}; e.g. angiogenesis)
Genomic Instability

two successive "selection barriers" encountered in the evolution of a cancer
Break-Fusion-Bridge and Telomeres

1. cell enters S phase and replicates its DNA despite unrepaird strand break
2. one daughter cell inherits chromosome lacking telomere
3. cell enters S phase and replicates its DNA
4. sister chromatid ends that lack telomeres fuse
5. fused sister chromatids are pulled apart at mitosis, creating breakage at new site
6. one daughter cell inherits chromosome with duplicated genes but again lacking telomere
7. BREAKAGE-FUSION-BRIDGE CYCLE
Invasiveness and Ectopic Survival

cells grow as a benign tumor in epithelium → break through basal lamina → invade capillary
connective tissue → basal lamina → capillary
travel through bloodstream (less than 1 in 1000 cells will survive to form metastases)
adhere to blood vessel wall in liver → escape from blood vessel (extravasation) → proliferate to form metastasis in liver
Multiple Hits are Required/Cancer Heterogeneity
# Environment versus Genetics

80-90% estimated delayable based on environmental factors! But what are they?

## Variation Between Countries in the Incidence of Some Common Cancers

<table>
<thead>
<tr>
<th>SITE OF ORIGIN OF CANCER</th>
<th>HIGH-INCIENCE POPULATION</th>
<th>LOW-INCIENCE POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOCATION</td>
<td>INCIDENCE*</td>
</tr>
<tr>
<td>Lung</td>
<td>USA (New Orleans, blacks)</td>
<td>110</td>
</tr>
<tr>
<td>Breast</td>
<td>Hawaii (Hawaiians)</td>
<td>94</td>
</tr>
<tr>
<td>Prostate</td>
<td>USA (Atlanta, blacks)</td>
<td>91</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>Brazil (Recife)</td>
<td>83</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japan (Nagasaki)</td>
<td>82</td>
</tr>
<tr>
<td>Liver</td>
<td>China (Shanghai)</td>
<td>34</td>
</tr>
<tr>
<td>Colon</td>
<td>USA (Connecticut, whites)</td>
<td>34</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Australia (Queensland)</td>
<td>31</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>Hong Kong</td>
<td>30</td>
</tr>
<tr>
<td>Esophagus</td>
<td>France (Calvados)</td>
<td>30</td>
</tr>
<tr>
<td>Bladder</td>
<td>Switzerland (Basal)</td>
<td>28</td>
</tr>
<tr>
<td>Uterus</td>
<td>USA (San Francisco Bay Area, whites)</td>
<td>26</td>
</tr>
<tr>
<td>Ovary</td>
<td>New Zealand (Polynesian Islanders)</td>
<td>26</td>
</tr>
<tr>
<td>Rectum</td>
<td>Israel (European and USA born)</td>
<td>23</td>
</tr>
<tr>
<td>Larynx</td>
<td>Brazil (São Paulo)</td>
<td>18</td>
</tr>
<tr>
<td>Pancreas</td>
<td>USA (Los Angeles, Koreans)</td>
<td>16</td>
</tr>
<tr>
<td>Lip</td>
<td>Canada (Newfoundland)</td>
<td>15</td>
</tr>
<tr>
<td>Kidney</td>
<td>Canada (NWT and Yukon)</td>
<td>15</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>France (Bas-Rhin)</td>
<td>14</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Canada (Ontario)</td>
<td>12</td>
</tr>
<tr>
<td>Testis</td>
<td>Switzerland (urban Vaud)</td>
<td>10</td>
</tr>
</tbody>
</table>

*Incidence = number of new cases per year per 100,000 population, adjusted for standardized population age distribution (so as to eliminate effects due merely to differences of population age distribution). Figures for cancers of breast, uterine cervix, uterus, and ovary are for women; other figures are for men. (Adapted from V.T. DeVita, S. Hellman, and S.A. Rosenberg (eds.), *Cancer: Principles and Practice of Oncology*, 4th edn. Philadelphia: Lippincott, 1993; based on data from C. Muir et al., *Cancer Incidence in Five Continents*, Vol. 5. Lyon: International Agency for Research on Cancer, 1987.)
Oncogenes vs. Tumour Suppressors

overactivity mutation (gain of function)

normal cell

single mutation event creates oncogene

activating mutation enables oncogene to stimulate cell proliferation

cells that proliferate abnormally

underactivity mutation (loss of function)

normal cell

mutation event inactivates tumor suppressor gene

no effect of mutation in one gene copy

second mutation event inactivates second gene copy

two inactivating mutations functionally eliminate the tumor suppressor gene, stimulating cell proliferation
Developmental Pathways in Cancer

Wnt, Hedgehog, Notch/Delta, TGFβ, RTK’s
Questions:

1. Does transformation require persistence of the initiating genetic perturbation?

2. Does transformation require persistence of the initiating genetic perturbation?
Conventional Cytotoxic Chemotherapy

- Ionizing radiation
- DNA damage
- Induction of p53 causes cell cycle arrest
- DNA repaired
- Normal cell division
- Damage too extensive to repair
- Apoptosis
- Massive mitotic failure and cell death
- Tumor regresses
- Cancer
- Continued mutation, selection, and tumor evolution
Alternate Directed Therapies

1. 

2. Anti-Receptor mAb’s (e.g. Herceptin) or soluble ligand/receptor proteins (e.g. Avastin)

3. Kinase Enzyme Inhibitors
30 Yr. Progress: the Case for Early Detection

Figure 1: Relative survival (5 year or 10 year) among cancer cases diagnosed with distant, regional or distant, and localized disease by year of diagnosis. a | Breast cancer; b | colorectal cancer; c | lung cancer; d | prostate cancer. Source: Surveillance, Epidemiology and End Results (SEER)*. Stage is SEER historic stage.
Human Kinome
Human Tyrosine Kinome
TK Signaling Pathways

- **EXTRACELLULAR SPACE**
  - signal molecule
  - inactive Ras protein
  - active Ras protein
  - Grb-2 adaptor protein
  - Ras GEF

- **CYTOSOL**
  - activated receptor tyrosine kinase
  - activated B cell receptor complex
  - activated PI 3-kinase
  - PI(4,5)P2
  - PI(3,4,5)P3
  - activated PLC-γ
  - IP3
  - diacylglycerol

- **ONWARD TRANSMISSION OF SIGNAL ALONG MULTIPLE PATHWAYS**

- **changes in protein activity**
  - protein X
  - protein Y

- **changes in gene expression**
  - gene regulatory protein A
  - gene regulatory protein B

- **Activation of PKC**
  - Release of Ca2+ from ER
Erb RTK Family
# Erb Receptor Cancer Involvement

Malignancies overexpressing wild-type and mutated forms of erbB receptors

<table>
<thead>
<tr>
<th>erbB1</th>
<th>erbB2</th>
<th>erbB3</th>
<th>erbB4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (14%–91%)</td>
<td>Breast (10%–37%)</td>
<td>Breast</td>
<td>Breast</td>
</tr>
<tr>
<td>Ovary (30%–75%)</td>
<td>Ovary (20%–32%)</td>
<td>Ovary</td>
<td>Ovary</td>
</tr>
<tr>
<td>Renal (50%–90%)</td>
<td>Renal (24%–40%)</td>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Lung (NSCLC) (40%–80%)</td>
<td>Lung (NSCLC) (3%–56%)</td>
<td>Lung (NSCLC)</td>
<td>Lung (NSCLC)</td>
</tr>
<tr>
<td>Head and neck (squamous) (30%–75%)</td>
<td>Head and neck (squamous) (32%–62%)</td>
<td>Head and neck (squamous)</td>
<td>Head and neck (squamous)</td>
</tr>
<tr>
<td>Colorectal (25%–77%)</td>
<td>Colorectal (7%)</td>
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</tr>
<tr>
<td>Pancreas (30%–50%)</td>
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<tr>
<td>Glioma (40%–50%)</td>
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<tr>
<td>Bladder (31%–48%)</td>
<td>Bladder (7%–36%)</td>
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</tr>
<tr>
<td>Esophagus</td>
<td>Esophagus (13%–73%)</td>
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<tr>
<td>Stomach</td>
<td>Stomach (5%–55%)</td>
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</tr>
<tr>
<td>Prostate</td>
<td>Prostate</td>
<td>Prostate</td>
<td>Prostate</td>
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<tr>
<td>Melanoma</td>
<td>Melanoma</td>
<td>Melanoma</td>
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<tr>
<td>Thyroid</td>
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<tr>
<td>Endometrial</td>
<td>Endometrial</td>
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<tr>
<td>Skin (squamous cell)</td>
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<tr>
<td>Lung (small cell)</td>
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<tr>
<td>Cervical</td>
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<tr>
<td>Sarcomas</td>
<td></td>
<td></td>
<td>Chronic myelogenous leukemia</td>
</tr>
</tbody>
</table>

\(^5\)Clinical studies have linked overexpression and/or mutation of this erbB receptor to a worse prognosis.
Erb Signaling Mechanism
Erb 1 Inhibitors

ZD1839
(gefitinib, Iressa)

OSI-774
(erlotinib, Tarceva)
Tarceva On Erb1
Erb1 Mutations in Glioblastoma

[Diagram showing various Erb1 mutants, including wild type and missense, deletion, and insertion mutants.]
Philadelphia Chromosome Rearrangement

9  22  9q⁺  22q⁻  (Ph₁)
Abl Domains

- **Src family**
  - Myristate/palmitate
  - Core: SH3, SH2, Kinase domain, Phosphorylated tail

- **Abl family**
  - Myristate
  - Core: SH3, SH2, Kinase domain
  - Last exon region: Abl, Arg

**Legend:**
- Yellow: PXXP motif
- Pink: DNA-binding domain
- Brown: SH3-SH2 connector
- Green: F-actin-binding domain
- Blue: Nuclear localization signal
- Red: SH2-kinase linker
- Black: Nuclear export signal
- Beige: Autoinhibitory Cap
- Blue: Coiled-coil domain

- **Bcr**
  - SH3, SH2, Kinase domain
  - **Bcr-Abl**
Abl Autoinhibition
Gleevec
Gleevec Resistance Mutations in Abl
Structural Basis for Gleevec Resistance
Questions:

Erb RTK K.O. in mice is embryonic lethal.

Abl TK K.O. in mice induces perinatal lethality, defects of eye/head formation, and hematopoietic problems.

Based on what evidence should one choose a target for inhibition?