Are we making any progress in the War on Cancer?

It starts with knowing what’s going on. And what have we learned about cancer?

Inspire2Live
Amsterdam, January 2020
Figure 2.11  *The Biology of Cancer* (© Garland Science 2007)
As cancer develops, cancer cells accumulate mutations in their genomes.
How even a subtle change in DNA structure can wreak havoc in a cell.

1982: One simple point mutation out of 2 billion bases of DNA
Artist’s depiction of multi-step tumor progression in the colon

Increasingly abnormal tissues
Why does it take **so long** for a colon tumor to develop?

Increasingly abnormal tissues

- intestinal epithelial crypts
- aberrant crypt focus
- adenoma
- carcinoma

Each of these steps take a long time to occur, e.g., 5-10 years.
As cells [and the tumors that they form] grow increasingly abnormal, they accumulate more and more damaged genes.

Documented genetic changes

Cancer formation in the gut
Over the past 40 years, we have learned an enormous amount about the internal circuitry governing the behavior of human cells.
As cancer develops, the mutations cause damage to multiple control circuits operating within individual cancer cells.
As cells [and the tumors that they form] grow increasingly abnormal, they accumulate more and more damaged genes.
Mutations in many of these genes lead to defective proteins and therefore malfunctioning components of this subcircuit.
Same process also operates in the pancreas.
Different colorectal carcinomas take different genetic paths en route to full-fledged cancer formation.
Another problem: The formation of metastases is not controlled by additional mutations in the DNA. Instead, non-genetic programs govern metastatic dissemination.
A Darwinian model of multistep tumor progression

(Each mutation confers and additional survival or proliferation advantage.)
Another inconvenient truth: What if the rate of diversification outpaces the rate of Darwinian selection?
Figure 11.21b The Biology of Cancer (© Garland Science 2014)
Carcinoma cell heterogeneity is a hallmark of breast cancer within a given tumor.
How do the multiple steps required to form a human tumor map to the multiple distinct traits that tumors develop? In spite of this heterogeneity, are there some common shared traits??
How do the multiple steps required to form a human tumor map to the multiple distinct traits that tumors develop? In spite of this heterogeneity, are there some common shared traits?
Back to the internal circuitry governing the behavior of human cells.
Some have tried to plot out the circuitry like a circuit diagram.
Some have tried to plot out the circuitry like a circuit diagram. PS They went pleite!
fragment of a tumor

a cancer cell

intracellular circuitry
Figure 16.9 The Biology of Cancer (© Garland Science 2014)
Molecular structure of the signaling molecule that misfires in chronic myelogenous leukemia.
A major success story:
Survival of patients with chronic myelogenous leukemia
Effects of Gleevec/imatinib treatment
But there are problems, as illustrated by this drug compound that shuts down the growth of certain lung and cancer cells. Initial responsiveness – drug works

But later, the “target” changes and no longer responds to drug

Consequence: acquired drug resistance

This protein drives cancer cell growth.

drug compound

2 years

Iressa

Consequence: acquired drug resistance

Figure 16.33c  The Biology of Cancer (© Garland Science 2007)
Lung cancer regression following treatment with an “anti-receptor” drug followed by eventual relapse.
The successes of Gleevec created a mirage that there would be a wave of similar successes:

OS = overall survival

Table 1. Estimated drug costs for indications cited in the text*

<table>
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<th>Drug (brand name)</th>
<th>Regimen</th>
<th>Dose†</th>
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<td>Bevacizumab (Avastin)</td>
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<td>600 mg every 14 d</td>
<td>13200 mg</td>
<td>$6.88/mg</td>
<td>$90816</td>
<td>1.5 mo§ (13)</td>
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<td>$34373</td>
<td>2.7 mo (15)</td>
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</table>

Total cost‡ | Increase in OS‡

- $80352 | 1.2 mo (1)
- $90816 | 1.5 mo§ (13)
- $15752 | 10 d (14)
- $34373 | 2.7 mo (15)

OS = overall survival
Background:
How much cancer is there (incidence)? Really?

pre-chemotherapy
longest dimension = 47 mm

post-chemotherapy
longest dimension = 16 mm

Figure 16.2 The Biology of Cancer (© Garland Science 2014)
About 1 in 8 U.S. women (about 12%) will develop invasive breast cancer over the course of her lifetime. In 2017, an estimated 252,710 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S., along with 63,410 new cases of non-invasive (in situ) breast cancer.

For women in the U.S., breast cancer death rates are higher than those for any other cancer, besides lung cancer.

About 40,610 women in the U.S. are expected to die in 2017 from breast cancer.
The breast cancer "epidemic"

Mark Messenbaugh
SomaLogic

breast cancer incidence and mortality in U.S.

incidence (beginning in 1975)

The breast cancer "epidemic"

age-adjusted incidence or mortality per 100,000 population

year of death

Figure 16.3 The Biology of Cancer (© Garland Science 2014)
Figure 16.4 The Biology of Cancer (© Garland Science 2014)
The overall breast cancer death rate has decreased consistently since 1989, attributed both to improvements in early detection (through screening as well as increased awareness of symptoms) and treatment for a total decline of 40% through 2017. As a result of this decline, 375,900 breast cancer deaths have been averted in U.S. women through 2017.

Mortality: total decline of 40%
The overall breast cancer death rate has decreased consistently since 1989, attributed both to improvements in early detection (through screening as well as increased awareness of symptoms) and treatment for a total decline of 40% through 2017. As a result of this decline, 375,900 breast cancer deaths have been averted in U.S. women through 2017.

Mortality: total decline of 40%

Who gets the credit??
- Tamoxifen
- Cessation of hormone replacement therapy
- Radiotherapy
- Chemotherapy
- Surgery
- Herceptin
- ??????mammography ????????
Well, how are doing in our fight to stave off cancer deaths?
Well, how are we doing in our fight to stave off cancer deaths?

**Background**

Who gets the credit?

- Colonoscopy
- Food preservation (?)
- Pap test
- Colon and rectum
- Uterus

**Figure 16.1a The Biology of Cancer (© Garland Science 2014)**
Who gets the credit?

Smoking cessation

Figure 16.1b The Biology of Cancer (© Garland Science 2014)
How long does it take to develop a cancer?
A ~30 year lag between the cause and the effect

The decades-long incubation of most tumors dictates that most cancers arise late in life.
Only solution: Reduce incidence:

In the US, tobacco use is responsible for nearly 1 in 5 deaths; this equaled an estimated 443,000 premature deaths each year between 2000 and 2004. In addition, an estimated 8.6 million people suffer from chronic conditions related to smoking, such as chronic bronchitis, emphysema, and cardiovascular diseases.
Only solution: Reduce incidence:

Stunning differences in lung cancer mortality

Fig. 2. Lung cancer mortality rates, by education level, sex, and race, for persons aged 25–64 years in the United States, 2001. Error bars correspond to 95% confidence intervals.
# Key State-Specific Tobacco-Related Data & Rankings

<table>
<thead>
<tr>
<th>State</th>
<th>Adult Smoking Rate</th>
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<td>5.8%</td>
<td>98,000</td>
<td>480,000</td>
<td>17+ mill.</td>
<td>5.6 mill.</td>
<td>$170 bill.</td>
<td>$1.81</td>
<td>///</td>
<td>$555.0</td>
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<td>19.2%</td>
<td>41st</td>
<td>10.1%</td>
<td>14.0%</td>
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<td>8,600</td>
<td>336,200</td>
<td>108,000</td>
<td>$1.88 bill.</td>
<td>$0.675</td>
<td>41st</td>
<td>$2.1</td>
<td>3.7%</td>
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<td>11.5%</td>
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<td>600</td>
<td>43,600</td>
<td>14,000</td>
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<td>$17.3</td>
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<td>10.2%</td>
<td>7.2%</td>
<td>1,000</td>
<td>4,400</td>
<td>191,200</td>
<td>61,000</td>
<td>$1.12 bill.</td>
<td>$1.29</td>
<td>33rd</td>
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<td>50th</td>
<td>18.4%</td>
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<td>2,000</td>
<td>8,900</td>
<td>371,700</td>
<td>119,000</td>
<td>$1.92 bill.</td>
<td>$1.10</td>
<td>36th</td>
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<td>44th</td>
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<td>7,200</td>
<td>307,400</td>
<td>98,000</td>
<td>$1.89 bill.</td>
<td>$1.08</td>
<td>37th</td>
<td>$5.4</td>
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<td>1,557,800</td>
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<td>1,300</td>
<td>120,800</td>
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<td>$542</td>
<td>$1.70</td>
<td>25th</td>
<td>$7.0</td>
<td>36.3%</td>
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<td>Vermont</td>
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<td>15.5%</td>
<td>9.3%</td>
<td>100</td>
<td>1,000</td>
<td>31,500</td>
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<td>$348</td>
<td>$3.08</td>
<td>7th</td>
<td>$3.8</td>
<td>45.2%</td>
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</table>
Reducing incidence: Other avoidable causes

Cancer mortality in obese vs. lean people:

Highest quartile of body mass index vs. lowest quartile

Lowest quartile: BMI of 24.9 and below; highest quartile: BMI no. is given

Figure 9.41a The Biology of Cancer (© Garland Science 2014)
More generally: Cancer is a disease of aging
The risk of developing cancer is different at different ages
Cancer annual death rates go up steeply with increasing age.

How big is the actual problem?
How big is the actual problem?

Cancer annual death rates are roughly the same over many years ~ constant death rates from cancer

Cancer annual death rates are roughly the same over many years

Figure 16.43b The Biology of Cancer (© Garland Science 2014)
How big is the actual problem?

Millions of Americans over the age of 65

<table>
<thead>
<tr>
<th>Year</th>
<th>U.S. population 65 and older (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>31.2</td>
</tr>
<tr>
<td>2000</td>
<td>34.7</td>
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<tr>
<td>2010</td>
<td>39.4</td>
</tr>
<tr>
<td>2020</td>
<td>53.2</td>
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<td>2030</td>
<td>69.4</td>
</tr>
<tr>
<td>2040</td>
<td>75.2</td>
</tr>
<tr>
<td>2050</td>
<td>78.9</td>
</tr>
</tbody>
</table>

Figure 16.43a The Biology of Cancer (© Garland Science 2014)
How big is the actual problem?

Actual numbers of deaths each year in the U.S.

Real U.S. GDP annual growth 2000-2017: ~2%
Is there hope on the horizon for new therapies?
A major success story: Gleevec & chronic myelogenous leukemia (CML)

This signaling molecule fires aberrantly in CML cells

N-terminal lobe

catalytic cleft

C-terminal lobe

Aberrant signal-emitting protein in CML

A custom-designed anti-cancer drug
A major success story:
Survival of patients with **chronic myelogenous leukemia**
Effects of Gleevec/imatinib treatment

![Graph showing survival rates over time with Gleevec treatment.](image-url)
But there are problems, as illustrated by this drug compound that shuts down the growth of certain lung and cancer cells.

Initial responsiveness – drug works

But later, the “target” changes and no longer responds to drug

Consequence: acquired drug resistance
- About 5,980 new cases will be diagnosed with CML (3,130 in men and 2,850 in women).
- About 810 people will die of CML (550 men and 260 women).

Figure 16.29  The Biology of Cancer (© Garland Science 2007)
The successes of Gleevec created a mirage that there would be a wave of similar successes:

OS = overall survival

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Gleevec

Table 1. Estimated drug costs for indications cited in the text*
Checkpoint blockade Immunotherapy: Much hope!!!!

- Blocking these interactions using anti-CTLA4 or anti-PD1/PDL1 unleashes the “brakes” on the immune system, allowing tumor cell killing
Once again: Cancer is a disease of aging
The risk of developing cancer is different at different ages

What are the societal implications of these curves?
Figure 16.45a  The Biology of Cancer (© Garland Science 2007)
Death rates from colorectal cancer have been decreasing but only slowly.
If we consider all three of these trends together.....
Total number of cancer-related deaths per year in the U.S.
It’s unclear how we are going to pay for all this.

We will soon not be able to treat all those diagnosed with cancer because of economic factors.
It’s unclear how we are going to pay for all this.
What's the ratio of no. of deaths annually per no. of diagnosed new cases?

- Pancreas: 85%
- Esophagus: 85%
- Colon: 52%
- Lung & bronchus: 87%

A major success!!

A major success!!
### Estimated Number* of New Cancer Cases and Deaths by Sex, US, 2014

<table>
<thead>
<tr>
<th></th>
<th>Estimated New Cases</th>
<th></th>
<th>Estimated Deaths</th>
<th></th>
</tr>
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<tr>
<td></td>
<td>Both Sexes</td>
<td>Male</td>
<td>Female</td>
<td>Both Sexes</td>
</tr>
<tr>
<td>All Sites</td>
<td>1,665,540</td>
<td>855,220</td>
<td>810,320</td>
<td>585,720</td>
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<tr>
<td>Esophagus</td>
<td>18.170</td>
<td>14.660</td>
<td>3.510</td>
<td>15.450</td>
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<tr>
<td>Colon†</td>
<td>96,830</td>
<td>48,450</td>
<td>48,380</td>
<td>50,310</td>
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<tr>
<td>Lung &amp; bronchus</td>
<td>224,210</td>
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<tr>
<td>Breast</td>
<td>235,030</td>
<td>2,360</td>
<td>232,670</td>
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<tr>
<td>Prostate</td>
<td>233,000</td>
<td>233,000</td>
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<td>29,480</td>
</tr>
<tr>
<td>Pancreas</td>
<td>46,420</td>
<td>23,530</td>
<td>22,890</td>
<td>39,590</td>
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What’s the ratio of no. of deaths annually per no. of diagnosed new cases?

<table>
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Wow! We seem to be making great progress!
A major problem at present: **Overdiagnosis**
These days we can find growths in the breast that would previously have eluded detection.
Incidence of breast cancer is ~ 6 times higher than mortality.
About 1 in 8 U.S. women (about 12%) will develop invasive breast cancer over the course of her lifetime. In 2017, an estimated 252,710 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S., along with 63,410 new cases of non-invasive (in situ) breast cancer.

For women in the U.S., breast cancer death rates are higher than those for any other cancer, besides lung cancer.

About 40,610 women in the U.S. were expected to die in 2017 from breast cancer.
How can we deal with this?

Dutch solution: don’t treat all patients aggressively

- **Good signature of tumor (40% of patients):**
  - ~4% die of breast cancer
  - ~96% survive breast cancer

- **Poor signature of tumor (60% of patients):**
  - ~50% die of breast cancer
  - ~50% survive breast cancer
Incidence of prostate cancer is \textit{many times higher} than mortality.
Prostate Cancer incidence upon autopsy

~3% of men die from prostate cancer
Melanoma screening & incidence in 9 U.S. geographical regions

- Visits to dermatologist
- Diagnosed cases (incidence)

Rate of skin biopsies performed in 9 U.S. regions (per 100,000 population)

- 1986
- 2001
- 1987–2000
The case of melanoma: The melanoma epidemic

- Total incidence
- Incidence of early-stage cases
- Incidence of late-stage cases

Figure 16.44a The Biology of Cancer (© Garland Science 2014)
The melanoma circus

The more you look, the more you find.

Overdiagnosis

Figure 16.44 The Biology of Cancer (© Garland Science 2014)
How Many People Alive Today Have Ever Had Cancer?

Approximately 13.7 million Americans with a history of cancer were alive on January 1, 2012. Some of these individuals were cancer free, while others still had evidence of cancer and may have been undergoing treatment.

What Percentage of People Survive Cancer?

The 5-year relative survival rate for all cancers diagnosed between 2003 and 2009 is 68%, up from 49% in 1975-1977 (see page 17). The improvement in survival reflects both progress in diagnosing certain cancers at an earlier stage and improvements in treatment. Survival statistics vary greatly by cancer
Where does all this leave us?!
1. The incidence of many cancers is a cultural artifact.

2. Only a portion of these will ever be life-threatening.

3. We will soon not be able to treat all those diagnosed with cancer because of economic factors.

4. The only solution to these trends will be to reduce incidence
Only solution: Reduce incidence:

In the US, tobacco use is responsible for nearly 1 in 5 deaths; this equaled an estimated 443,000 premature deaths each year between 2000 and 2004. In addition, an estimated 8.6 million people suffer from chronic conditions related to smoking, such as chronic bronchitis, emphysema, and cardiovascular diseases.
Only solution: Reduce incidence:

Stunning differences in lung cancer mortality
Let's hear it for the Home Team!!

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<td>200</td>
<td>600</td>
<td>43,600</td>
<td>14,000</td>
<td>$438</td>
<td>$2.00</td>
<td>17th</td>
<td>$9.1</td>
<td>89.4%</td>
</tr>
<tr>
<td>Arizona</td>
<td>14.0%</td>
<td>12th</td>
<td>4.8%</td>
<td>7.1%</td>
<td>2,000</td>
<td>8,300</td>
<td>359,800</td>
<td>115,000</td>
<td>$2.38 bill.</td>
<td>$2.00</td>
<td>17th</td>
<td>$17.3</td>
<td>26.9%</td>
</tr>
<tr>
<td>Kansas</td>
<td>17.3%</td>
<td>31st</td>
<td>10.2%</td>
<td>7.2%</td>
<td>1,000</td>
<td>4,400</td>
<td>191,200</td>
<td>61,000</td>
<td>$1.12 bill.</td>
<td>$1.29</td>
<td>33rd</td>
<td>$0.8</td>
<td>3.0%</td>
</tr>
<tr>
<td>Kentucky</td>
<td>23.4%</td>
<td>50th</td>
<td>18.4%</td>
<td>14.3%</td>
<td>2,000</td>
<td>8,900</td>
<td>371,700</td>
<td>119,000</td>
<td>$1.92 bill.</td>
<td>$1.10</td>
<td>36th</td>
<td>$3.8</td>
<td>6.7%</td>
</tr>
<tr>
<td>Louisiana</td>
<td>20.5%</td>
<td>44th</td>
<td>6.8%</td>
<td>12.3%</td>
<td>1,700</td>
<td>7,200</td>
<td>307,400</td>
<td>98,000</td>
<td>$1.89 bill.</td>
<td>$1.08</td>
<td>37th</td>
<td>$5.4</td>
<td>9.0%</td>
</tr>
<tr>
<td>Texas</td>
<td>14.4%</td>
<td>13th</td>
<td>3.3%</td>
<td>11.3%</td>
<td>8,700</td>
<td>28,000</td>
<td>1,557,800</td>
<td>498,000</td>
<td>$8.85 bill.</td>
<td>$1.41</td>
<td>29th</td>
<td>$4.2</td>
<td>1.6%</td>
</tr>
<tr>
<td>Utah</td>
<td>9.0%</td>
<td>1st</td>
<td>3.0%</td>
<td>3.8%</td>
<td>600</td>
<td>1,300</td>
<td>120,800</td>
<td>39,000</td>
<td>$542</td>
<td>$1.70</td>
<td>25th</td>
<td>$7.0</td>
<td>36.3%</td>
</tr>
<tr>
<td>Vermont</td>
<td>13.7%</td>
<td>10th</td>
<td>15.5%</td>
<td>9.3%</td>
<td>100</td>
<td>1,000</td>
<td>31,500</td>
<td>10,000</td>
<td>$348</td>
<td>$3.08</td>
<td>7th</td>
<td>$3.8</td>
<td>45.2%</td>
</tr>
</tbody>
</table>
Reducing incidence: Other avoidable causes
Cancer mortality in obese vs. lean people:
Highest quartile of body mass index vs. lowest quartile

Lowest quartile: BMI of 24.9 and below; highest quartile: BMI no. is given

Figure 9.41a The Biology of Cancer (© Garland Science 2014)
Other avoidable causes:
Cancer mortality in obese vs. lean people:
Highest quartile of body mass index vs. lowest quartile

Lowest quartile: BMI of 24.9 and below; highest quartile: BMI no. is given

Figure 9.41b The Biology of Cancer (© Garland Science 2014)
Reducing incidence: avoidable risk factors

Table 2.7 Known or suspected causes of human cancers

<table>
<thead>
<tr>
<th>Type</th>
<th>% of total cases²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers due to occupational exposures</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>Lifestyle cancers</strong></td>
<td></td>
</tr>
<tr>
<td>Tobacco-related (sites: e.g., lung, bladder, kidney)</td>
<td>34</td>
</tr>
<tr>
<td>Diet (low in vegetables, high in nitrates, salt) (sites: e.g., stomach, esophagus)</td>
<td>5</td>
</tr>
<tr>
<td>Diet (high fat, low fiber, broiled/fried foods) (sites: e.g., bowel, pancreas, prostate, breast)</td>
<td>37</td>
</tr>
<tr>
<td>Tobacco plus alcohol (sites: mouth, throat)</td>
<td>2</td>
</tr>
</tbody>
</table>

²A large number of cancers are thought to be provoked by a diet high in calories (see Sidebar 9.10) acting in combination with many of these lifestyle factors.
⁴ER+, estrogen receptor–positive.
⁵E + P, therapy containing both estrogen and progesterone.

Table 2.7 (part 1 of 2) The Biology of Cancer (© Garland Science 2014)
Through the miracle of PhotoShop!!
Native born Americans
<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Both Sexes</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both Sexes</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Pancreas</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>87%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What’s the ratio of no. of deaths per no. of diagnosed new cases?

Pancreas 85%
Esophagus 85%
Colon 52%
Lung & bronchus 87%
Death rates from disseminated tumors remain high.
breast cancer incidence and mortality in U.S.

incidence (beginning in 1975)

Mark Messenbaugh
SomaLogic

The breast cancer “epidemic”

Figure 16.3 The Biology of Cancer (© Garland Science 2014)
Breast cancer diagnosis
Prostate Cancer incidence upon autopsy

% of autopsy

Age

30-39 (n=4)  40-49 (n=23)  50-59 (n=38)  60-69 (n=43)  70-79 (n=40)  80-89 (n=14)  90+ (n=1)
Prostate Cancer incidence upon autopsy

What % of men die of prostate cancer?

~3%