A Physicist Looks at Cancer

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Cancer Incidence Worldwide

Breakdown of the estimated 12.7 million new cases, World-age standardised incidence rates and the most commonly diagnosed cancers by the different regions of the world, 2008.

Western Europe
- Numbers: 1,029,993
- Breast: 16%
- Prostate: 16%
- Colonrectum: 13%
- Lung: 11%

Northern Europe
- Numbers: 482,080
- Breast: 15%
- Prostate: 13%
- Colonrectum: 13%
- Lung: 12%

Central and Eastern Europe
- Numbers: 983,408
- Lung: 14%
- Colorectum: 13%
- Breast: 12%
- Stomach: 7%

Central and Eastern Asia
- Numbers: 3,720,658
- Lung: 17%
- Stomach: 16%
- Liver: 13%
- Colorectum: 10%

South-Eastern Asia
- Numbers: 725,446
- Lung: 14%
- Breast: 12%
- Liver: 10%
- Colorectum: 9%

Melanesia
- Numbers: 7,028
- Lip, oral cavity: 12%
- Cervix uteri: 10%
- Breast: 7%
- Liver: 7%

Caribbean
- Numbers: 79,347
- Prostate: 20%
- Breast: 17%
- Lung: 13%
- Colonrectum: 11%

South America
- Numbers: 650,097
- Breast: 16%
- Prostate: 14%
- Colonrectum: 13%
- Lung: 8%

Middle Africa
- Numbers: 46,959
- Liver: 16%
- Breast: 12%
- Cervix uteri: 12%
- Prostate: 6%

Southern Africa
- Numbers: 79,179
- Breast: 11%
- Prostate: 10%
- Colonrectum: 9%
- Cervix uteri: 8%

Eastern Africa
- Numbers: 22,076
- Cervix uteri: 14%
- Kaposis sarcoma: 11%
- Breast: 8%
- Colonrectum: 7%

South-Central Asia
- Numbers: 1,423,213
- Cervix uteri: 12%
- Breast: 12%
- Lung: 7%
- Lip, oral cavity: 7%

Australia/New Zealand
- Numbers: 127,022
- Prostate: 17%
- Colonrectum: 14%
- Breast: 13%
- Melanoma of skin: 11%

South-Eastern Europe
- Numbers: 725,446
- Lung: 16%
- Breast: 14%
- Colorectum: 13%
- Lung: 12%

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Incidence of Cancer

• This year:
  – Approximately 12.7 million cases of cancer will be diagnosed worldwide.
  – 8 million people will die of cancer worldwide (2012). (15% of deaths)
  – In United States, about 600,000 people will die of cancer (about 1 in 4 deaths).

• It is estimated that during their lifetime
  – 1 in 2 men will be diagnosed with cancer.
  – 1 in 3 women will be diagnosed with cancer.
All cancers excl. non-melanoma skin cancer: both sexes, all ages

Age Standardized Rate (ASR) per 100,000

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia/New Zealand</td>
<td>13.3</td>
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<tr>
<td>Northern Europe</td>
<td>299.9</td>
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<tr>
<td>Western Europe</td>
<td>286.6</td>
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<tr>
<td>Northern developed regions</td>
<td>269.1</td>
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<tr>
<td>Southern Europe</td>
<td>255.8</td>
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<td>More developed regions</td>
<td>244.4</td>
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<tr>
<td>Central and Eastern Europe</td>
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<td>209.8</td>
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<td>Polynesia</td>
<td>189.6</td>
<td>188.4</td>
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<td>Southern Africa</td>
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<td>Eastern Asia</td>
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<td>World</td>
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<tr>
<td>Caribbean</td>
<td>146.8</td>
<td></td>
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<tr>
<td>South America</td>
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<td>Micronesia</td>
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<tr>
<td>Less developed regions</td>
<td>134.4</td>
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<tr>
<td>South-Eastern Asia</td>
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<tr>
<td>Melanesia</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Central America</td>
<td>122.8</td>
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<tr>
<td>Western Asia</td>
<td>119.5</td>
<td></td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>96.5</td>
<td></td>
</tr>
</tbody>
</table>

GLOBOCAN 2008 (IARC) (18.2.2012)
Cancer Statistics

- Most commonly diagnosed cancers:
  - Lung
  - Breast
  - Colorectal

- Most common causes of cancer death
  - Lung
  - Stomach
  - Liver

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix uteri</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus uteri</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
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<tr>
<td>Bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
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</tr>
</tbody>
</table>

Age Standardized Rate

From Globocan 2008
Causes of Cancer

• Genes (family history matters, but some cancers are genetically heterogeneous)
• Environment
  – Carcinogens
  – Radiation
  – Sunlight
• Lifestyle
  – Diet (lack of fruit and veggies, excess salt increase cancer risk)
  – Alcohol
  – Smoking
  – Body weight
  – Occupation (chemical exposure, asbestos, night shift)
• Infectious agents (viruses and bacteria) caused 16% of cancers in 2008, e.g.,
  – Human Papilloma Virus (HPV) can cause cervical cancer.
  – Hepatitis B and C increases the risk of liver cancer.
  – HTLV1 causes leukemia.
  – *H. Pylori* (ulcers) increases the risk of stomach cancer.
  – Epstein-Barr can cause Burkitt’s lymphoma and nasopharyngeal cancer.
Cancer Death Rates Saturating

In United States

Siegel et al., CA: A Journal for Clinicians (2011)
What can be done about lowering cancer mortality?

- **Prevention**
  - Healthy lifestyle: Don’t smoke, eat healthy, exercise
  - Vaccine (Gardasil prevents cervical cancer)

- **Early detection**
  - PSA test for prostate cancer
  - Colonoscopy for colorectal cancer
  - Mammograms for breast cancer

- **New scientific advances**
  - New approaches
  - New technologies
  - Greater exchange of research information
    - Preprint library
90% of cancer research results are not reproducible
What can be done about lowering cancer mortality?

• Prevention
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• Early detection
  – PSA test for prostate cancer
  – Colonoscopy for colorectal cancer
  – Mammogram for breast cancer

• New scientific advances
  – New approaches
  – New technologies
  – Greater exchange of research information
    • Preprint library
Physical Sciences Oncology Centers
http://physics.cancer.gov

- In 2009, the National Cancer Institute (NCI) decided physicists should look at cancer.
- $150 million was used to start 12 Physical Sciences Oncology Centers.
Location, Location, Location
Location Question

- Why are some cancers more prevalent in some parts of the world than others?

**Prostate, all ages**

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australasia and New Zealand</td>
<td>104.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Western Europe</td>
<td>93.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>85.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Caribbean</td>
<td>73.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>71.1</td>
<td>6.2</td>
</tr>
<tr>
<td>South America</td>
<td>61.7</td>
<td>6.2</td>
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<tr>
<td>Polynesia</td>
<td>53.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Central America</td>
<td>50.2</td>
<td>4.1</td>
</tr>
<tr>
<td>South Central America</td>
<td>49.1</td>
<td>2.6</td>
</tr>
<tr>
<td>South Eastern Africa</td>
<td>34.8</td>
<td>1.2</td>
</tr>
<tr>
<td>West</td>
<td>22.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>17.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Less developed regions</td>
<td>11.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

GLCBOCAN 2008 (IARC) (18.2.2012)
Age-Standardized Breast Cancer Incidence and Mortality Rates by World Area. Source: GLOBOCAN 2008

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>89.9</td>
<td>17.5</td>
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<tr>
<td>Australia/New Zealand</td>
<td>85.5</td>
<td>15.4</td>
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<tr>
<td>Northern Europe</td>
<td>84.0</td>
<td>17.8</td>
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<tr>
<td>Northern America</td>
<td>76.7</td>
<td>14.8</td>
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<tr>
<td>Southern Europe</td>
<td>68.9</td>
<td>15.3</td>
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<tr>
<td>Micronesia/Polynesia</td>
<td>58.0</td>
<td>13.2</td>
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<td>Central and Eastern Europe</td>
<td>45.3</td>
<td>16.9</td>
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<td>South America</td>
<td>44.3</td>
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<td>Southern Africa</td>
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<tr>
<td>Western Asia</td>
<td>32.5</td>
<td>14.3</td>
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<tr>
<td>Western Africa</td>
<td>31.8</td>
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<td>South-Eastern Asia</td>
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<td>Central America</td>
<td>26.0</td>
<td>9.6</td>
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<td>Eastern Asia</td>
<td>25.3</td>
<td>6.3</td>
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<tr>
<td>South-Central Asia</td>
<td>24.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Melanesia</td>
<td>22.8</td>
<td>13.2</td>
</tr>
<tr>
<td>Middle Africa</td>
<td>21.3</td>
<td>13.1</td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>19.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Age standardized rates per 100,000
Liver Cancer

Age Standardized Rate per 100,000

- Eastern Asia: 24
- South-Eastern Asia: 14.8
- Middle Africa: 3.6
- Western Africa: 14.6
- World: 13
- Southern Africa: 12.2
- Melanesia: 2.3
- Central America: 10.8
- Polynesia: 8.9
- Micronesia: 8.8
- Caribbean: 9.9
- Eastern Africa: 7.1
- Southern Europe: 7.1
- Micronesia: 6.9
- More developed regions: 6.6
- Northern Africa: 5.4
- South America: 5.2
- Western Europe: 4.9
- Northern America: 4.8
- Australia/New Zealand: 4.4
- Africa: 3.5
- Global: 2.6

Incidence and Mortality

GLOBOCAN 2008 (IARC) (18.2.2012)
Why do tumors metastasize to some organs but not to others?

- Tumors spread to other organs via lymph fluid and blood vessels.
- For example, breast cancer metastasizes to lymph nodes, lungs, liver, bones, and brain.
Tumor Location Question

- Why does a tumor start where it does in an organ?

Brain Tumor

Lung Tumor

Crypts with stem cells are found in both colon and small intestine, but colon cancer is common while small intestine cancer is rare. Why?
Why does a tumor usually start in the upper outer quadrant of the breast?

S. L. Kwong, *Breast Cancer in California*, 2003, Ch. 9
Breast Cancer

It is estimated that in the United States this year:
• Over 200,000 women will be diagnosed with invasive breast cancer.
• About 60,000 women will be diagnosed with *in situ* (stage 0) breast cancer.
• About 40,000 women will die of breast cancer.
• About 2000 men diagnosed with breast cancer.

From American Cancer Society
Structure of Mammary Gland (Breast)

Epithelial cells line cavities and surfaces in the body.

Basement membrane is tough outer layer. It’s an example of extracellular matrix.

Normal bilayer architecture in fixed cross section. (Tlsty lab)
Genes are not the only important factor in cancer

After 30 years of extensive genomic studies, there is no genetic smoking gun that can explain 95% of breast cancers.

Very Heterogeneous Genetically: Whole genome sequencing of 50 (ER+) breast cancer tumors found 1700 gene mutations of which only 3 appeared in ≥10% of the tumors (American Association of Cancer Research meeting, 2011).

(A gene is a strand of DNA that codes for a protein. A protein is a chain of amino acids.)
The Importance of the Tumor Microenvironment

Changes to microenvironment can unleash premalignant cells!

Dolberg and Bissell, Nature, 1984

Barcellos-Hoff Can Res 2000

Radiation changes stroma

Cancer-Causing Virus (RSV) + wound \( \rightarrow \) tumor

Also Mintz and Illmensee, PNAS (1975)

Damaging the microenvironment can cause premalignant cells to become malignant.
Why does a tumor usually start in the upper outer quadrant of the breast?

S. L. Kwong, Breast Cancer in California, 2003, Ch. 9
Why are more than 50% of breast tumors found in the upper outer quadrant (near armpit)?

<table>
<thead>
<tr>
<th>Part of Breast</th>
<th>Upper Outer</th>
<th>Upper Inner</th>
<th>Lower Outer</th>
<th>Lower Inner</th>
<th>Central Portion, Nipple, Areola</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>57%</td>
<td>15%</td>
<td>10%</td>
<td>8%</td>
<td>11%</td>
</tr>
</tbody>
</table>

S. L. Kwong, *Breast Cancer in California*, 2003, Ch. 9

137,000 CA Patients, 1988-1999
Why are more than 50% of breast tumors found in the upper outer quadrant (near armpit)?

<table>
<thead>
<tr>
<th>Upper Outer</th>
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<th>Lower Outer</th>
<th>Lower Inner</th>
<th>Central Portion, Nipple, Areola</th>
</tr>
</thead>
<tbody>
<tr>
<td>57%</td>
<td>15%</td>
<td>10%</td>
<td>8%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Why is this an important question?

• Because it implies something is causing tumors that we are not aware of – unknown risk factor.
• Genes and toxins, which are the same throughout the breast, cannot explain this.

S. L. Kwong, *Breast Cancer in California, 2003, Ch. 9*
Why do most tumors occur in the upper outer quadrant near the arm pit?

- 35-40% of breast tissue in upper outer quadrant but over 50% of tumors occur there (breast is teardrop shaped)
- Large breasts do not seem to have higher risk than small breasts (large breasts have more fat but roughly the same amount of fibroglandular tissue)
- Higher incidence in upper outer quadrant in 3rd world countries (Trinidad, Brazil, India, Nigeria) and from 1927-1946 in Costa Rica – not due to modern food additives and pollutants
- Incidence in upper outer quadrant increased from 48% in 1979 to 53% in 2000 in England and Wales.
- Cancer that metastasizes to the breast (primary tumor elsewhere) has higher incidence in upper outer quadrant
- In mice, rats, cats, and dogs, most mammary tumors occur near the limbs
Breast Tumor Incidence in Upper Outer Quadrant Increased With Time

Figure 1. England and Wales: Trend in proportional annual incidence of female breast cancer in the upper outer quadrant (UOQ) of the breast from 1979 to 2000. Each point represents the ratio of recorded incidence in UOQ to the total incidence recorded in that year with site-specific information. Linear regression analysis was used to calculate a line of best fit. Table I gives the slope of the line, its standard error and the correlation coefficient (R) together with the standard deviation (SD) of the fit; the probability (p value) that R is zero was obtained from the F distribution.

Darbre et al., Anticancer Res. (2005)
Why do most tumors occur in the upper outer quadrant near the arm pit?

• 35-40% of breast tissue in upper outer quadrant but over 50% of tumors occur there (breast is teardrop shaped)
• Large breasts do not seem to have higher risk than small breasts (large breasts have more fat but roughly the same amount of fibroglandular tissue)
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• Cancer that metastasizes to the breast (primary tumor elsewhere) has higher incidence in upper outer quadrant
• In mice, rats, cats, and dogs, most mammary tumors occur near the limbs
Why do most tumors occur in the upper outer quadrant?

- Antiperspirants? No evidence for this. Doesn’t explain animals or 3\textsuperscript{rd} world countries.
- Arm motion? Probably not due to mechanical stress/strain because tumor incidence is not higher (or lower) near chest (pectoral) muscle.
- Temperature? Probably not. Upper outer quadrant not warmer or colder than other quadrants.
- Increased mammographic density?
- Lymph fluid carrying waste products from cells drains through the upper outer quadrant to lymph nodes under the arm? (Lymph is like the sewage system for cells.) Probably not. Lymph is in lymph vessels.
- More blood flow means more favorable tumor locations (angiogenesis)?
Stiffer, Denser Breasts Have a Higher Risk for Breast Cancer

Higher mammographic density (white stuff) is correlated with increased risk of breast cancer. White stuff is fibro glandular tissue (collagen).
Tumor Location Question

Why does a tumor usually start in the upper outer quadrant of the breast?

Is the mammographic density higher in the upper or outer (lateral) half of the breast?

S. L. Kwong, Breast Cancer in California, 2003, Ch. 9
Mammographic Density Scales with Area

Data for Craniocaudal (Top down) View

Seems that mammographic density does not explain increase tumor incidence in upper outer quadrant
Mammographic Density Scales with Area

Seems that mammographic density does not explain increase tumor incidence in upper outer quadrant.
Why do most tumors occur in upper outer quadrant?

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Lymph vessels in breast draining to sentinel lymph nodes under arm

**RESULTS**

Superficial Lymphatic System

Lymphatic collectors were identified in the subcutaneous tissues near the peripheral cut edges of the specimens and the lateral border of the sternum. The collectors often branched in the peripheral region then combined to form larger collectors that remained approximately uniform in diameter until they reached the first lymph node (Figs. 3 and 4). Some collecting lymph vessels joined with others within the same sentinel node territory, rarely with others, before reaching the lymph node. All superficial lymph vessels in these dissections entered a lymph node in the axilla, which was always close to the lateral edge of the pectoralis minor muscle. The findings were similar in both sexes (Fig. 4). In all of the specimens we examined, many of the lymphatic collectors that passed over or through the breast ended by draining into the same first-tier lymph node. In some, almost the entire breast drained to one sentinel node. In others however, there was at least one other node that was the first-tier node for a collecting lymphatic that passed through part of the breast.

The lymphatics deep to the nipple and areola area were different from those of the other areas we examined. Microscope-assisted dissection of the areolar region revealed a dense network of lymph capillaries and precollectors in the dermis. This structure is presumably the subareolar plexus identified by Sappey. In most areas, dye injected subcutaneously over the breast mound was not taken up by the lymphatics. Dye injected in the nipple and areolar region was taken up by 2 or 3 superficial lymph collectors.

**FIG. 3.** Radiographs in antero-posterior views of a male (left) and female (right) specimen after completing injections with the lead oxide mixture. Note that the torso lymph vessels radiate centripetally towards the axilla.

**FIG. 4.** Tracing distally of lymphatics of both hemi upper torsos (male: A and C, female: B and D) from each first-tier lymph node colour coded; pectoral node (green, orange, black and yellow), subclavicular node (light blue), and internal mammary node (red). Note (i) that the lymph collecting vessels from the nipple and areolar region on each specimen drain into the green-colored lymph node; (ii) the similar pattern of chest and breast drainage between the male and female studies; (iii) that the breast lies in the pathway of collecting lymphatics that start peripherally and (iv) that, although the majority of the breast drains to one sentinel node in D, every breast area is drained by more than one first-tier node in each study.

From Suami et al. 2007
Why do most tumors occur in upper outer quadrant?

- Antiperspirants? No evidence for this. Doesn’t explain animals or 3rd world countries
- Arm motion? Probably not due to mechanical stress/strain because tumor incidence is not higher (or lower) near chest (pectoral) muscle
- Temperature? Probably not. Upper outer quadrant not warmer or colder than other quadrants.
- Increased mammographic density? Probably not.
- Lymph fluid carrying waste products from cells drains through the upper outer quadrant to lymph nodes under the arm? (Lymph is like the sewage system for cells.) Probably not. Lymph is in lymph vessels.
- More blood flow means more favorable tumor locations (angiogenesis)?
Could increased blood flow in the upper outer quadrant of the breast make a more suitable habitat for tumor growth?

• More tissue in the upper outer quadrant means more blood supply.
• Tumors don’t grow larger than about 1 mm without a blood supply (vascularization).
• Oxygen diffuses about 100-200 μm from a capillary.
Angiogenesis

- Tumors entice blood vessel growth to provide oxygen and nutrients (Judah Folkman).
- Tumors send out chemical signals (e.g., VEGF) to attract blood vessels to grow toward them.
- Could the larger number of arteries in the upper outer quadrant mean there is more prime tumor real estate?
Scaling of Blood Vessel Sizes

- Blood vessels branch and get smaller
- Scaling laws of branching arterial vessels (Geoffrey West, Van Savage, et al.)
  \[ n = \frac{N_{k+1}}{N_k} \]
  \[ \frac{\ell_{k+1}}{\ell_k} = n^{-\frac{1}{3}} \]
- Use scaling laws to estimate cylindrical volume near capillary vessels
- Oxygen diffuses about 100 μm
- Result: Desirable volume near capillaries proportional to volume of tissue
- More tissue, more blood supply
- Cannot explain increased tumor incidence in upper outer quadrant assuming uniform perfusion (blood supply)
- But tissue does not have uniform perfusion...
More blood flow in upper outer quadrant of the breast

Table 1  Distribution of blood flow to breast regions in women with normal breasts

<table>
<thead>
<tr>
<th>Breasts skin blood flow (mean ± 1 SD) flux</th>
<th>Site</th>
<th>UOQ</th>
<th>UIQ</th>
<th>LOQ</th>
<th>LIQ</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td></td>
<td></td>
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</table>

- 47 normal patients
- Laser Doppler Imager
- Arbitrary units of “flux”

Hemoglobin Concentration Varies Spatially Among Different Quadrants

Total Hemoglobin Concentration (µM)


Plots imply that capillary density varies spatially, but not enough to explain why half of breast tumors occur in the upper outer quadrant.
Could tumors form at rare hot spots where capillary concentration is high?

What is the probability $P_n$ that at least $n$ randomly placed capillaries are within, say, 200 μm of black spot?

Need the capillary density distribution. Count number of capillaries in sampling circles and make a histogram.

Example:
Probability for at least 1 capillary assuming Poisson Distribution

$$P_1 = 1 - e^{-\rho \pi r^2}$$
Could tumors form at rare hot spots where capillary concentration is high?

What is the probability that there is at least one hot spot in a region/quadrant of the breast?

Biggest region (upper outer quadrant) has the highest probability of having at least one hot spot.

Assumed capillary density obeys a Poisson distribution.
Could tumors form at rare hot spots where capillary concentration is high?

- Need capillary density distribution in 3D to calculate the probability of hot spots.
- Capillary density = capillary length in a sphere of radius \( R \) \( \sim \) diffusion length of oxygen \( \sim 100 \) microns

Blinder et al. (2013)
Most Breast Cancer Recurrence Occurs Within 2 years After Surgery

Figure 1 Hazard of relapse for premenopausal patients treated at Istituto Nazionale Tumori in Milan, Italy. Hazard is the number of events that occur in a time interval divided by the number of patients who enter that time as event free. Patients were treated by mastectomy well before the routine use of adjuvant therapy. The time interval in all hazard figures used here is 3 months. Average and standard deviations are indicated as diamonds and bars. The curve was obtained by a kernel-like smoothing procedure.

Figure 2 Hazard of relapse for postmenopausal patients treated at Istituto Nazionale Tumori in Milan, Italy. Definitions are the same as indicated in Figure 1 but the patient population is postmenopausal.

Retsky et al., Clinical Translational Medicine 1, 17 (2012)
Most Breast Cancer Recurrence Occurs Within 2 years After Surgery

Figure 2 Hazard of relapse for postmenopausal patients treated at *Istituto Nazionale Tumori* in Milan, Italy. Definitions are the same as indicated in Figure 1 but the patient population is postmenopausal.

Retsky *et al.*, Clinical Translational Medicine 1, 17 (2012)
Non-Steroidal Anti-Inflammatory Drug (NSAID) Reduces Early Recurrence of Breast Cancer

- Is this due to reduction of inflammation, a risk factor in cancer?
- Or, could this be due to remodeling of vasculature during healing so that there are no capillary hot spots?

**Figure 1.** Kaplan-Meier recurrence-free survival estimated for 319 patients receiving (or not receiving) intraoperative analgesics (sufentanil, clonidine, ketorolac, and ketamine). Univariate analysis by log-rank tests.

**Table 4. Multivariate Association with Cancer Recurrence After Mastectomy: Cox Regression Model**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Beta</th>
<th>Hazard Ratio 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.03</td>
<td>1.03 (1–1.06)</td>
<td>0.02</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>0.85</td>
<td>2.34 (1.67–3.01)</td>
<td>0.015</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td>0.83</td>
<td>2.28 (1.87–2.69)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.98</td>
<td>0.37 (0–0.79)</td>
<td>0.019</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.31</td>
<td>0.73 (0–1.83)</td>
<td>0.57</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.77</td>
<td>2.15 (0.74–3.56)</td>
<td>0.08</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.56</td>
<td>0.57 (0–1.49)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Data are presented as factor effect (beta) estimated from multivariate Cox regression model, hazard ratio (HR) and associated 95% confidence interval (CI), and P value.

Forget et al., Anesthesia & Analgesia 110, 1630 (2010)
High Field **Magnetic Resonance Imaging (MRI)**

- Highly successful both clinically and commercially—roughly 30,000 systems worldwide.
- Standard clinical system operates at 1.5 T: Trend is to 3 T and higher.
- Typical cost is about $2M.
- What if we lowered the field by a factor of $10^4$ to 150 mT?
- Could we still obtain MR images?
- If so, might they be better in some way?
Introduction to Superconductivity

Superconductivity was discovered in 1911 by Kamerlingh Onnes.

• Zero electrical resistance
Meissner Effect

- Magnetic field expelled. Superconducting surface current ensures $B=0$ inside the superconductor.
Flux Quantization

where the "flux quantum" $\Phi_o$ is given by

$$\Phi = \int \vec{B} \cdot d\vec{A} = n\Phi_o$$

where

$$\Phi_o = \frac{hc}{2e}$$

$$= 2 \times 10^{-7} \text{ gauss cm}^2$$
Explanation of Superconductivity

Ginzburg-Landau Order Parameter

\[ \psi = \psi e^{i\theta} \]

Think of this as a wavefunction describing all the electrons. Phase \( \theta \) wants to be spatially uniform ("phase rigidity").
If we put 2 superconductors next to each other separated by a thin insulating layer, the phase difference ($\theta_2 - \theta_1$) between the 2 superconductors will cause a superconducting current to flow between the superconductors. Current flow without batteries! This is the Josephson effect.

$$J = J_o \sin(\theta_2 - \theta_1) = J_o \sin \delta$$ where $J_o$ is the critical current density and $\delta$ is the phase difference.
SQUIDs
(~ 2 slit device for superconducting wave functions)

- SQUID is a Superconducting QUantum Interference Device.
- DC SQUID is a loop with 2 Josephson junctions.
- Phase difference around the loop proportional to magnetic flux through loop.
- Current through the SQUID is modulated by the magnetic flux through loop.
- SQUIDs are sensitive detectors of the amount of magnetic flux $\Phi$ through the loop.
Magnetic Resonance Imaging (MRI)
Nuclear Magnetic Resonance (NMR) or Magnetic Resonance Imaging (MRI)

- Nuclear spin $\mu$ in a static magnetic field $H_0$ precesses at the Larmor frequency $\omega_0$

$$\omega_0 = \gamma H_0$$

$$\gamma = \text{gyromagnetic ratio}$$
\[ T_1 = \text{Spin Relaxation Time} \]

- \( T_1 \) is the characteristic time for the spin to relax and align with the magnetic field \( H_0 \)
- \( 1/T_1 = \text{Spin Relaxation Rate} \)
- Magnetization \( M \) and \( T_1 \) can be measured by SQUIDs.
$T_1 = \text{Spin Relaxation Time}$

- $T_1$ is the characteristic time for the spin to relax and align with the magnetic field $H_0$
- $1/T_1 = \text{Spin Relaxation Rate}$
- Magnetization $M$ can be measured by SQUIDs
Dependence of $T_1$ on Larmor Frequency $\omega_0$ and Correlation Time $\tau_c$

- Spectral density of fluctuations in local magnetic field:
  \[ S(\omega_0) = \left\langle B_{loc}^2 \right\rangle \cdot \frac{2\tau_c}{1 + (\omega_0 \tau_c)^2} \]

- Relaxation rate: $1/T_1 \propto S(\omega_0) \propto \tau_c$ for $\omega_0 << 1/\tau_c$.
- $\omega_0 = \gamma H_0$ = Larmor frequency

$\tau_{c1} > \tau_{c2}$

Area under $S(\omega_0)$ curves is conserved for different $\tau_c$

- $T_1$ contrast is enhanced in low fields.
**$T_1$-Weighted Contrast:**
Relaxation Rate $1/T_1$ Different in Different Tissues

- Greater contrast ($1/T_1$ difference) at lower magnetic fields
- (High field MRI contrast = Gd)

Sample: Water columns in agarose gel, 1 – 6 mm diameter

*Figure*: $T_1$ dispersion of water and agarose gel


$T_1$ contrast at high field

$T_1$ contrast at low field

100 mT

132 µT
Prostate Cancer

• Approximately 230,000 new cases in the U.S each year
  • 60% of prostate cancer diagnoses in men over 65
  • Over 90% of men over 80 have prostate cancer
• Approximately 30,000 men die of prostate cancer each year
• Broad range of malignancy resulting in wide range of treatment:
  • Surgery
  • Radiation
  • Cryosurgery
  • Active surveillance (“watchful waiting”)
• Accurate diagnosis and optimum treatment requires knowledge of location and extent of the disease
• Prostate cancer: heterogeneous mixture of cancer and non-cancerous cells
• Imaging is difficult at best; for example, high field MRI shows no $T_1$ contrast even with a contrast agent.
Ultra-Low Field Measurements of $T_1$ in Ex Vivo Prostate Tissue

- Malignant prostate removed surgically at UCSF hospital.
- Pathologist cuts two small tissue samples, one healthy and one cancerous (Blind: they did not know which is which).
- Samples rushed to Berkeley in a biohazard bag placed on ice.
- About two hours after surgery, the relaxation times of the two samples are measured simultaneously.
- The next day, the specimens are returned to UCSF and the pathologist characterizes a thin slice of each specimen.
- Specimen pairs obtained from 35 patients.
Ultra-Low Field MRI Prostate Cancer Results Agree Well With Pathology

Contrast $(T_{1A} - T_{1B})/T_{1A}$ vs. % Difference in Tumor for Each Specimen Pair: 35 Patients

- $T_{1A}$ (normal) > $T_{1B}$ (cancer)
- Line is linear regression fit to data
- Outliers: Possibly the % tumor in the thin histology slice is not representative of the original thicker slice

$T_1(100\%$ normal) = $(1.43 \pm 0.10) \ T_1(100\%$ tumor)

Summary

• Why do tumors start where they do in an organ? (Not known.)
  – Why do over half of breast tumors start in the upper outer quadrant?
• Do tumors prefer to start where there is a high concentration of capillaries?
• Ultra-low field MRI has the potential to image prostate cancer, which currently is poorly done, and be substantially less expensive.
• Recommended book on cancer:

Emperor of All Maladies: A Biography of Cancer

By

Siddhartha Mukherjee

(won Pulitzer Prize)