Petos Paradox

Peto's Paradox: Why Big Animals Don't Get More Cancer

1. The Paradox (The Problem)

- **The Logic:** Cancer risk is proportional to the number of cell divisions (1016 in a human lifetime). Logically, larger, longer-lived animals (like blue whales with >2,000x more cells than humans) should have vastly higher cancer rates.
- **Peto's Paradox:** Named for Richard Peto, the reality is that **body size and lifespan are not associated with cancer rates** across species (e.g., mice and humans have similar rates).

2. Biological Defenses (The Solution)

Large animals have evolved highly effective anti-cancer mechanisms:

- **Tumor Suppressor Genes:** They possess **redundancy** in tumor suppression.
  - *Example:* Elephants have **20 copies** of a key tumor suppressor

gene; humans have one.

- **Metabolic Rate:** Slower metabolic rates in larger animals mean **fewer DNA-damaging byproducts** are created per cell.
- **Physical Size/Competition:** Tumors must grow "gigantic" to impact a large animal's health. Smaller, aggressive tumors may act as **parasites** on the main tumor, starving it before it becomes lethal.
- **Evolutionary Pressure:** Any species that evolved to be giant *had* to develop stronger cancer defenses to survive.

3. Human Risk Factors (The Exception)

Human cancer rates are considered "shockingly high," suggesting natural defenses are overridden by modern factors:

- **Environmental Carcinogens:** Pollution and chemical exposure contribute to up to **75%** of human cancers (e.g., whales in polluted estuaries get high cancer rates).
- **Diet and Lifestyle:** Modern diets

(high in calories, fat, sugar) and low physical activity increase risk.
    - Increased weight puts humans at risk for at least 13 types of cancer.
- **Hormonal Influence:**
    - **Estrogen:** This hormone **encourages cells to divide** (proliferation). Longer lifetime exposure is linked to increased risk in some cancers.
    - **Melatonin:** This hormone (related to sleep cycle disruption) has strong **anti-cancer properties** (protective effect).

4. Conclusion

- Humans must study these giant animals to learn new ways to treat cancer, as we have the advantage of applying evolutionary solutions.

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Melatonin has a lot of anti cancer properties: related to sleep
Estrogen encourages the cells to divide

Key Points: The Rise of Early-Onset Cancer

1. The Alarming Trend

- **Massive Increase:** Cancer rates in people **under 50** have increased by nearly **80%** over the last three decades.
- **Aggressive Nature:** These early-onset tumors are often more **aggressive** and have a different underlying biology than cancers found in older people.
- **Widespread:** The rise affects about **17 different cancers**, including colorectal, breast, and pancreatic.
- **Geographic Focus:** The trend is most prominent in **high-income countries** (e.g., US, UK, Japan).

2. Primary Causes (Theories)

Scientists believe this rise is driven by a combination of modern lifestyle factors:

- **Gut Health Disruption:** Increased **antibiotic use** wipes out beneficial gut flora, allowing harmful bacteria to grow, which produce **toxins** linked to cancer.
- **Obesity:** Higher rates of obesity are a clear driver due to links with chronic **inflammation**.
- **Hormonal Exposure:** For women, having children later or not at all means **longer exposure to estrogen**, which encourages cell division.
- **Disrupted Sleep:** Excessive exposure to **artificial light** disrupts the body's sleep cycle, potentially lowering levels of the protective, anti-cancer hormone **melatonin**.

3. Challenges & Solutions

- **Delayed Diagnosis:** The primary problem is that doctors are **not screening** or expecting cancer in young people, leading to late diagnosis (often Stage Four).
- **Solutions Focus:**
  - **Educate Doctors** to recognize warning signs (like fatigue or digestive changes) in young patients.
  - Increase **public awareness** of the risk and available screening tools.
  - Fund more research into the **specific causes** of this early-onset phenomenon.

Linear accelerator to generate x rays
Normal cells heal better than cancer cells: principle of radiotherapy
Fractionation allows normal cells to recover
4Rs: Repair, Repopulation, Reassortment, Reoxygenation

Most radiation damage is done indirectly through radicals. Oxygen is a key in producing very toxic superoxide radicals

How Radiotherapy Works (Key Principles)

1. **Fundamental Mechanism**

- **Energy Source:** Uses high-energy ionizing radiation (X-rays, Gamma rays).
- **Action:** Radiation **ionizes atoms** in cells, which directly or indirectly leads to **DNA damage**.
- **Goal:** The primary objective is to cause a **double-strand break** in the DNA—the hardest type of damage for cells to fix.

2. **Targeting and Selectivity**

- **Vulnerable Phase:** Cells are most susceptible to damage when they are in the **M phase** (mitosis/division) of the cell cycle.
- **Cancer Advantage:** Cancer cells are targeted because they **divide more**

frequently than normal cells, spending more time in the vulnerable M phase.

3. **Fractionation (The 4 R's)**

Radiotherapy is delivered in multiple small doses (fractionation) to protect normal tissue and maximize cancer cell death.

1. **Repair:** Allows **normal cells** to repair damage effectively between doses.
2. **Repopulation:** Ensures the dose is strong enough to destroy more cells than the tumor can regrow (repopulate).
3. **Reassortment:** Gives surviving tumor cells time to **shuffle into the vulnerable M phase** for the next dose.
4. **Reoxygenation:** Oxygen is vital for radiation damage. Fractionation allows previously oxygen-starved (hypoxic) tumor cells to become **reoxygenated**, making them susceptible to subsequent doses.

Gut Microbiome and Cancer (Key Principles)

1. **Importance of the Gut Microbiome**

- **Definition:** The gut microbiome is a massive collection of microorganisms (bacteria) living in the gut.
- **Function:** It acts like a **"big pharmacy"** in the body, producing molecules essential for health and regulating the **immune response**.

2. **Impact on Cancer Management**

- **Dysfunction in Cancer:** In cancer patients, the gut microbiome often **shifts and becomes less diverse**, negatively affecting its protective functions.
- **Therapeutic Potential:** Restoring the health of the gut microbiome can **boost the immune response**, improving the effectiveness of cancer treatments, particularly **immunotherapy**.

3. **Clinical Application**

- **Fecal Microbiome Transplantation**

(FMT): Research has shown that using FMT from healthy donors can restore the gut microbiome and lead to **significantly better outcomes** when patients are treated with immunotherapy.

- **Expanding Trials:** This approach, first tested in melanoma patients, is now being expanded in phase two trials for other cancers, including lung, kidney, pancreatic, and breast cancer.

Can We Eat to Starve Cancer? (Key Principles)

1. Angiogenesis: The Common Denominator

- **Definition:** Angiogenesis is the process the body uses to grow new blood vessels.
- **Role in Disease:** Abnormal angiogenesis is the common denominator in **over 70 major diseases**, including cancer, obesity, arthritis, and blindness. * **Balance:**

Healthy bodies maintain an **elegant balance** between natural stimulators and inhibitors of angiogenesis.

2. **Angiogenesis and Cancer Growth**

- **Cancer's Tipping Point:** Cancer begins as a harmless, microscopic cluster of cells that **cannot grow larger than 1/12th of a cubic millimeter** without a blood supply.
- **The Switch:** Cancer cells mutate to release huge amounts of angiogenic factors (natural fertilizer), tipping the balance and forcing new blood vessels to invade the tumor.
- **Deadly Outcome:** Once blood vessels invade, the tumor grows exponentially and the same vessels allow cancer cells to escape into the bloodstream as **metastases** (the late, deadly stage).

3. **Anti-Angiogenic Therapy**

- **Mechanism:** Anti-angiogenic drugs aim to **cut off the blood supply** by targeting the abnormal, vulnerable vessels feeding the tumor.

- **Effectiveness:** Approved drugs have shown significant (70-100%) survival improvement in several cancers (e.g., kidney, colorectal).
- **Limitation:** Treatments are often given **too late** (when cancer is already established and metastasized).

4. Preventing Cancer through Diet (Eating to Starve)

- **Preventative Approach:** The key is to prevent angiogenesis from starting in the first place, shifting the focus to **prevention**.
- **Food Synergy:** Many foods, beverages, and herbs contain naturally occurring **anti-angiogenic inhibitors** that can boost the body's defenses.
    - *Examples:* Cooked tomatoes (lycopene), red grapes (Resveratrol), berries, soy, tea (green tea, jasmine), parsley, and garlic.
- **Human Evidence:** Men who consumed cooked tomatoes 2-3 times a week had up to a **50%**

reduction in prostate cancer risk, and those who developed cancer had fewer blood vessels feeding the tumor.

- **Empowerment:** Diet is referred to as **"chemotherapy three times a day,"** providing an accessible, global, and sustainable solution for cancer prevention.