"Just Five Numbers" Critical Parameters That Shape Human Cancer

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Just Six Numbers

by Martin Rees (1999)

Idea That Certain "Values" Allow For "Life"

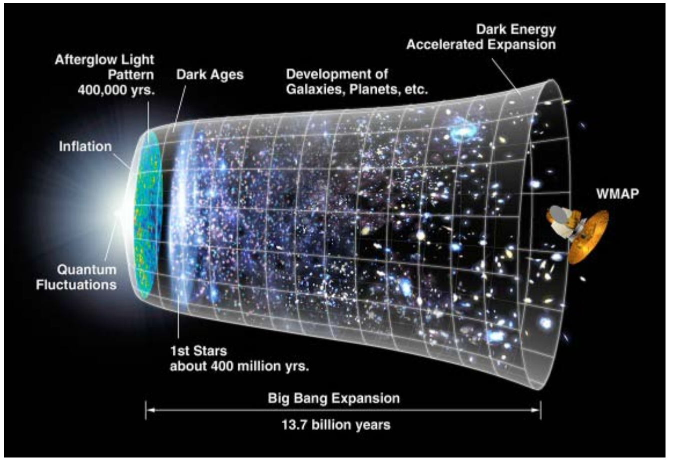
- N: electrical forces that hold atoms together versus gravity (10^{36})
- Ɛ : forces between atomic nuclei (0.007)
- Ω: amount of material in the universe
- λ : dark energy
- Q: ratio of gravity versus total energy (10^{-5})
- D: number of spatial dimensions (3)

Idea of Feasibility

- Just Six Numbers: If these numbers were different, the universe would either collapse or not coalesce
- For Cancer: Are their critical values that allow for cancer? (a “mechanism” that accounts for human cancer)
- Problem that with many cancer “mechanisms” either everyone gets cancer or no one gets cancer (but no one calculates if this is a problem)

Physics Envy

- Modern Physics Connects the Largest (Cosmology) With the Smallest (Baryons and so on) With a “Standard” Model
- Possible to use a similar approach to cancer?



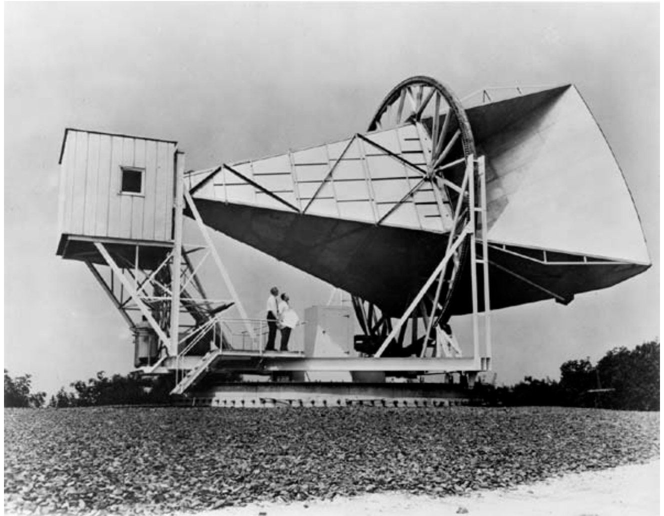
Largest and Smallest Features of Human Cancer

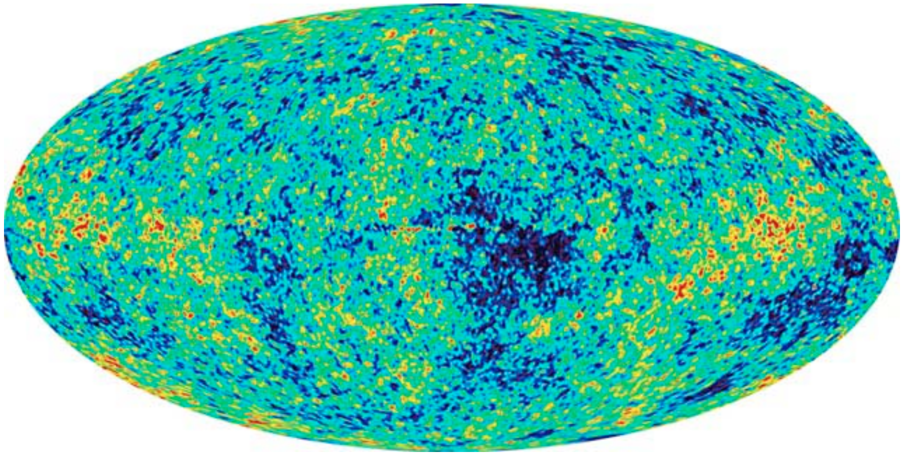
- Largest Feature: Cancer Epidemiology

  (outcome of trillions of stem cells)

- Smallest Feature: Single Stem Cell

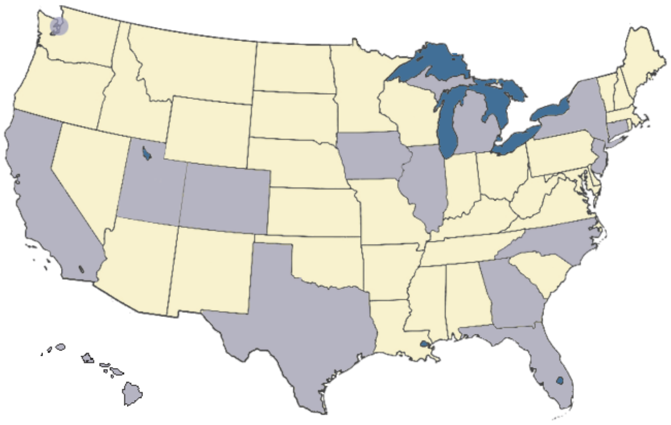
  (behavior of single stem cells)





Cancer Epidemiology

- Essentially Giant Multi- mirror Telescope
- Cancer Registries Record All Cancers Within Set Geographic Areas
- Probably Capture >90% of all Cancers in the USA



Cancer is Common (1 of 3 individuals affected)

Men: Death Rates

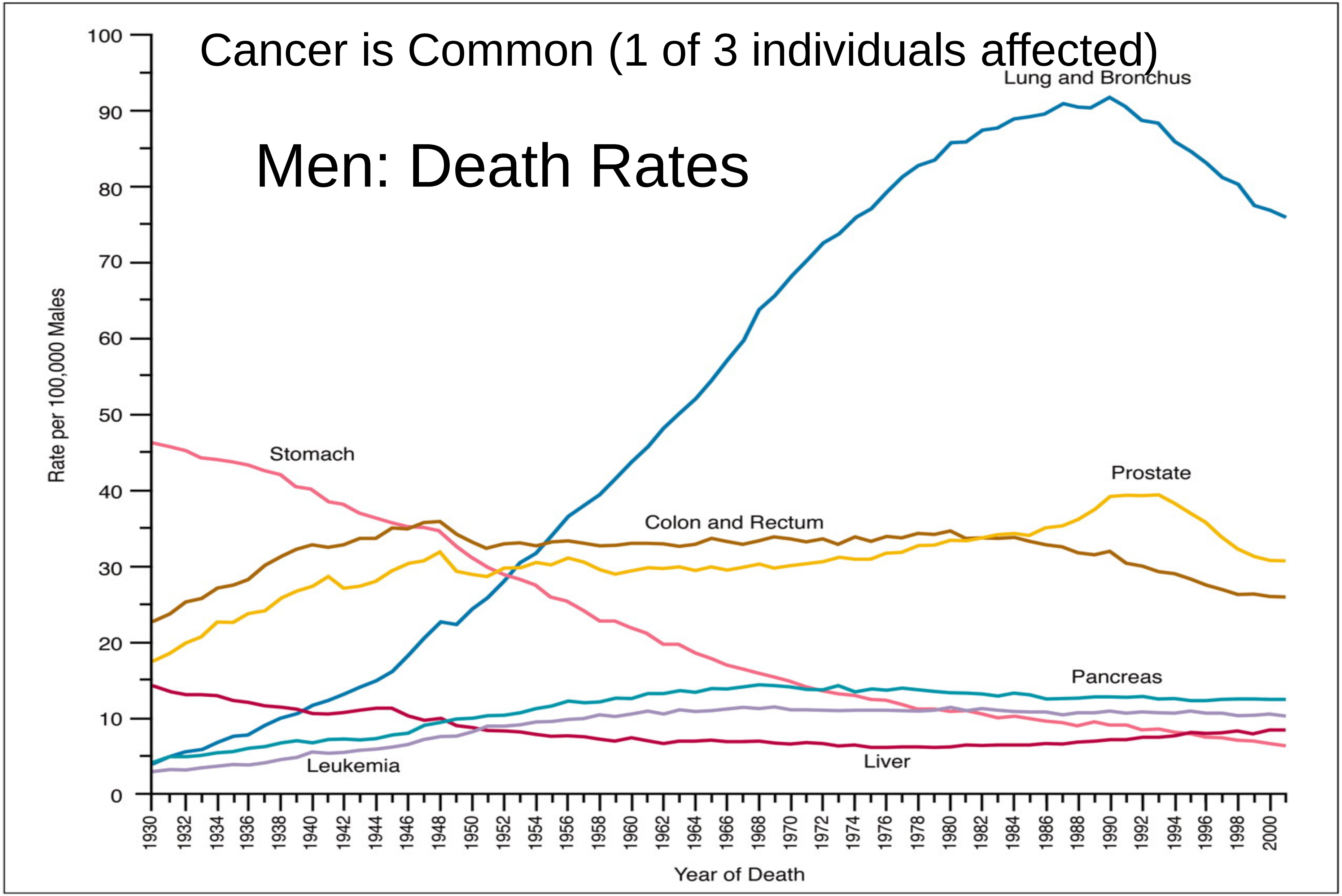


FIGURE **4** Annual Age-adjusted Cancer Death Rates* Among Males for Selected Cancer Types, US, 1930 to 2001.
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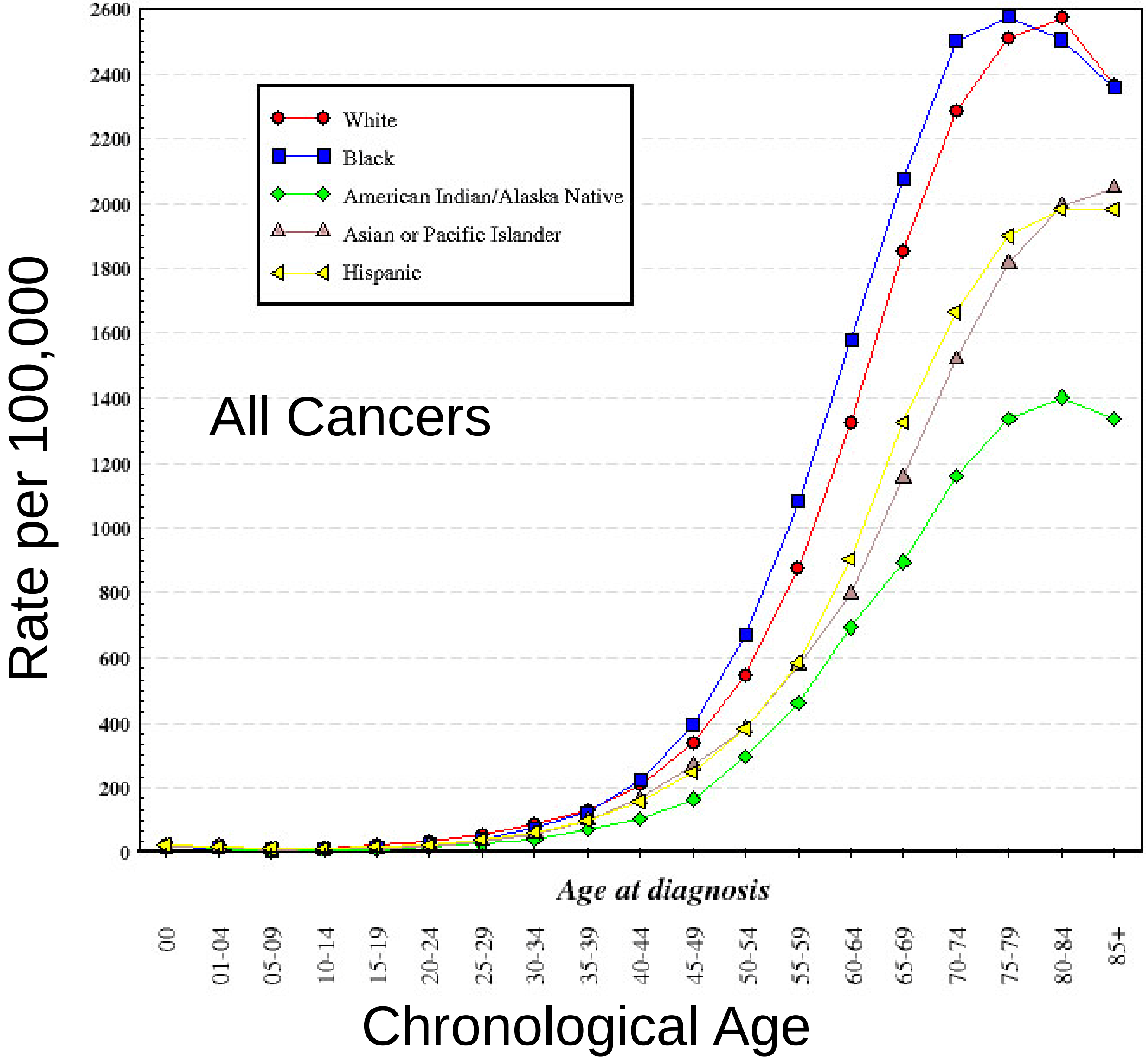
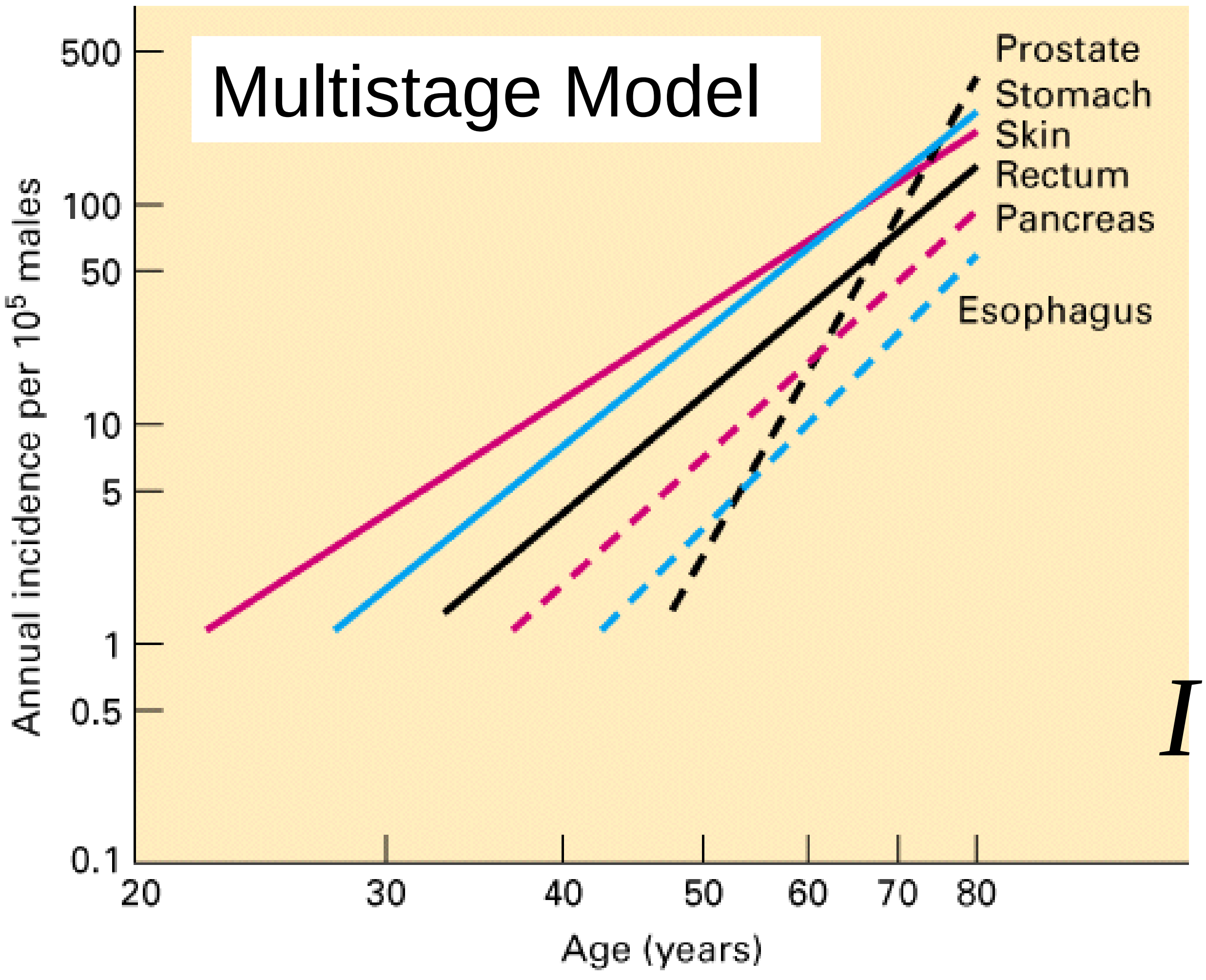
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes.
Source: US Mortality Public Use Data Tapes, 1960 to 2001, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

Cancer Incidence Increases With Age



Armitage-Doll Frequency/Age Log/Log Plots (1955)



Slope is Proportional To Numbers of Mutations (k = 5-7)

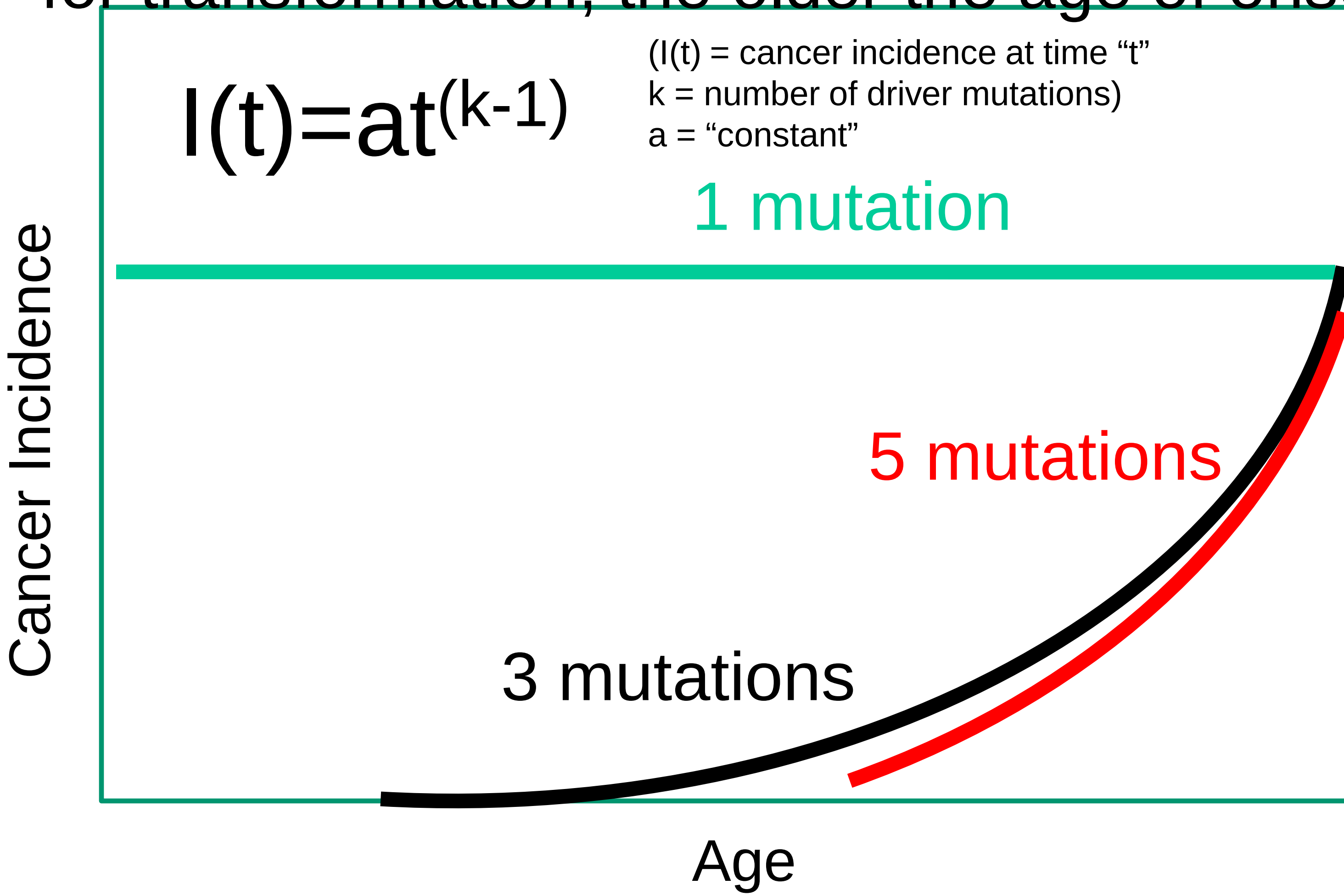
$$I(t) = (at)^{k-1}$$

Shape of Age-Incidence Curve: Number of Rate-limiting Mutations

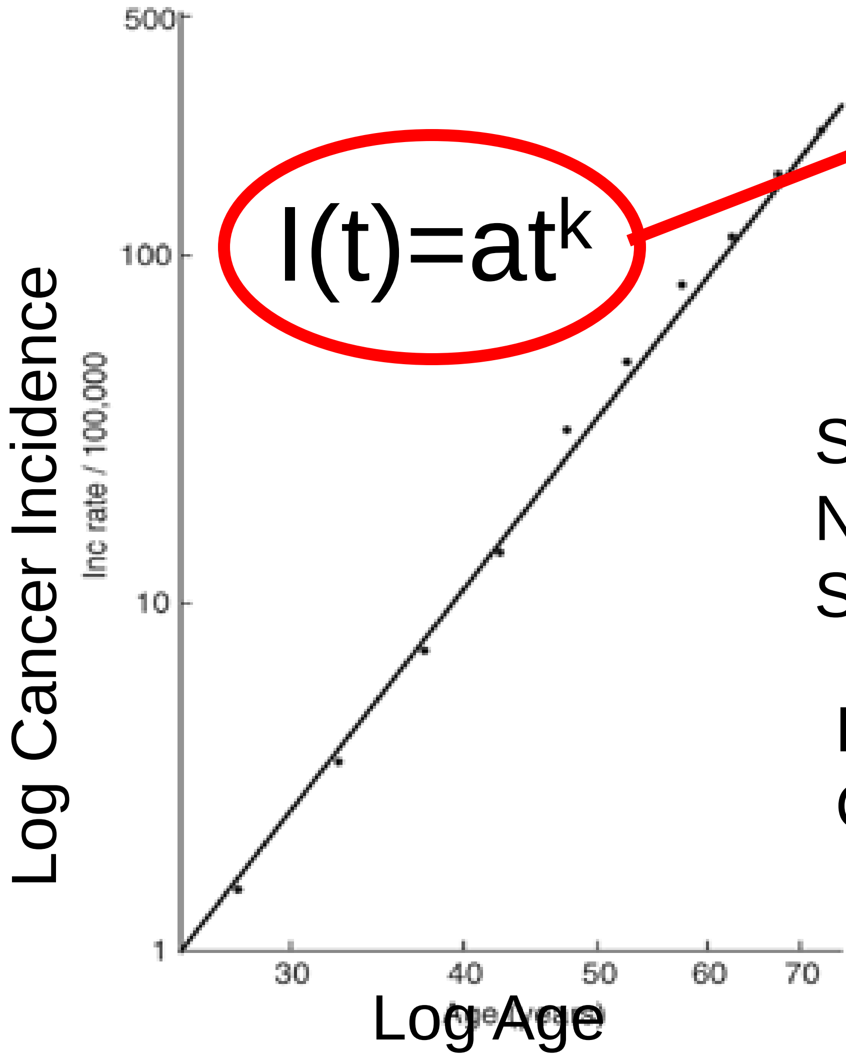
The greater the number of mutations required for transformation, the older the age of onset

$$I(t)=at^{(k-1)}$$

(I(t) = cancer incidence at time "t"
k = number of driver mutations)
a = "constant"

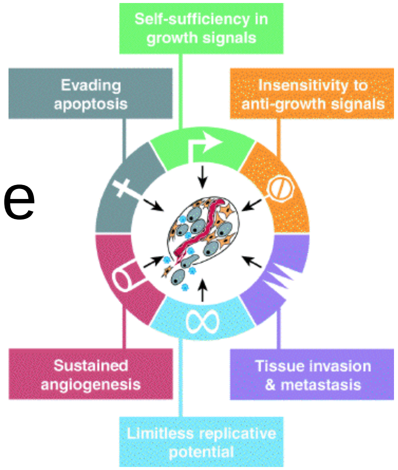


Example: Colorectal Cancer



$I(t)=at^{k}$

Where is the biology?



Slope (k) =
Number of rate-limiting Stages

K= 5 to 6 for
Colorectal Cancer

How Cancer Biologist Do Math
(Or What "Causes" Cancer)

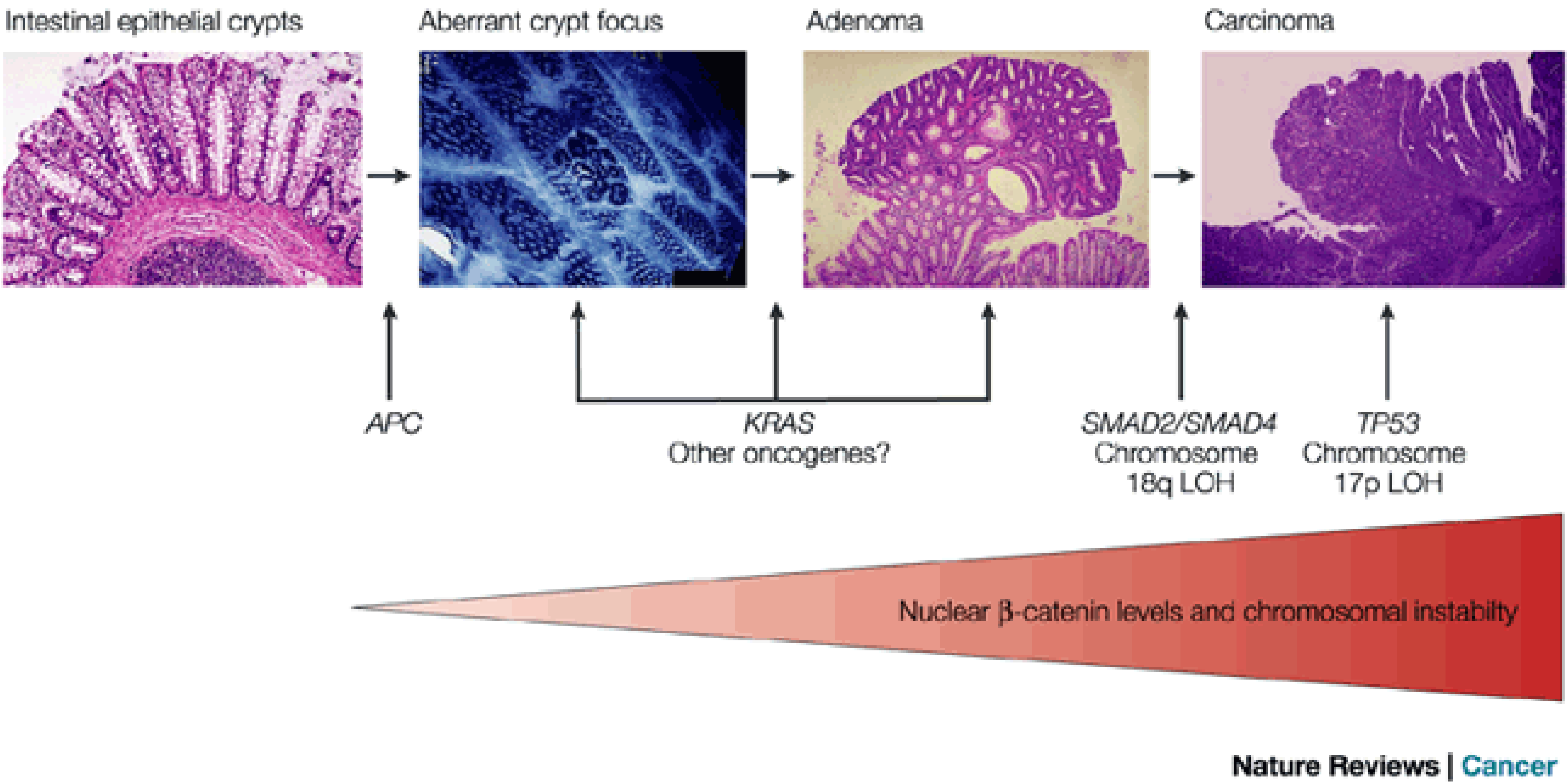
- Odds of A "Mutation" In A Gene Is About 1 Mutation Per Million Divisions (10^{-6})
- If You Need Five Mutations, Then The "Odds" of Cancer Is:

$$(10^{-6})^5 = 10^{-30}$$

Underlying "Assumption" Is That Getting Cancer is "Impossible" Unless "Something" Goes Wrong (Hence the search for "causes" of cancer)

How Biologists Do "Models"

Adenoma-Cancer Sequence (Vogelstein) Paradigm For Colorectal Cancer



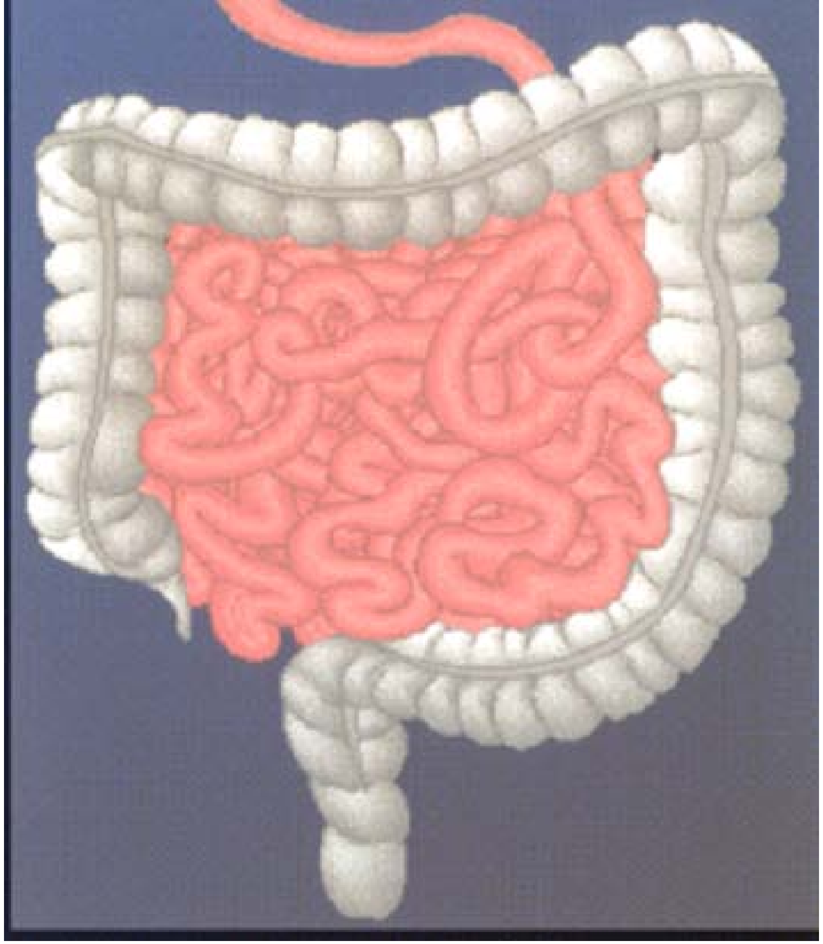
Alternative Hypothesis

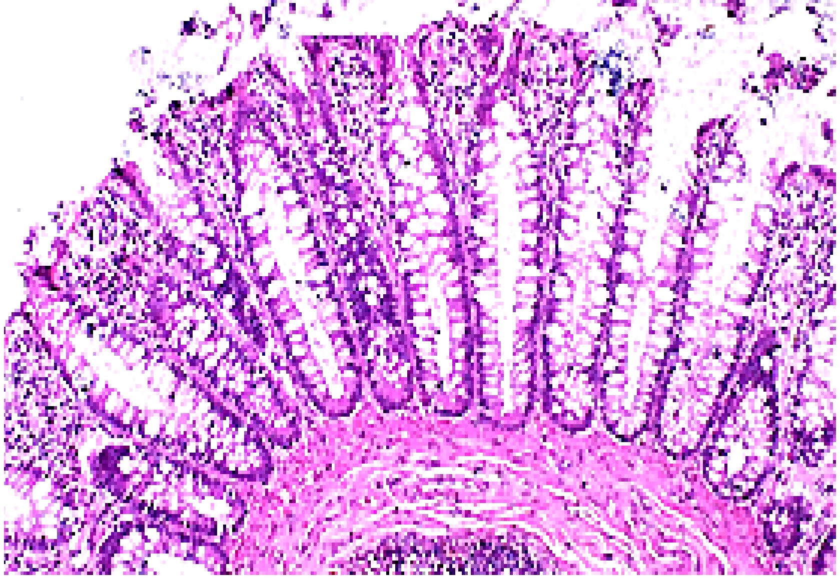
Cancer Is A Natural Outcome of Living

(Occurs By "Chance")

Possible To Calculate The Odds of Human Cancer With Just Five Numbers!

1. Number of Stem Cells In A Crypt (eight)
2. Number of Crypts Per Colon (15 million)
3. Stem Cell Division Rate (once every 4 days)
4. Mutation Rate (3 $X10^{-6}$ per division)
5. Number of Required Cancer Mutations (six)





~15 million crypts/colon

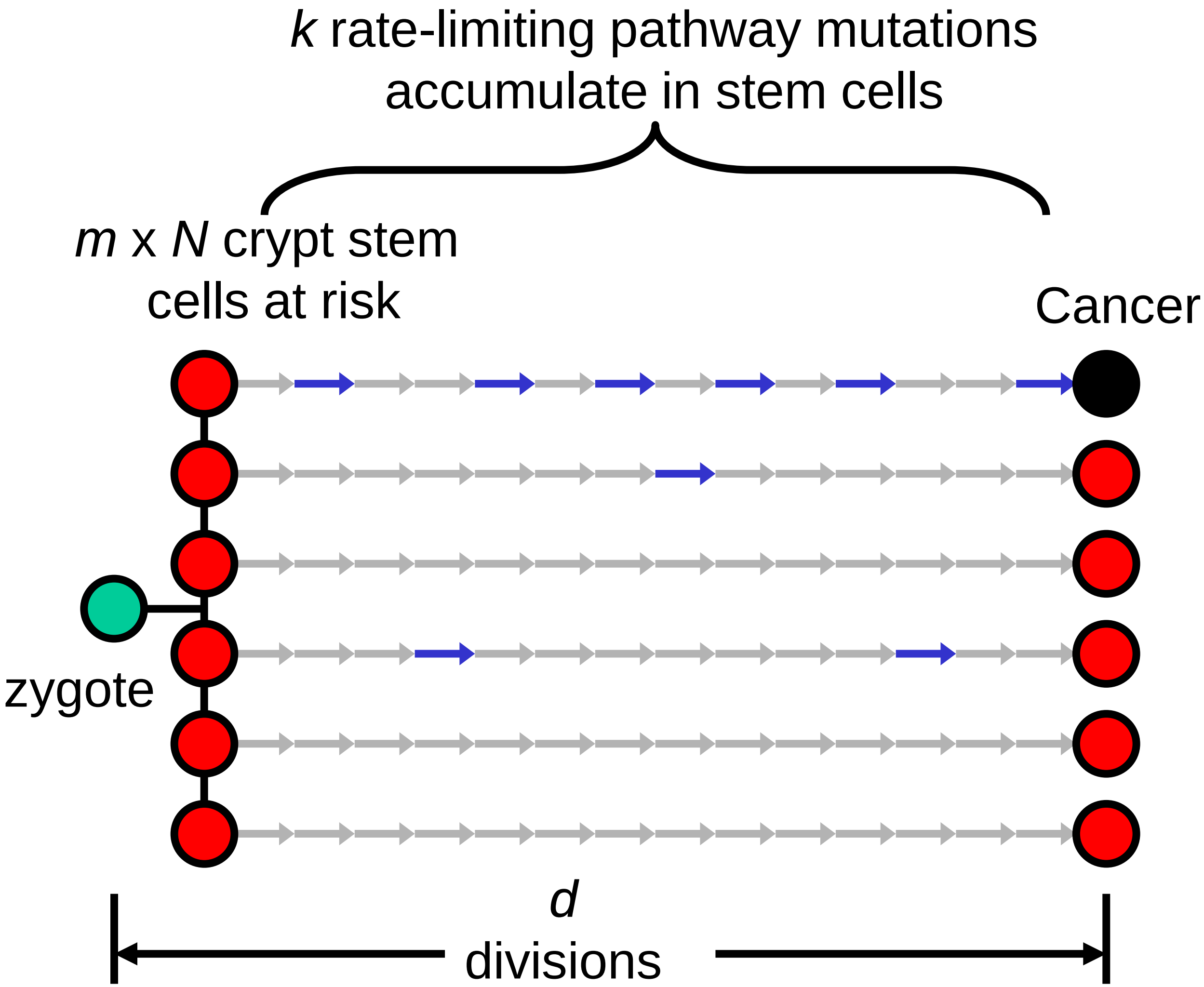
5% lifetime risk of CA by 100 years of age

15 million crypts X 100 individuals = 1.5 X 10^{9} total crypts

5 “crypts” lead to cancer

Transformation Efficiency ~3 X 10^{-9} per Crypt After 100 Years

Cancer Model



Cancer Equation

P (mutation) = (u)

P (no mutation) = (1-u)

P (no mutation after d divisions) = $(1-u)^d$

P (mutation after d divisions) = $1-(1-u)^d$

P (mutation in all k genes after d divisions) = $(1-(1-u)^d)^k$

P (no mutation in all k genes after d divisions) = $1-(1-(1-u)^d)^k$

P (no mutation in all k genes
after d divisions in a colon) = $(1-(1-(1-u)^d)^k)^{Nm}$

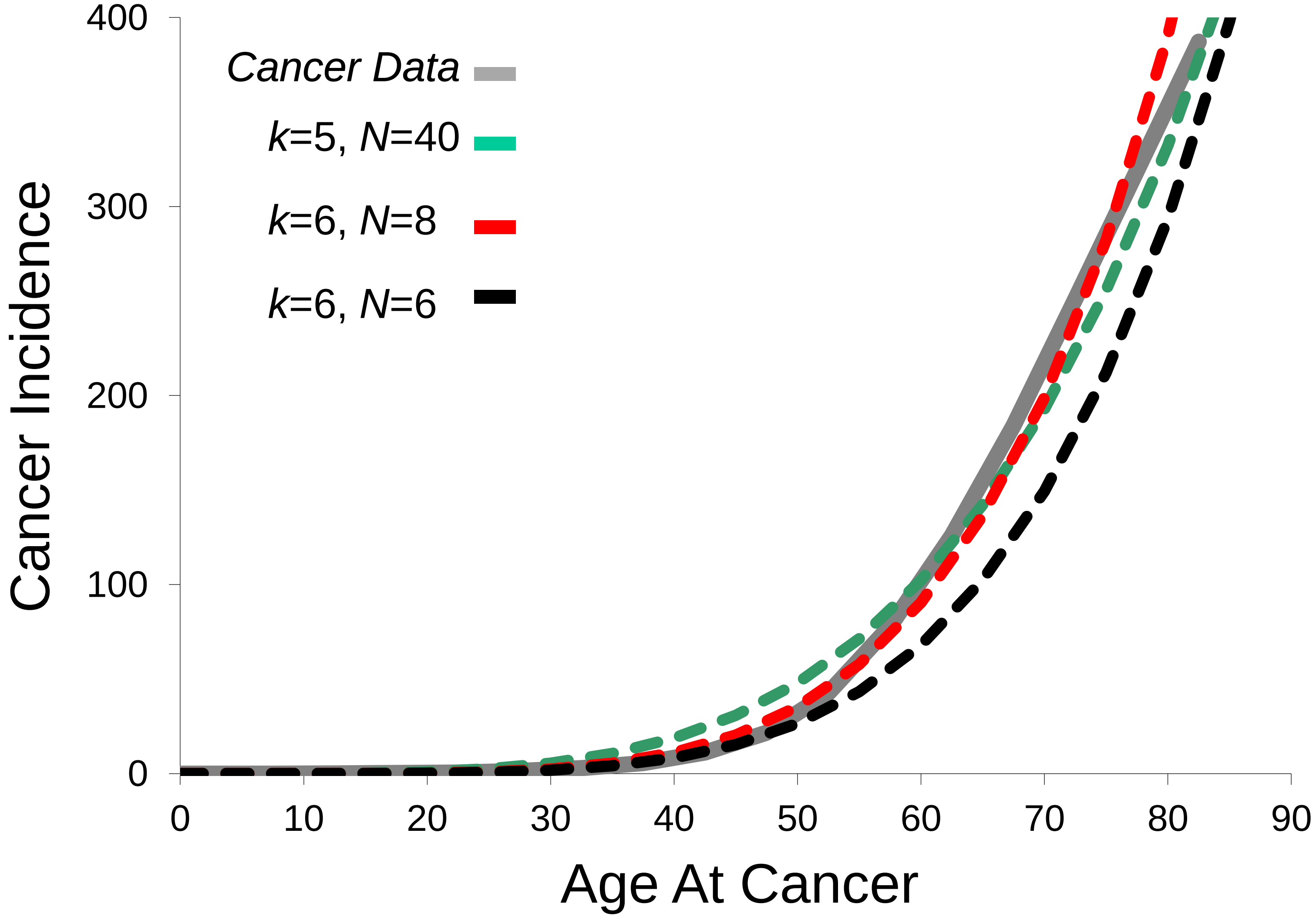
P (mutation in all k genes
after d divisions in a colon) = $1-(1-(1-(1-u)^d)^k)^{Nm}$

Does Normal Cell Division Cause Cancer?

$$p = 1 - (1 - (1 - (1 - u)^{d})^{k})^{Nm}$$

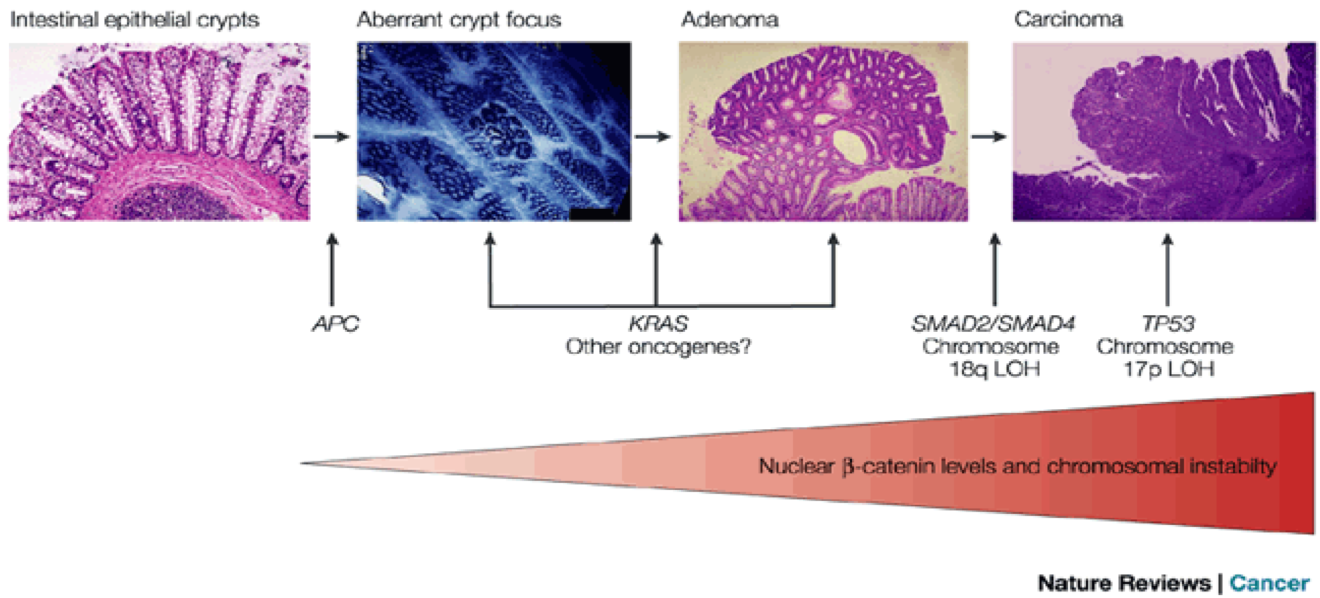
Parameter	Description	Colorectal Cancer With Pathway Gene Targets
k	rate-limiting stages	6 pathway mutations
m	number of crypts	15,000,000
n	stem cells per crypt	8
u	target mutation rate	3×10^{-6} per pathway per division
d	divisions since birth	once every four days
p	probability of cancer	-

$$p = 1 - \left(1 - \left(1 - (1-u)^{d}\right)^{k}\right)^{Nm}$$



Major Difference: The “Start”

(at conception vrs later in life)



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Adenoma-Cancer Sequence
(after 50 years of age)

Evidence For Cancer Mechanisms Should Be Present Within Cancer Genomes

(How Many Mutations in a Cancer?)

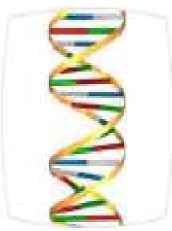
Results From Cancer Genome Projects:

Mutation Frequencies Are

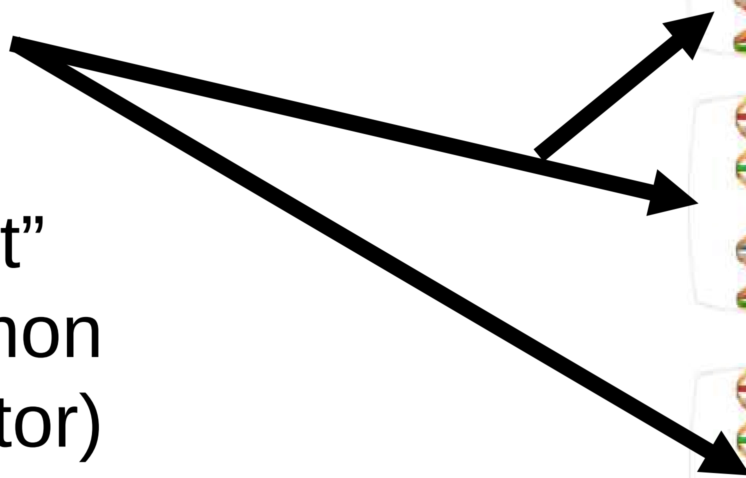
< 1 mutation per 100,000 bases

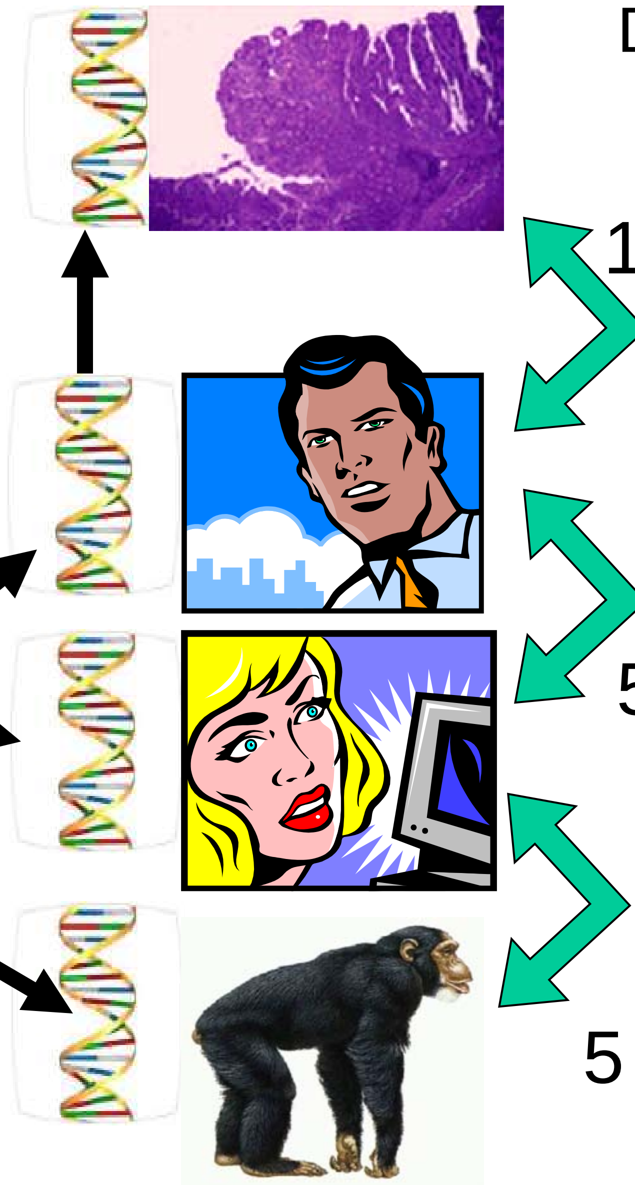
Relative Numbers of Genome Changes = Time

<u>Molecular Clock Hypothesis:</u>
Number of Genome Changes
= Time Since
Common Ancestor



“start”
(common
ancestor)





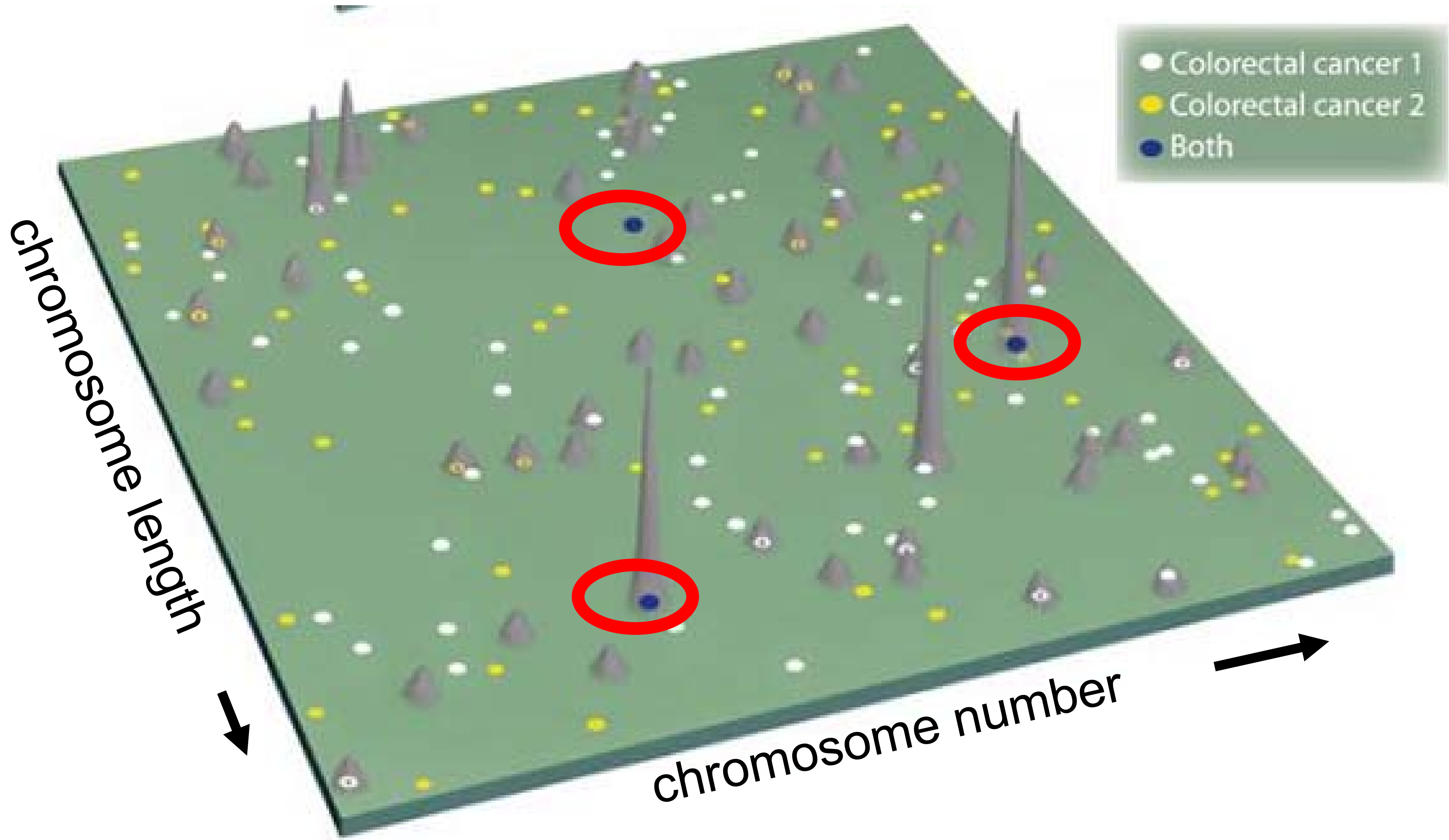
Difference

~1 per
100,000 bp
70 yrs

~1 per
1,000 bp
50,000 yrs

~1 per
100 bp
5 million yrs

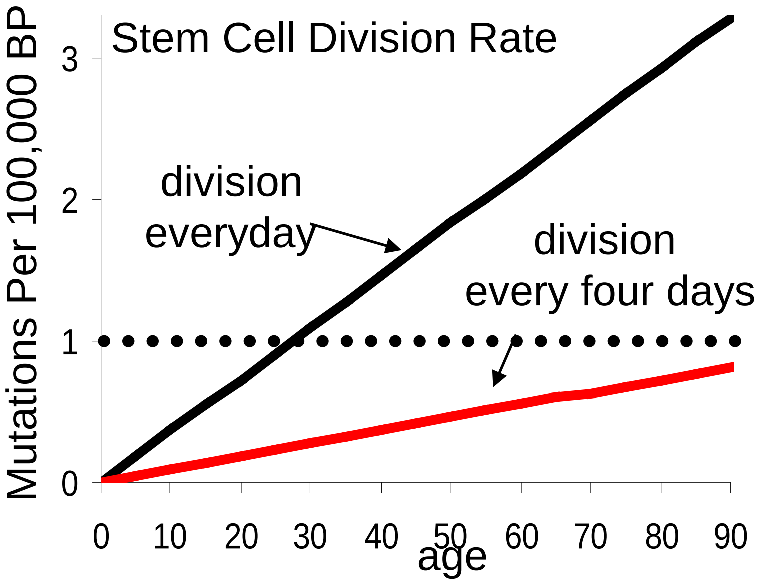
Present Day



Cancers Have Unique Sets of Mutations (only about 3 genes in common between any two cancers)

Summary of Cancer Genomes

1) Mutation Frequencies Low: less than one mutation per 100,000 bases
2) Passenger Mutations >>> Driver Mutations
3) Each Cancer Genome is Unique



Mutation rate = 1 X 10^{-9} per base per division

Cancers May Arise With Normal Mutation And Division Rates

Cancer Cell Genealogy: Simple Molecular Clock Analysis With Data

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cancer cell

~3 mutations per million bp

(# mutations) = MR X (# divisions)

(3/million) = 10^{-9} X (# divisions)

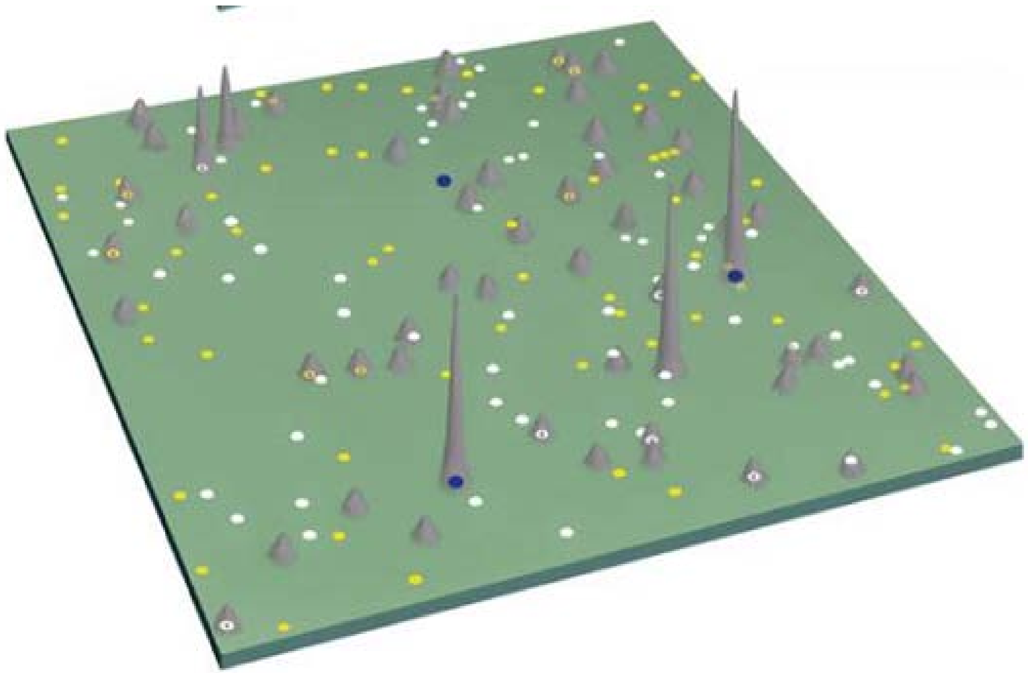
(# divisions) = ~3,000 divisions to a tumor cell

or

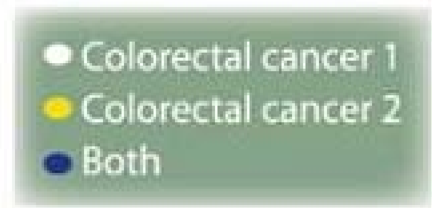
~43 divisions per year for a 70 year old

No need to evoke greatly elevated mutation or division rates

Random Replication Errors Could Account For Many Cancer Mutations



chance & contingency & passenger mutations



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Adenoma-Cancer Sequence (after 50 years of age)

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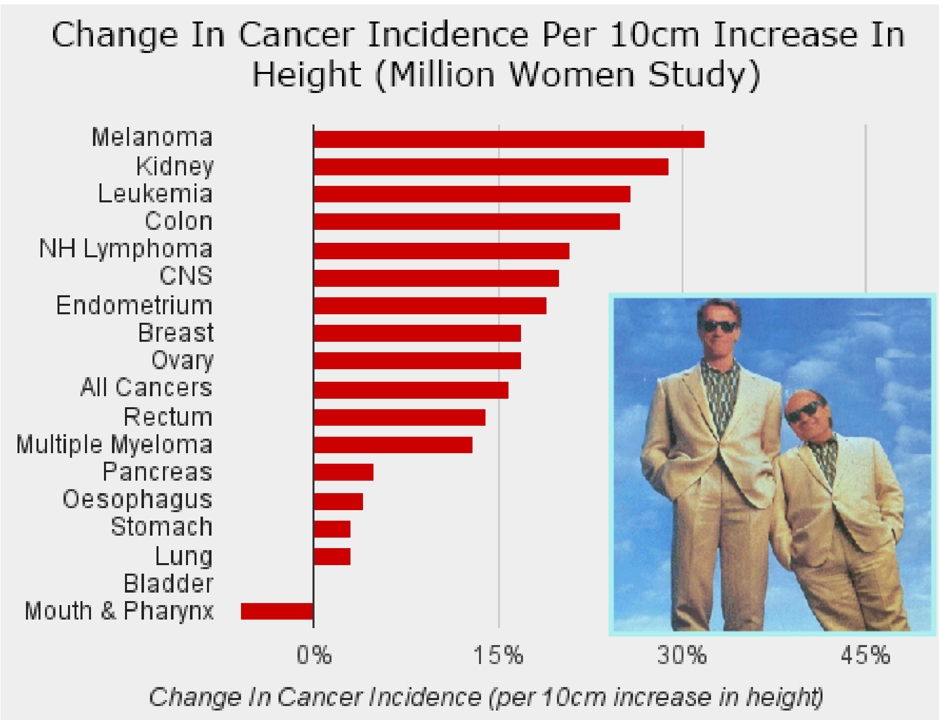
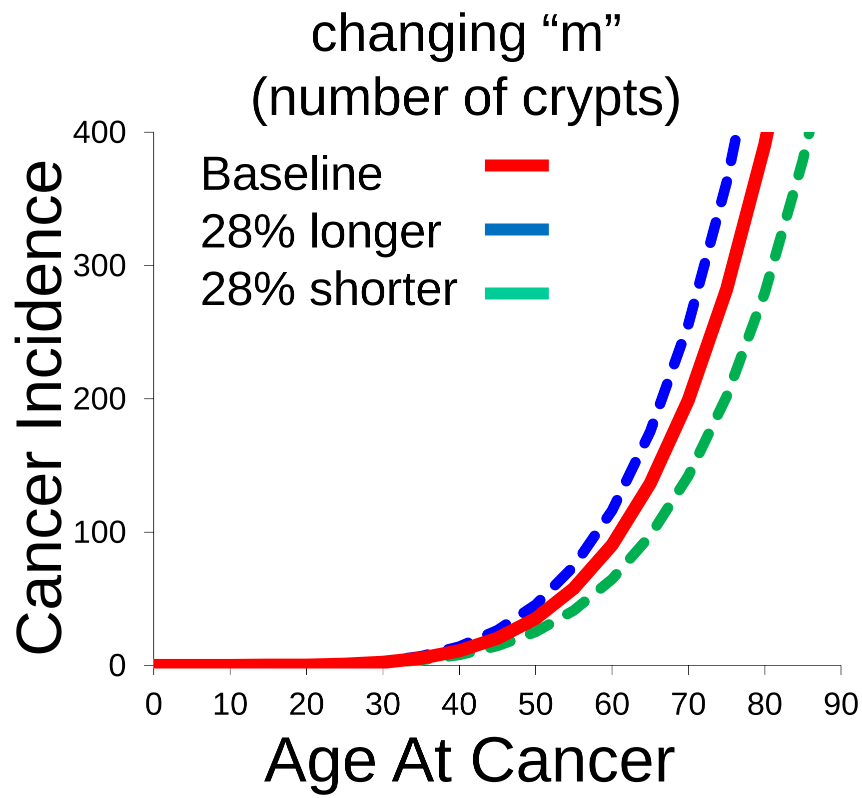
Some Implications…………

Taller Individuals Get More Cancer

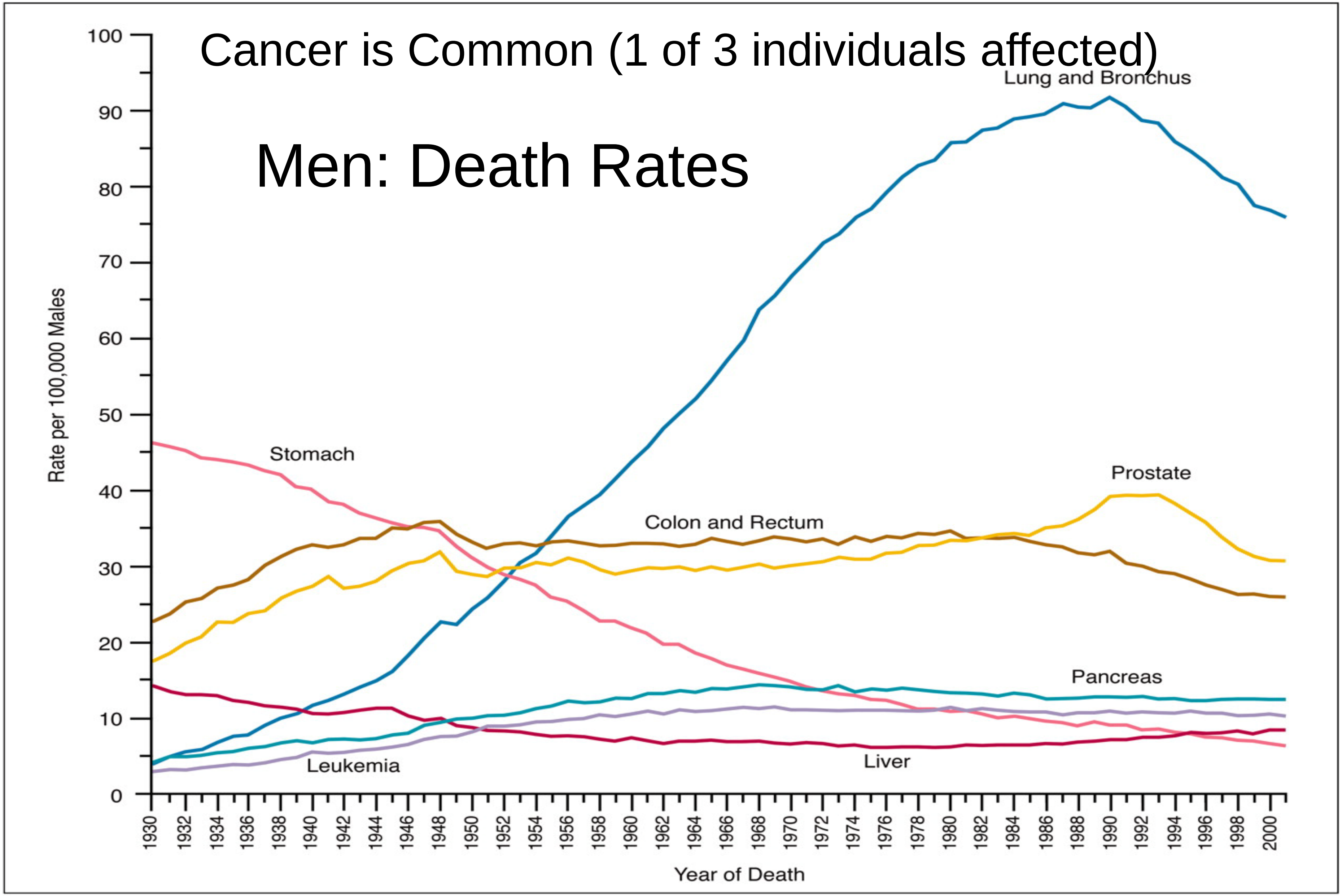




$$p = 1-(1-(1-(1-u)^{d})^{k})^{Nm}$$

Cancer is Common (1 of 3 individuals affected)

Men: Death Rates



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$$p = 1-(1-(1-(1-u)^d)^k)^{Nm}$$

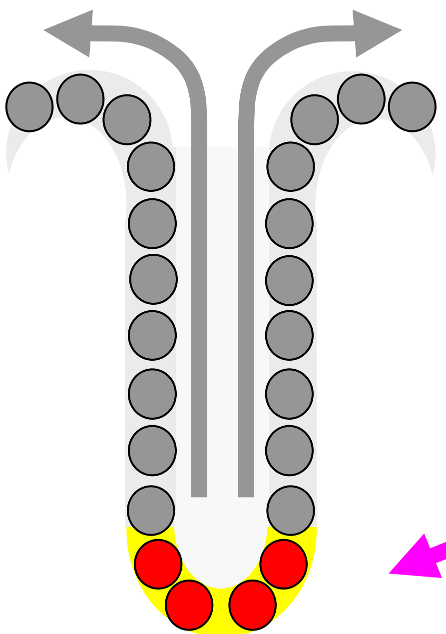
Stem Cell Number (n):
Hard To Define!!!!!

Why: Uncertainty Principle

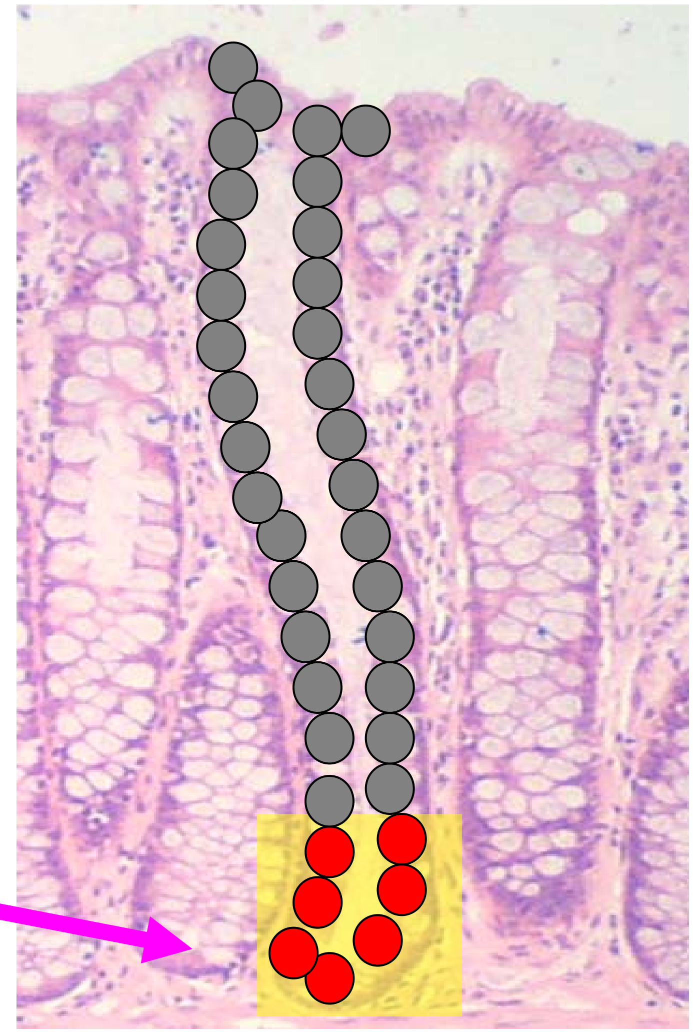
Human Colon Crypts: Mitotic With Constant Cell Replacement

1 crypt = 2,000 cells
All cells but stem cells
die in a week

die in 1 week



multiple
stem cells



Stem Cells: Two Models

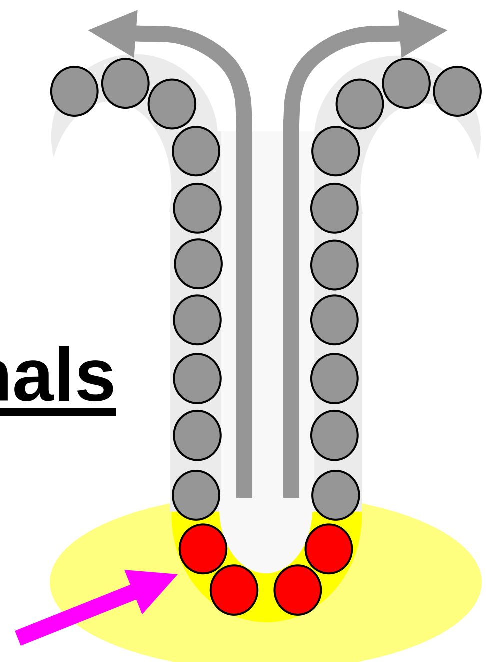
1) Immortal Stem Cell Lineages (Intrinsic)

2) Stem Cell Niches (Two Components)

--- Epithelial Stem Cells

--- Surrounding Stroma

(Extrinsic Signals)



<u>Stroma Niche Signals</u>

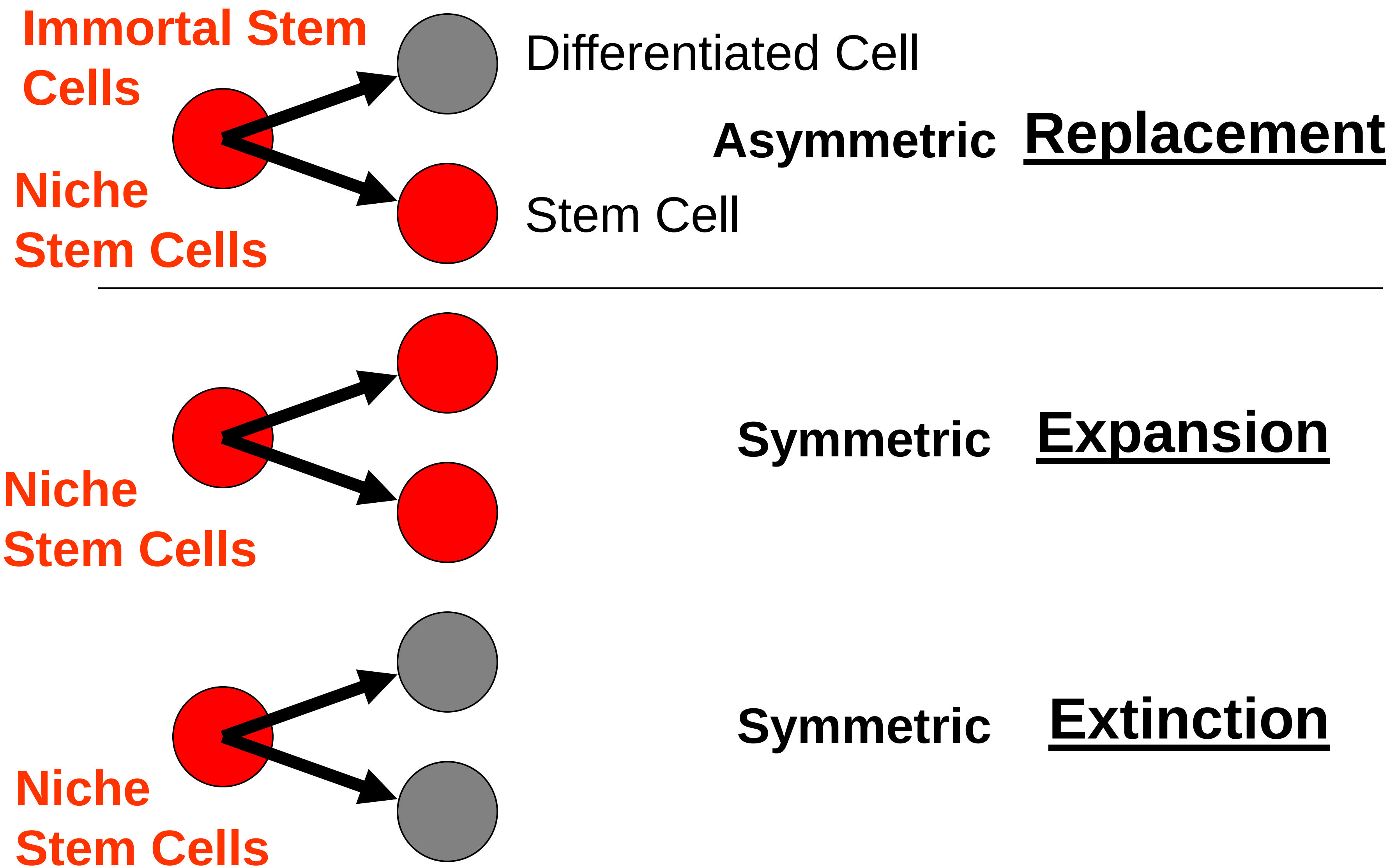
Wnt Pathway?

TGFRII Pathway?

COX2 Pathway?

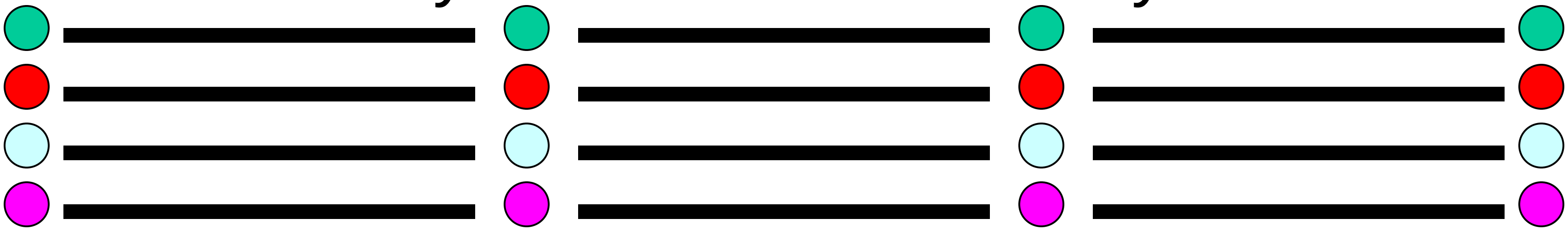
<u>Cells That Leave A Niche Are No Longer Stem Cells</u>

Types of Cell Division: (Always Binary)

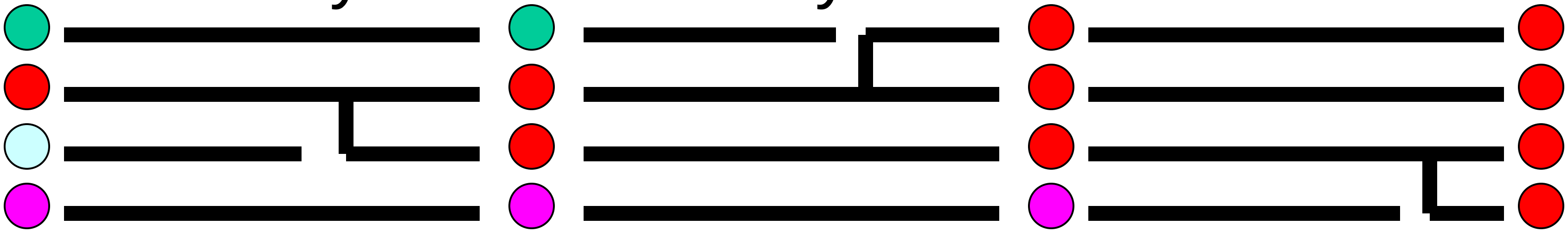


Immortal Vrs Niche Stem Cell Lineages

Immortal: Asymmetric Divisions Only



Niche: Asymmetric And Symmetric Divisions



Immortal Vrs Niche
Stem Cell Lineages

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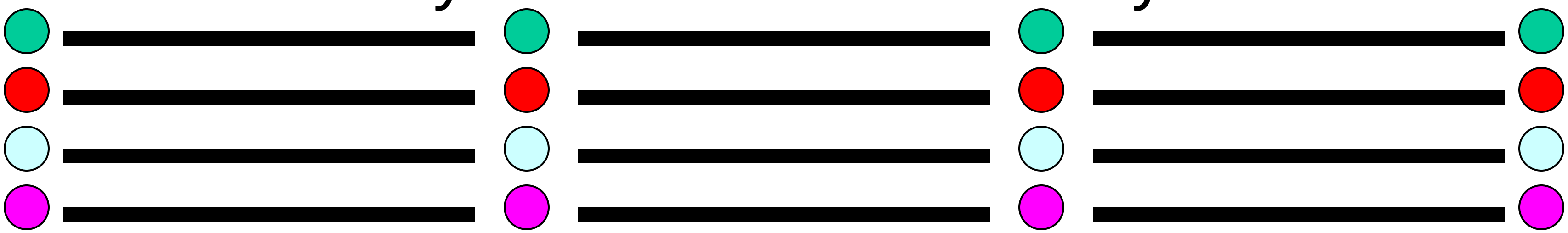

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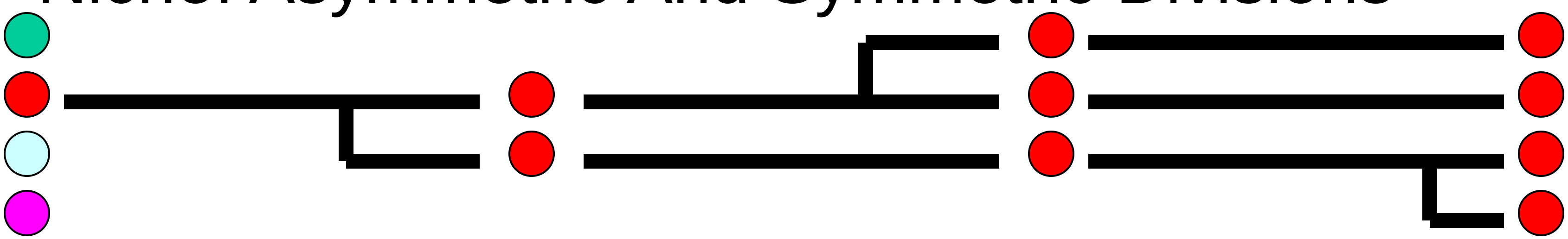
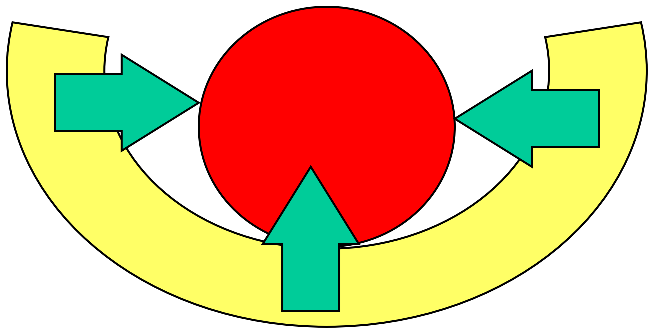


Appears All Mammalian Stem Cells Are Maintained By Niches (Stem Cell Clonal Evolution)

Niche Stem Cells

A Niche Has Two Parts:
--- Mesenchymal
--- Epithelial "Stem Cells"

WNT And Other Factors

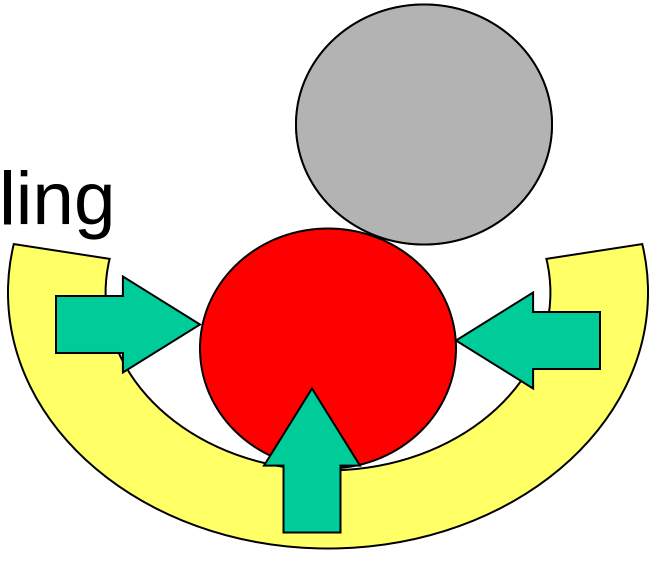


Niche Stem Cells

NICHE STEM CELLS

1) Extrinsically Defined
2) Will Differentiate Outside of Niche

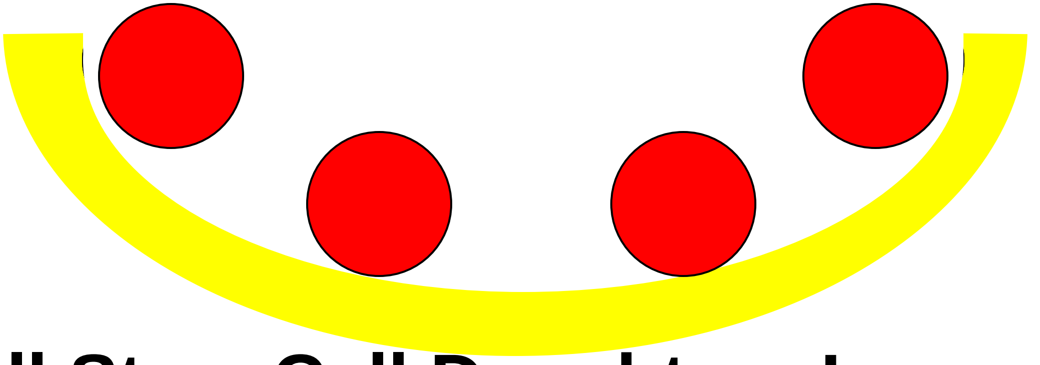
Wnt Signaling
Pathway
and
Others



Stem Cell Niche Dynamics

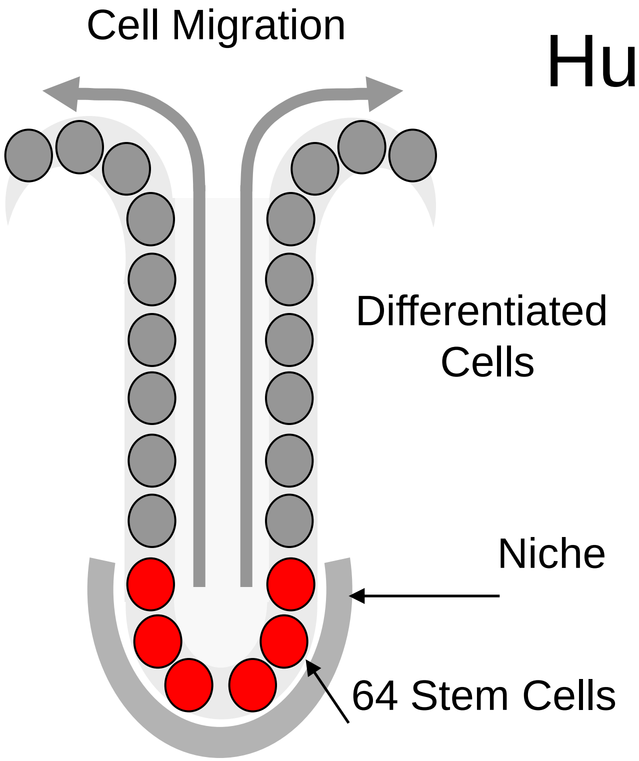
Stem Cell Niche = Multiple Dividing Stem Cells and Random Loss With Replacement

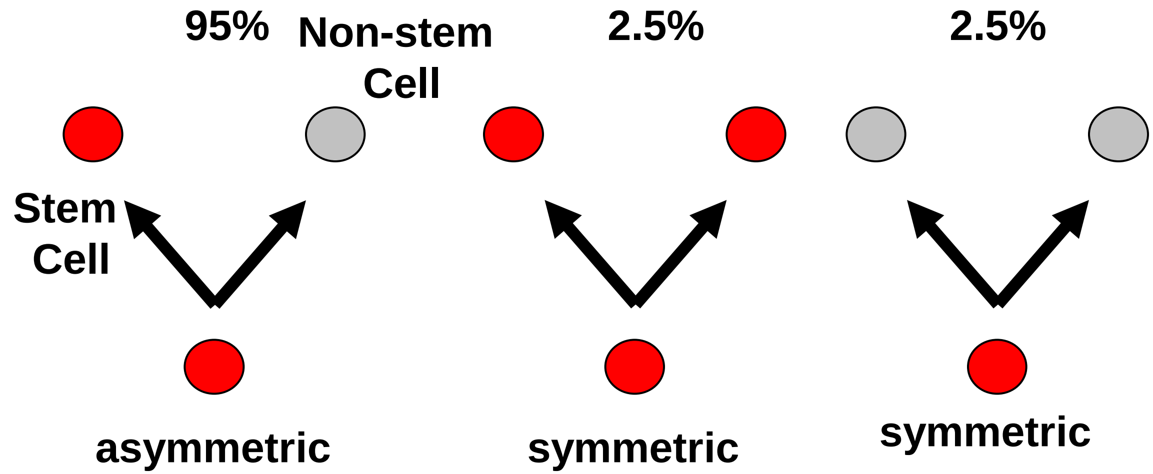
Loss of All Lineages Except One = Stem Cell Clonal Evolution



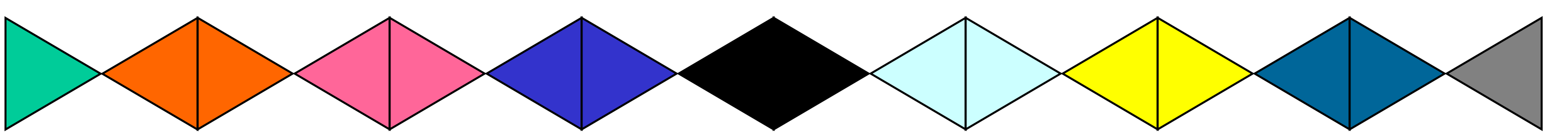
Half of All Stem Cell Daughters Leave The Niche

Human Colon Crypt Niche: Summary





1) More Consistent With Niche Rather Than Immortal Stem Cells
2) Multiple Non-quiescence Stem Cells Per Crypt
3) Most Stem Cell Divisions Are Asymmetric (95%)
4) Crypt Niche Succession Recurs About Every 8 Years



So How Many Stem Cells At Risk For Cancer?

1. Only One Long Term Surviving Stem Cell Lineage Per Crypt
2. Multiple Potential Stem Cells Per Crypt (N = 64?)
3. Potential To Change Niche Stem Cell Turnover
   --- Bigger Niche (more potential stem cells)
   --- Faster Stem Cell Division (almost never seen?)
   --- Change Probability of Symmetric vrs Asymmetric Division

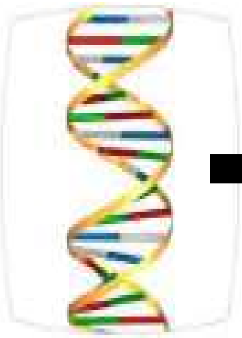
Changes in Niche Stem Cell Survival May Be Critical For Cancer Prevention (Aspirin?) Because These Dynamics Are Occult To Normal Examinations

Summary: Just Five Numbers

1. Cancer Biologists Are Math Challenged
2. May Be Possible To Link the Biggest Features of Cancer (Epidemiology) With the Smallest (Stem Cells)
3. Many Cancers May Simply Arise By “Chance”
4. Approaches From Physics May Greatly Advance Cancer Biology (Cosmology, Quantum Uncertainty)

$$p = 1 - (1 - (1 - (1 - u)^{d})^{k})^{Nm}$$

Genomes Are “Historical” Documents (almost perfect copies of copies)



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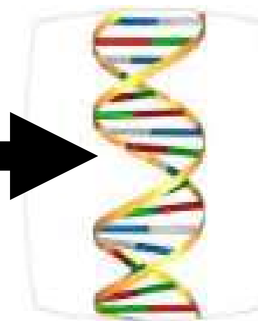
(start)



current cell
(end)

Acknowledgements

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