



CANCER INCIDENCE AND BAD LUCK

Presenter: Abhinav T. M.
BIOL4202A



Introduction

- Numerous Studies now conclude that cancer incidence is attributable to Environmental (E) factors and Hereditary (H) factors
- Examples of E factors include Smoking, Radiation Exposure and Mutagens (e.g., Aristolochic Acid)
- H factors include deleterious mutant alleles (BRCA1, BRCA2, TP53)

Unexplained Points

- APC gene heritable mutation known to cause cancer in large and small intestine
- But more common in Large intestine
- H factor influenced by something in cellular environment
- Brain cancer more common than small intestine even if brain protected by BBB and small intestine get more E exposure
- E factor influenced by something else

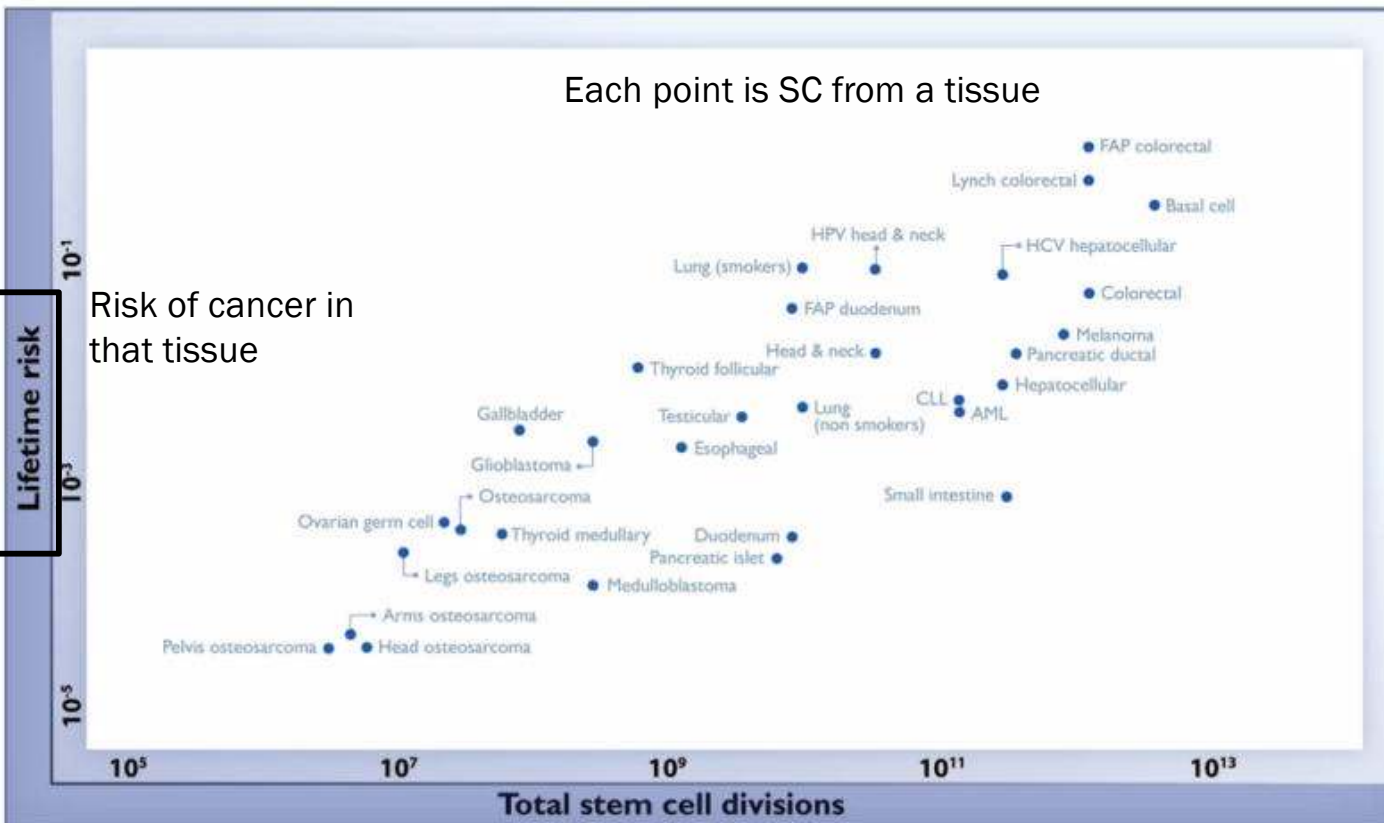
Tomasetti and Vogelstein posit Replicative (**R**) factor

- Before cancer incidence were attributed to H factors and non-H factors termed E factors.
- The R factor is inherent to biological constitution. Evolution by natural selection needs mutations. These could be from DNA Repair errors.
- Prior to their publication, R factors were grouped with E factors
- They showed that this R factor could be estimated and distinguished from purely Environmental (E) factors.

Methods and Findings

- Analysis of **stem cells** cells in the tissues are the ones that have **capacity for neoplasia**
- Extensive literature search for quantification of SC division in 31 different tissues
- Data from **United States** population (SEER Database)
- Plot on x axis avg. SC division during lifetime and lifetime cancer risk on y axis
- Stunning correlation **$r = 0.804$**
- Utilized ML to distinguish R from E and H factors
- Grouped into R and D (**E+H**)

Each point is SC from a tissue

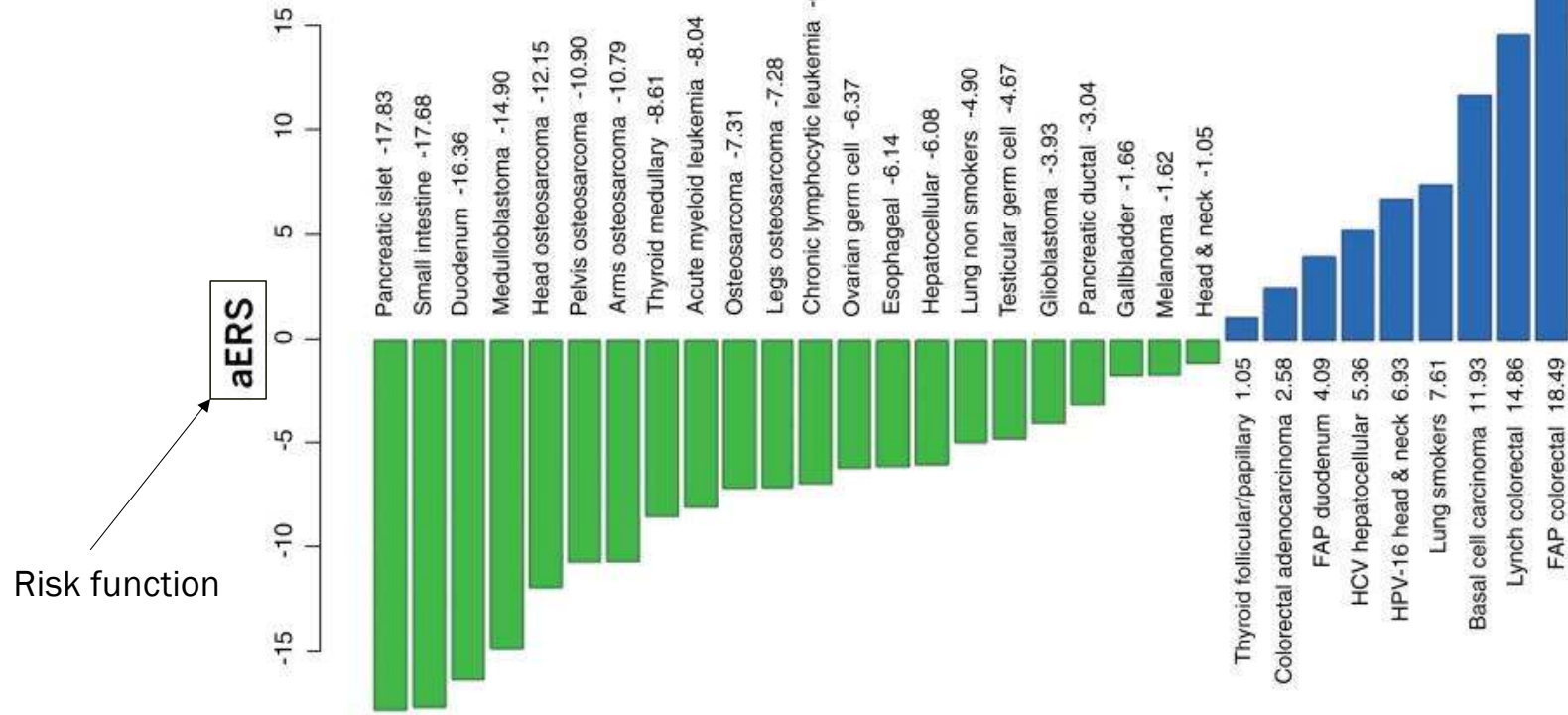


FAP = Familial Adenomatous Polyposis ♦ HCV = Hepatitis C virus ♦ HPV = Human papillomavirus ♦ CLL = Chronic lymphocytic leukemia ♦ AML = Acute myeloid leukemia

Green Cluster represent R attributed by ML

Clustering of cancer types

Blue Cluster represent D attributed

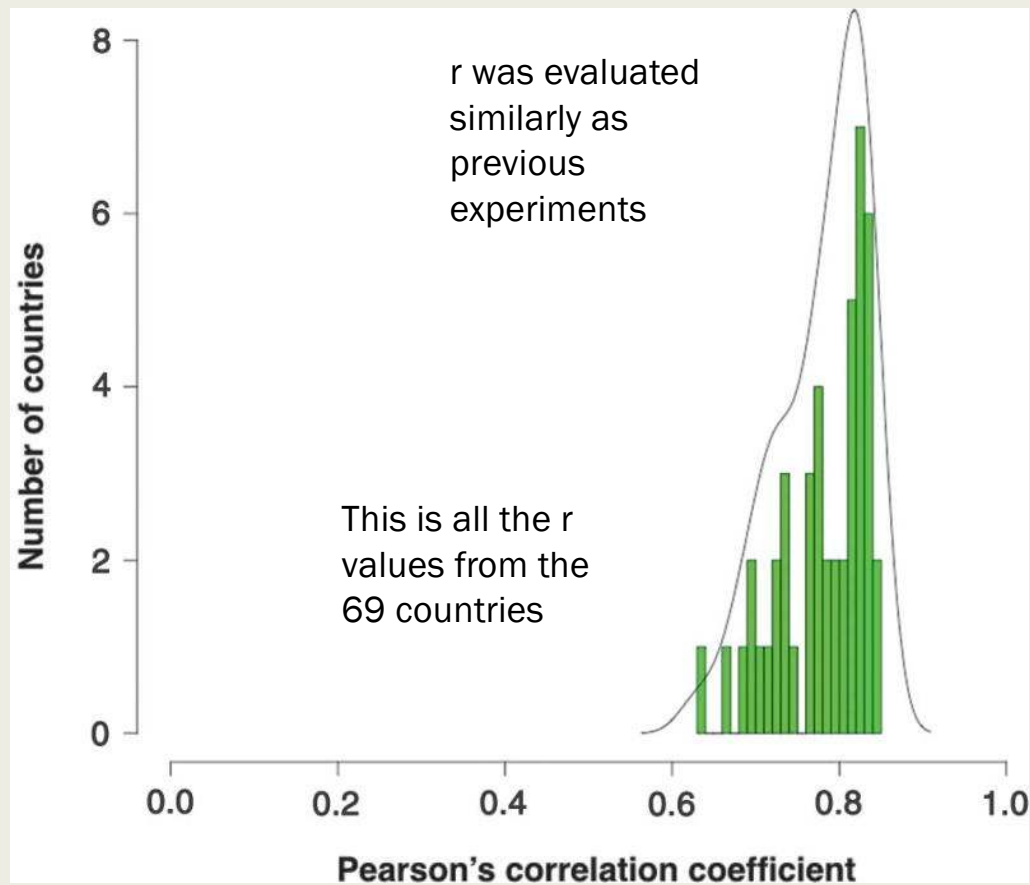


Backlash

- Study was restricted to US Population only
- Homogeneity in exposure to Environmental (E) factors
- 11 points of criticism ranging from typos to perceived mathematical “fallacy”.
- R could be an emergent property which vanishes on worldwide scale???
- Study only explained relative risks of E, H and R
- Some cancer incidences could have high enough E and H contribution masking effect of R

The Response

- Second study explores 69 countries and 17 cancer types
- No homogeneity in E conditions this time
- Perform a more thorough analysis of R to show it is a real effect
- Data from 4.8 billion people (2/3 world population)-IARC Database
- Higher statistical power by increasing n



Main Findings

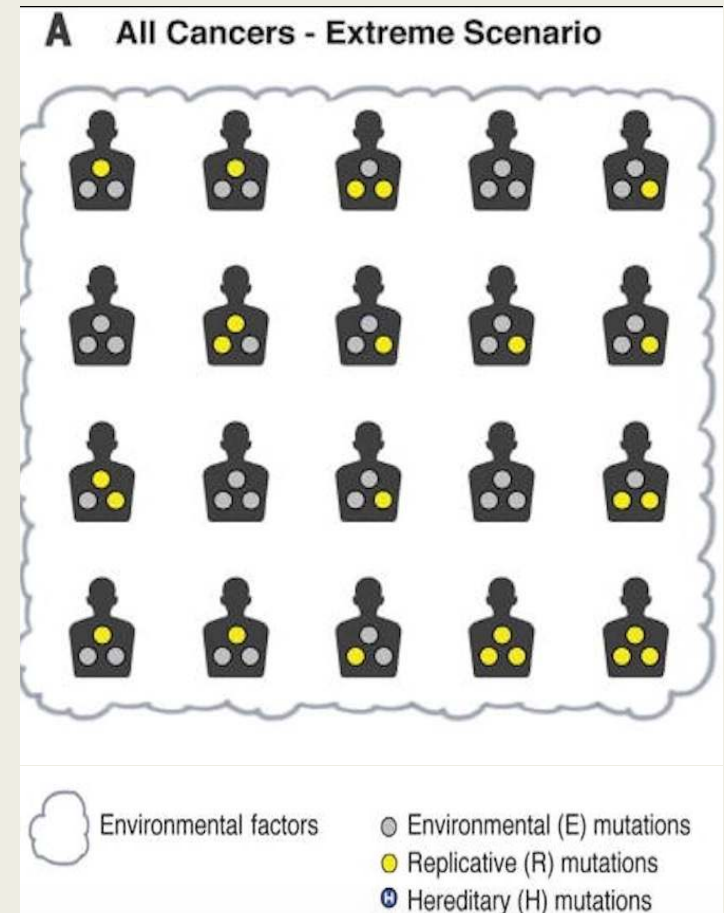
- $r_{\text{median}} = 0.804$ (Identical to previous study)
- 89% of countries have $r > 0.7$
- Derived from largest age interval available [0,85+)

But.. Still need improvement to R factor

- Previous description of masked R by H and E
- Also, as person grows older, cancer incidence rises exponentially
- However, stem cell count does not increase proportionally with age
- Increasing number of youth in sample mathematically increases correlation of lifetime SC division and cancer risk
- Also, there is numerous literature on different E factors and associated cancer incidence worldwide
- There is a need to thoroughly define and prove existence of R factor separate from E and H

Planet B Model

- Assume Population where H corrected and free of E mutagen; only cause of cancer incidence would be from R ($R > 0$ as evolutionary biology is incompatible without mutation)
- Hit them all with powerful mutagen E (Environment) such that somatic mutation rate increase in stem cells and 90% of cancer incidence attributed to E
- Therefore, 90% of cancer incidence could be prevented by limiting exposure to E
- Even in that case, shown 40% of driver mutations attributed to R



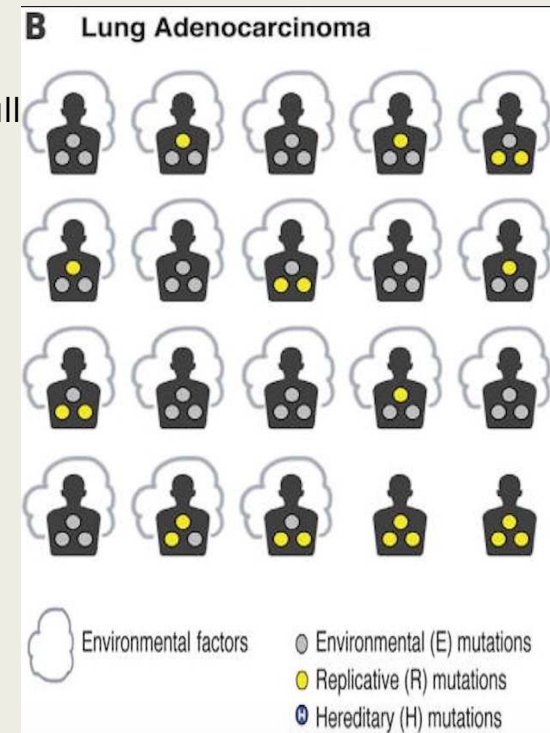
Planet B implications

- Demonstrate that even if reducing exposure to environmental factors, some mutations remain attributed to R as long as number of mutations in stem cell division >0 .
- Like lung adenocarcinoma and 90% attribution to E, tobacco smoke and no hereditary factors H were found to be implicated.
- If an E factor cause an x-fold increase in mutation then $(x-1)/x$ of somatic mutations can be attributed to that E factor, independent of any knowledge of normal stem cell division

Application of model to Lung adenocarcinoma data

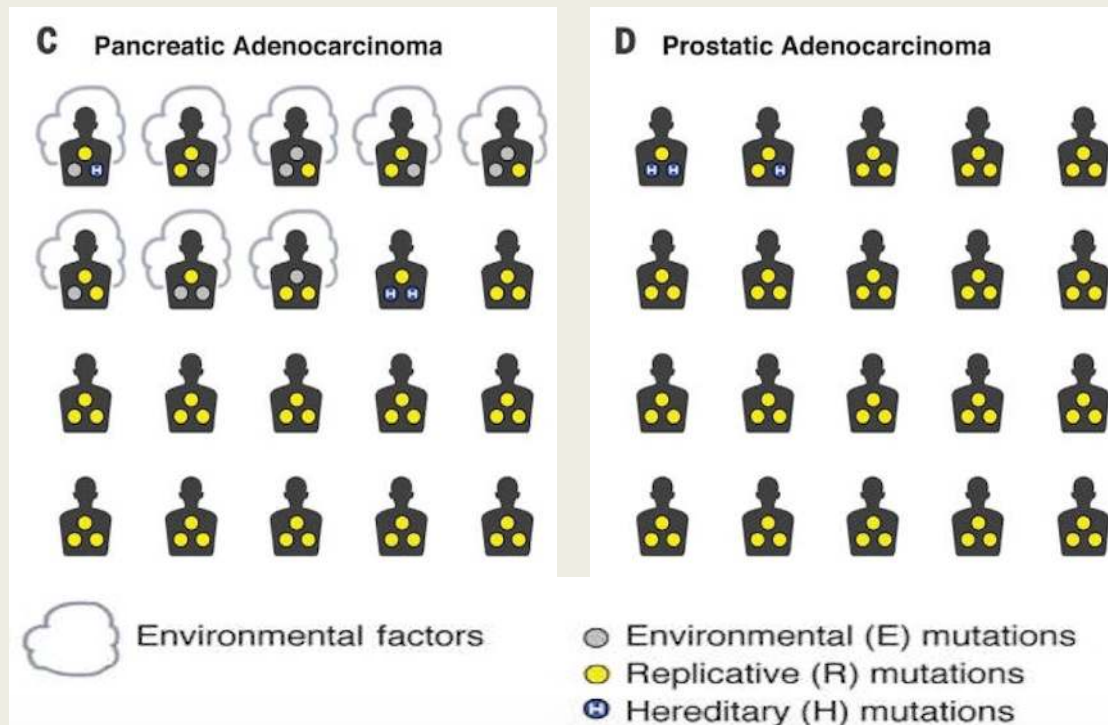
- 8/20 mutations attributed to E
- 10/20 portion of mutations **attributable** to E
- 2 remaining patients unrelated to H or E thus presume R
- Assumed that other E factors such as poor diet contribute similarly to smoking

Individuals with 3 full grey circles



Cont..

- Cancer Research UK: 89% of cancers preventable, but even so, more than a third can be attributed to R.
- Similar application to pancreatic ductal adenocarcinoma
- 18% E, 5% H and 77% R
- All this independent of stem cell division inferences



Application of model to cases of even less E and H effect

- Brain, Bone and Prostate
- 95% attributed to R
- Even if E and H factors identified for 90% of cases, mutation rate due to R would still be high (Planet B analogy)

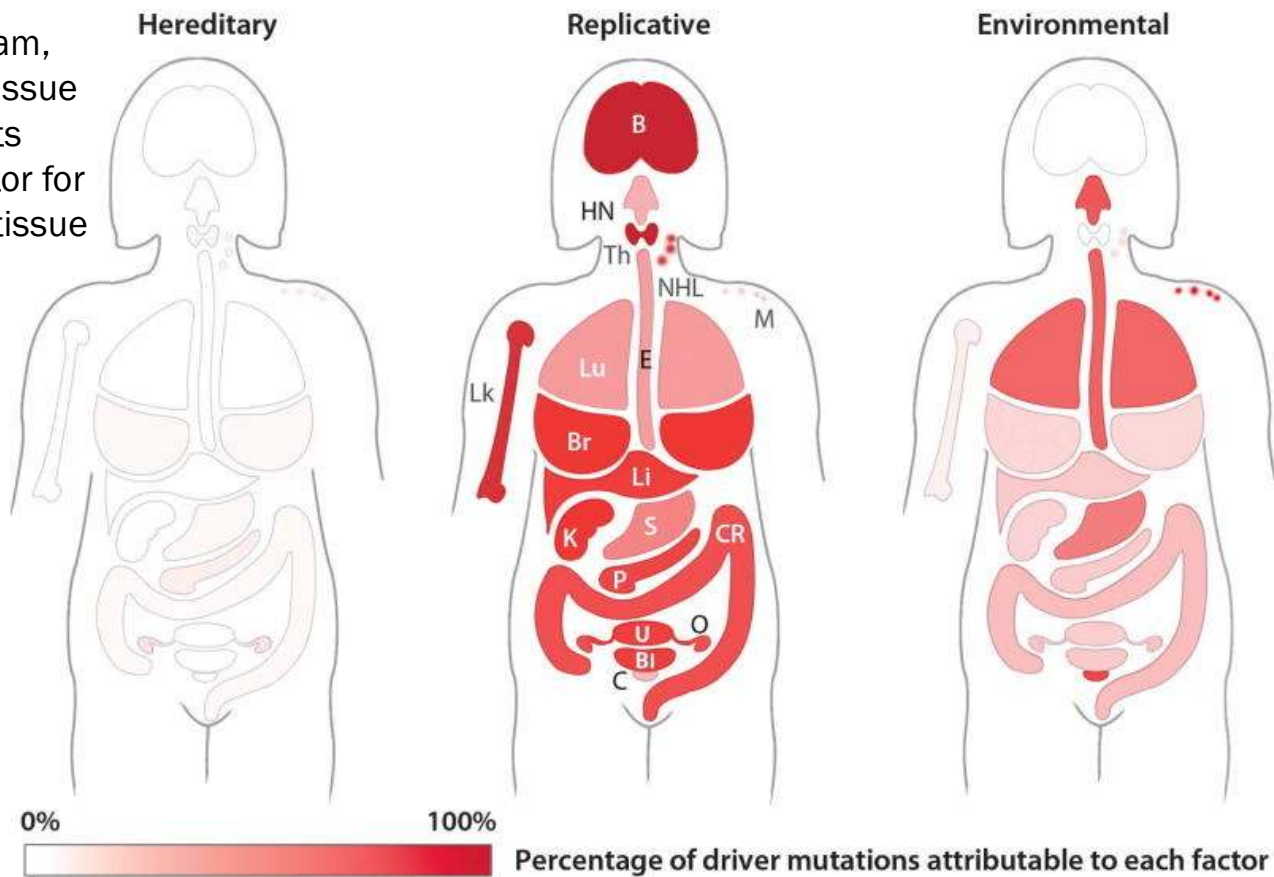
Model tested against Cancer Research UK Database

- In 32 cancer types, a calculated portion was attributed to neither E nor H. These were considered due to R
- Attribution to E median was 23%-Cancer Research UK
- After normalization, 29% E, 5% H and 66% R

Cont..

- Cancer Research UK say 42% preventable
- Proportion of mutation caused by E < Proportion of cancer preventable by avoidance of E factors
- Findings that 29% of mutations due to E, compatible with 42% preventable by avoiding E factors
- Cancer could result from 2 gene knock out; 1 influenced by E and the other by R or more combinations
- Even if R is hit, still prevented by preventing E exposure

For each diagram,
more intense tissue
color represents
most likely factor for
cancer in that tissue



Conclusion

- High correlation between stem cell division and cancer risks observed in countries with high environmental differences
- Supports idea that R mutations are significant
- In tissues less attributed to E factors, R factors are significant
- Explain that relation between stem cell division and cancer incidence cannot be explained by American E factors.

Cont..

- A cancer with 50% mutations due to R can still be preventable
- Reason: Requires more than 1 mutation to develop disease; if 2 mutations required for development of disease, 1 due to R and the other due to E, still preventable by limiting exposure to E.
- Targets preventive measures towards DNA repair mechanisms and emphasizes early detection and intervention.



Thank You