

# Importance of Adaptive Response in Cancer Prevention and Therapy

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The 109th Scientific Meeting of the Japan  
Society of Medical Physics

# Conflict of Interest Disclosure

Name of Author:

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The author has no conflicts of interest to disclose concerning the presentation.

利益相反無し<sup>2</sup>

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[http://www.j-rc.org/jrc/2015/jsmp\\_prog\\_taikai.pdf](http://www.j-rc.org/jrc/2015/jsmp_prog_taikai.pdf)

# **【JSMP Program】**

## **(A) Plenary Lectures**

(1) April 17 (Fri) 11:00–11:50 (418, 419)

Moderator: Kyushu Univ.      Hidetaka Arimura

Importance of Adaptive Response in Cancer Prevention and Therapy

Invited Speaker:      Fox Chase Cancer Center, USA      Dr. Mohan Doss

# Current Approach to Cancer

is based on

Somatic Mutation Theory of Cancer

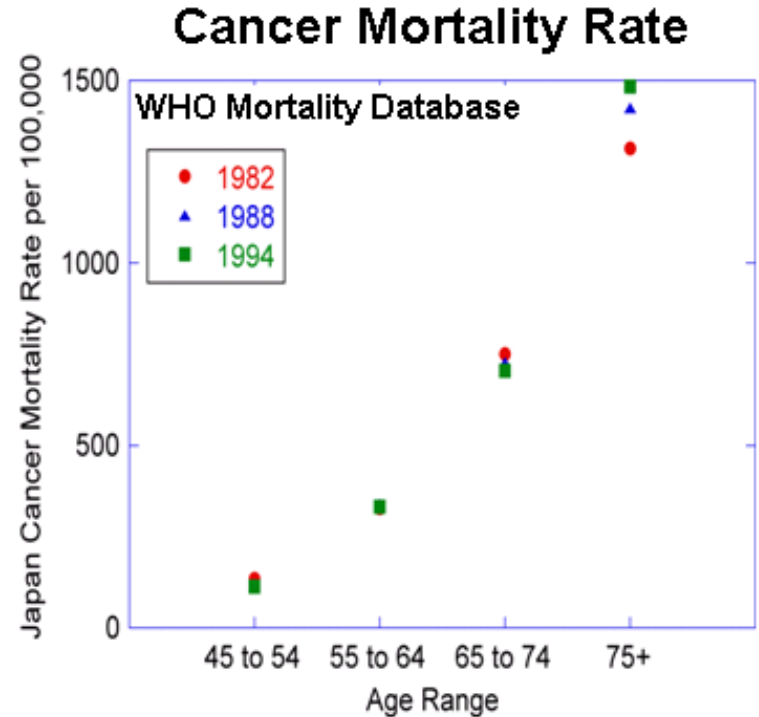
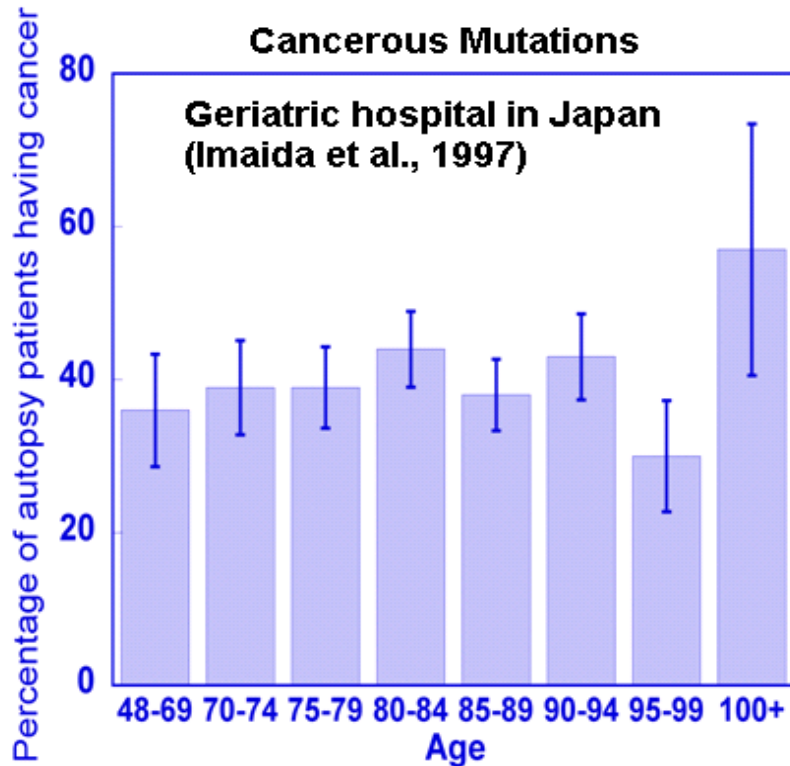
# Somatic mutation theory of cancer

- Normal cell → mutations → cancer cell → uncontrolled growth → cancer
- Cancer occurs because of random mutations transforming a normal cell to a cancer cell, i.e. cancer is due to bad luck
- With aging, mutations accumulate → increased risk of cancer with aging

# Cancer Prevention and Treatment

- An emphasis on early diagnosis (awareness and screening), to reduce the rate of late-stage disease and decrease cancer mortality
- Treatment consists of removal of cancer cells, radiation therapy, chemotherapy, etc.

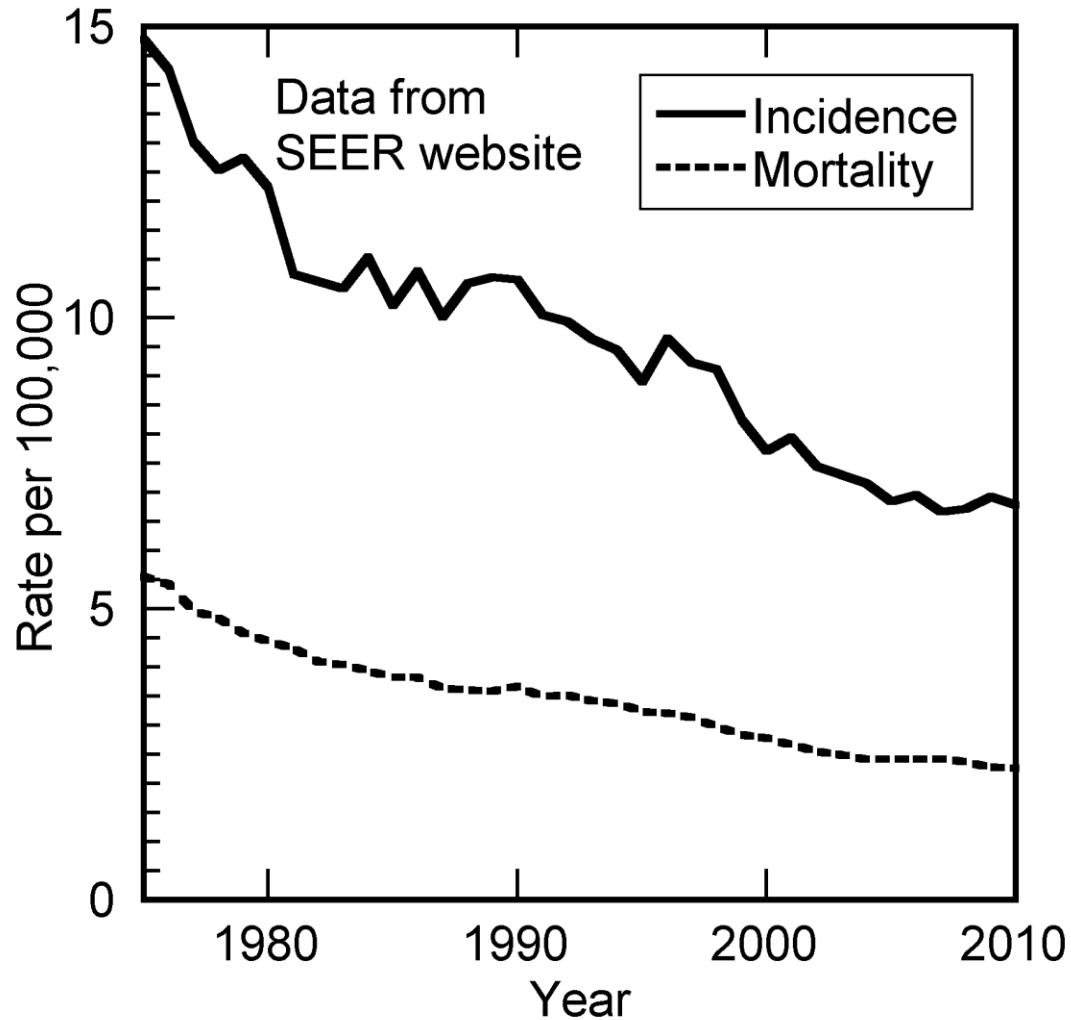
# Presence of Cancer Cells is however $\neq$ Clinical Cancer



Percentage of patients having cancer cells in their bodies is nearly the same for middle and old age, but cancer rate increases drastically with age.

# Success of Cancer Screening Program

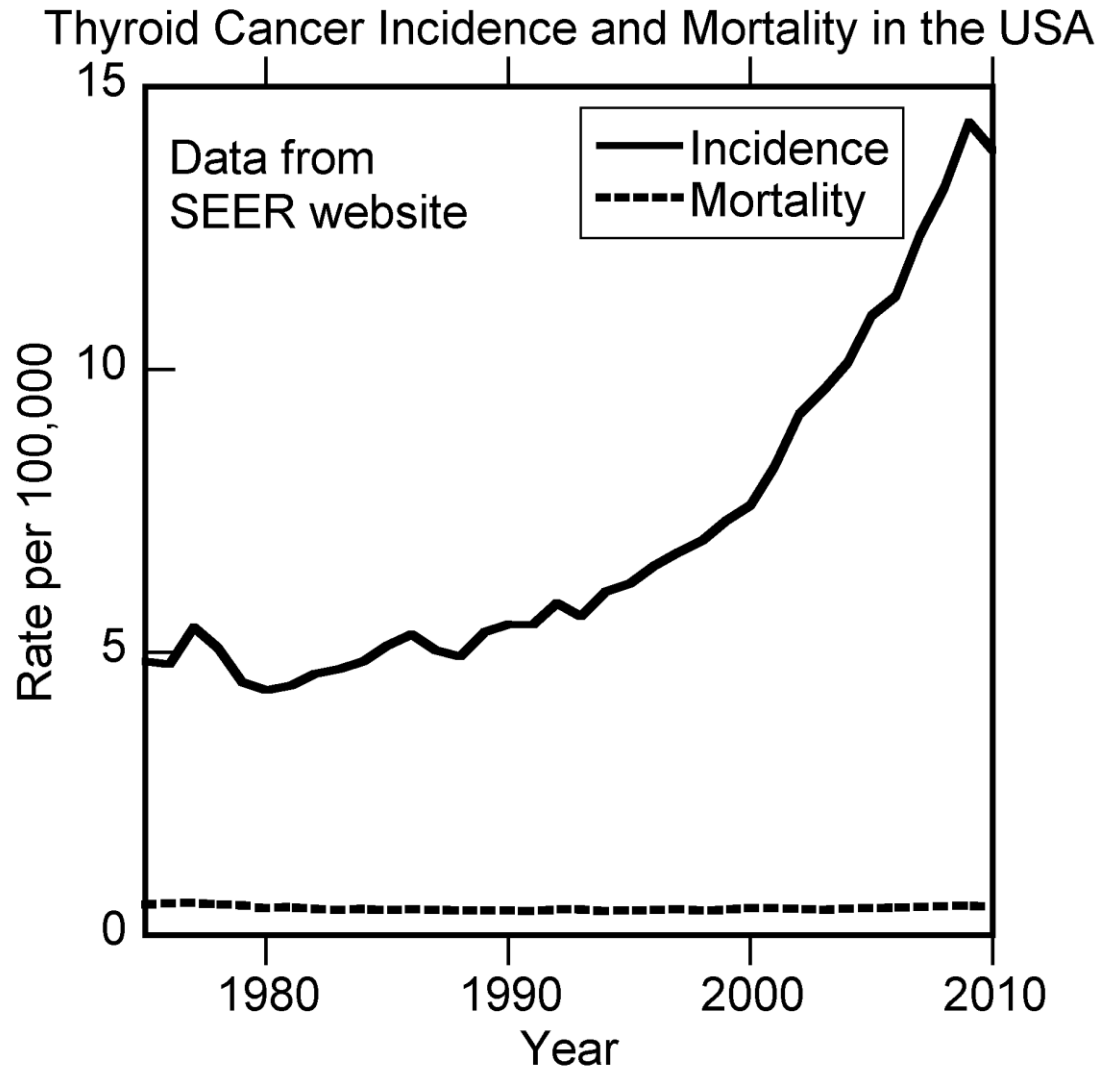
Cervical Cancer Incidence and Mortality in the USA



Considerable reduction of mortality from cervical cancer with the implementation of Pap smear testing.



# Ineffectiveness of detection of indolent cancers



No reduction of mortality from thyroid cancer in spite of large increase in detection of thyroid cancers.

# Screening and Early Detection for Cancer Prevention

Though there are some successes,  
screening is not effective for many cancers.

→ Results in Overdiagnosis and Overtreatment.

Cancer Treatments have adverse side effects.

# Possible side effects of cancer treatments

## For Radiation Therapy:

Diarrhea  
Fatigue  
Hair Loss  
Mouth Changes (dry mouth, cavities, bone loss in the jaw)  
Nausea and Vomiting  
Sexual and Fertility Changes  
Skin Changes (dryness, itching, peeling, or blistering)  
Throat Changes  
Urinary and Bladder Changes  
memory loss, problems doing math, movement problems, incontinence, trouble thinking, or personality changes.  
Infertility  
Joint Problems  
Lymphedema  
Headache, Blurry vision  
Tenderness, swelling (breast)  
Cough, Shortness of breath  
Earaches, Taste changes

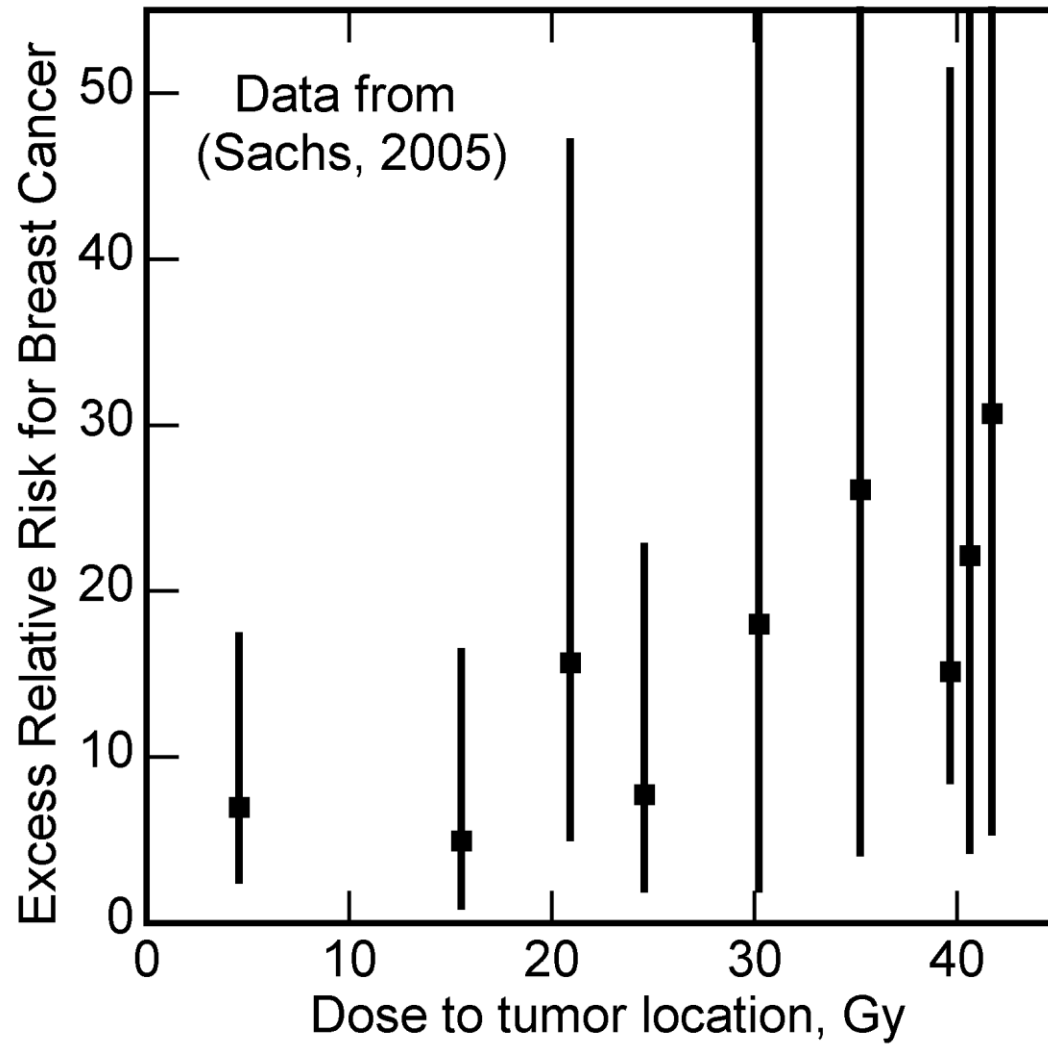
## For Chemotherapy:

Anemia  
Appetite Changes  
Bleeding Problems  
Constipation  
Diarrhea  
Fatigue (Feeling weak and very tired)  
Hair Loss (Alopecia)  
Infection  
Memory Changes  
Mouth and Throat Changes  
Nausea and Vomiting  
Nerve Changes  
Pain  
Sexual and Fertility Changes  
Skin and Nail Changes  
Swelling (Fluid retention)  
Urination Changes

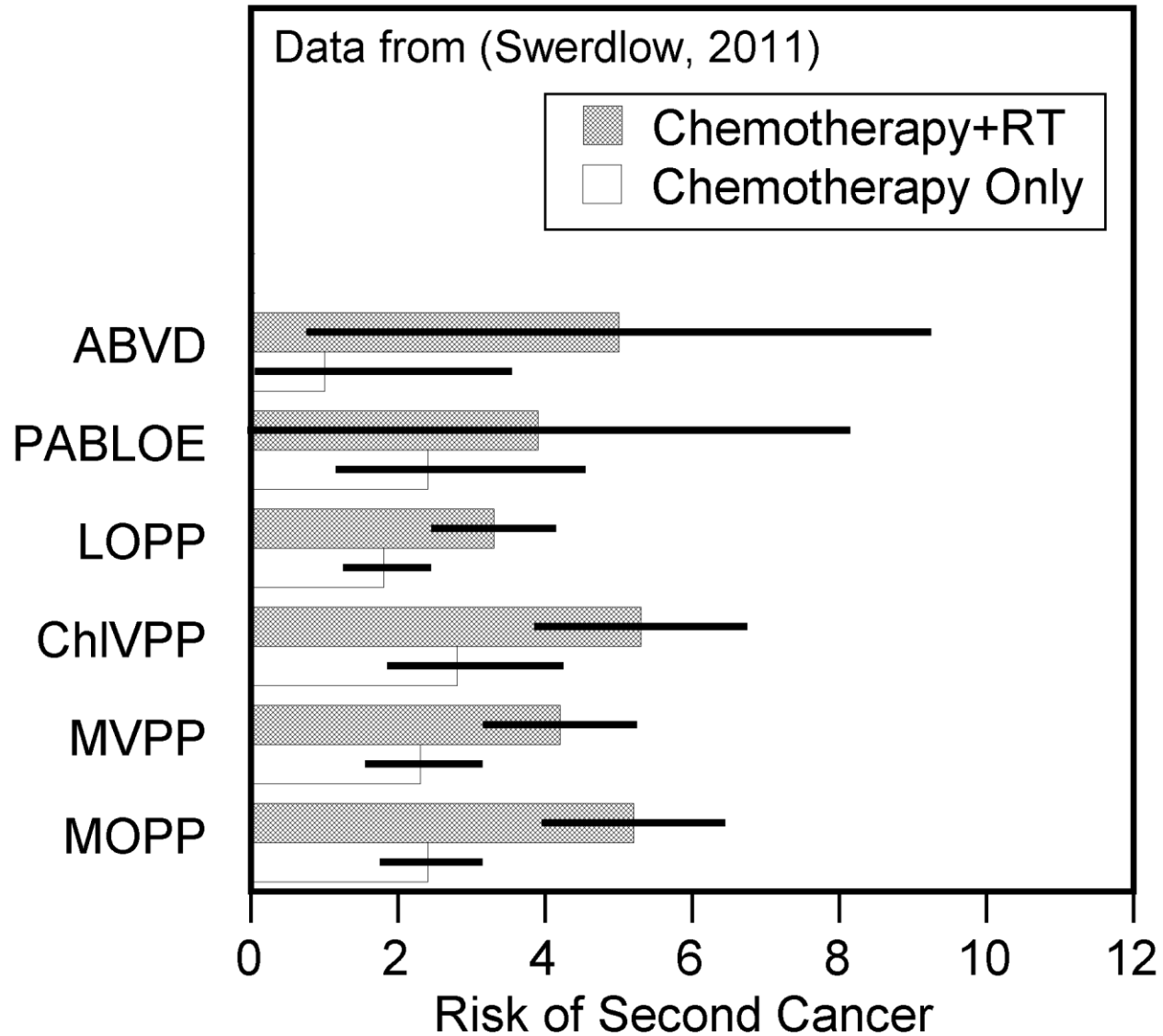
# Another adverse side effect of cancer treatments

Increased risk of second cancers

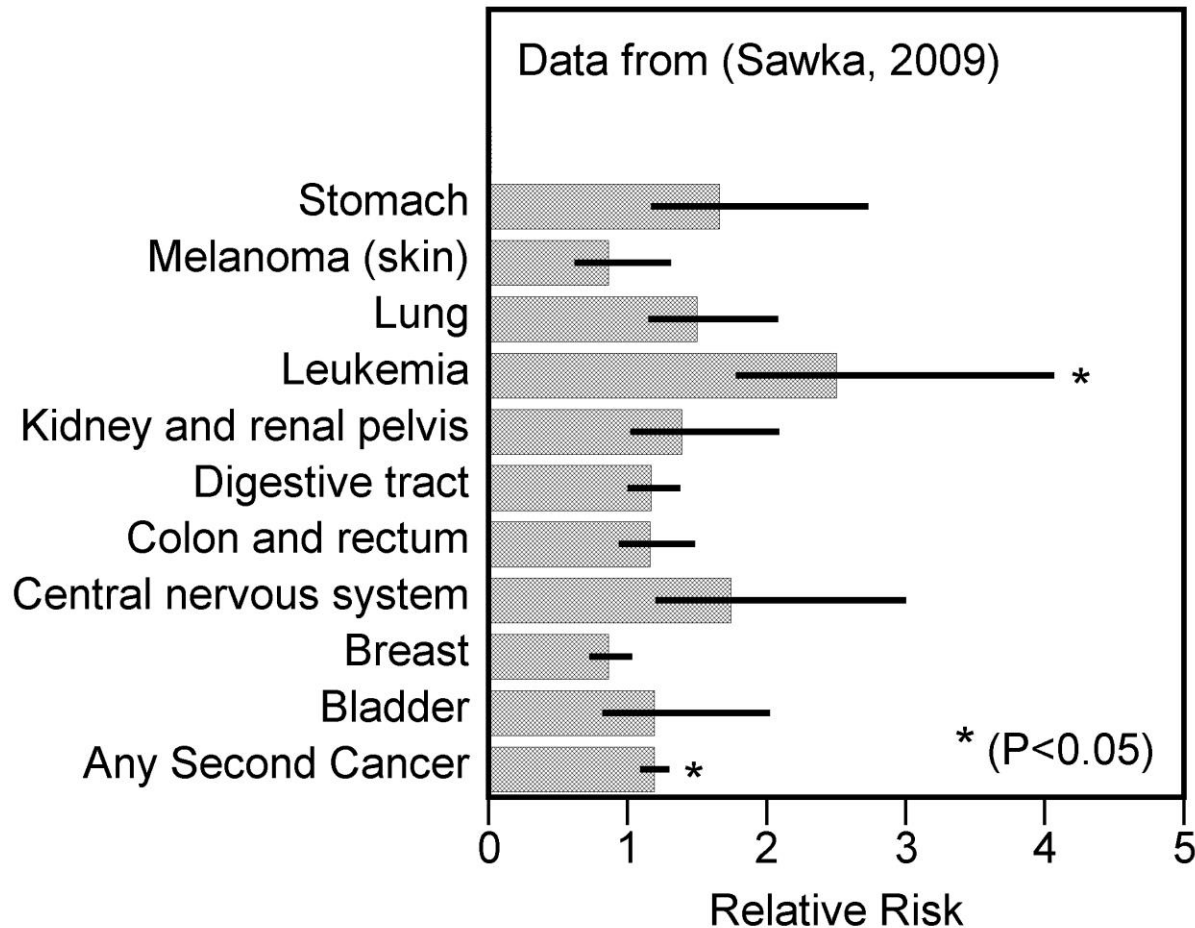
## Second Cancers in Breast in non-Hodgkin's lymphoma Radiation Therapy Patients



# Risk of Second Cancer following Chemotherapy or Chemotherapy + RT



## Relative Risk of Second Cancers in Thyroid Cancer Patients Treated with I-131 Relative to Those Not Treated with I-131



Risk significant for Leukemias and any second cancer.  
Risk not significant for any other individual cancer.

**Increased risk of second cancers** is an indication the current treatments are not addressing the basic cause of cancers, since new cancers are occurring at higher rates following the treatments.

Alternatives to Radiation Therapy and Chemotherapy are being explored.



# Targeted Therapies

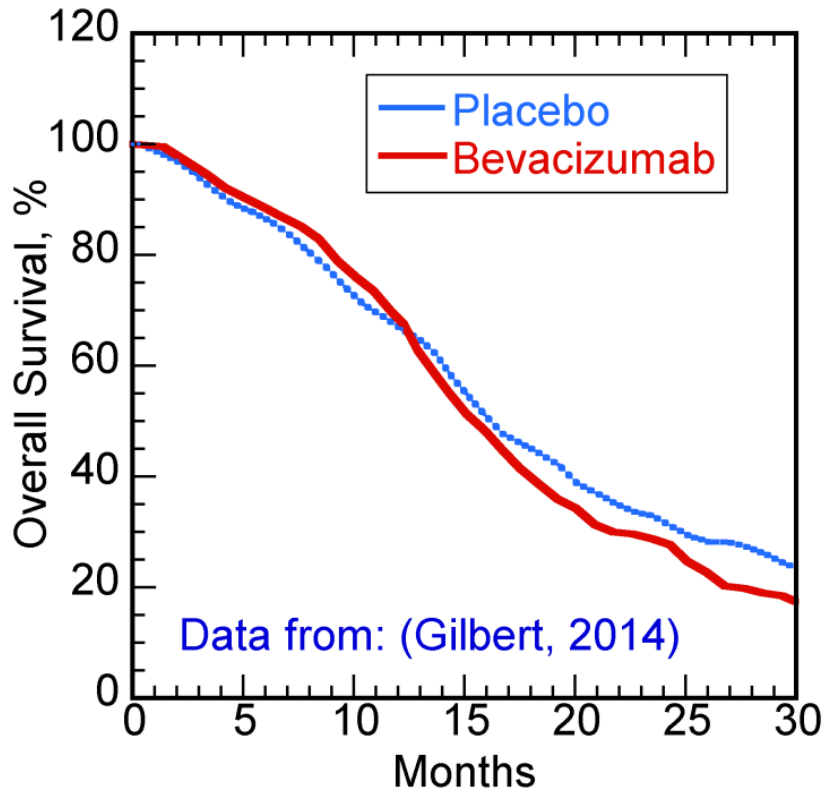
Targeted Therapies have failed to live up to initial expectations:

Some temporary successes but  
tumors develops resistance

Things are more complicated.....

# Anti-angiogenesis Therapy

Glioblastoma Patients - Randomized Trial

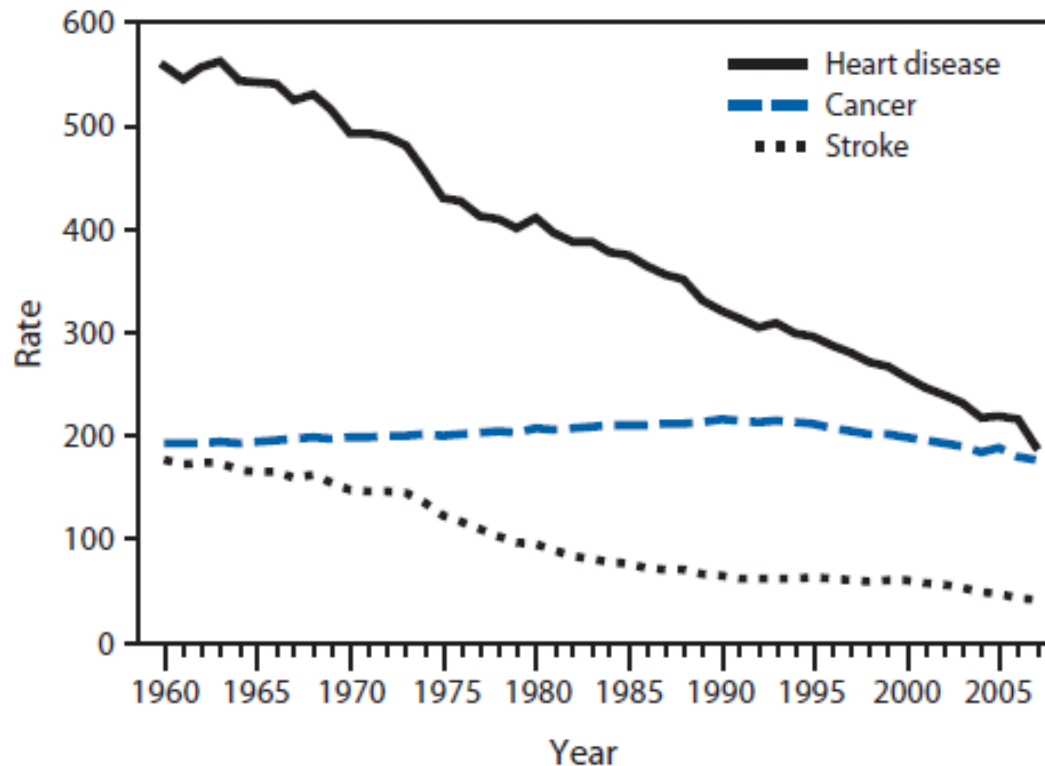


**Adaptive response** of tumors to anti-angiogenesis treatment is to increase other angiogenesis factors, resulting ultimately in more aggressive tumors, more metastases ([Paez-Ribes, 2009](#))

A randomized, double-blind, placebo-controlled trial showed the bevacizumab treatment resulted in no improvement in survival compared to placebo. Resulted in: “higher rates of neurocognitive decline, increased symptom severity, and decline in health-related quality of life” ([Gilbert, 2014](#)).

# Lack of Progress in Reducing Cancer Mortality Rates during the past 50 Years

FIGURE 2. Trends in age-adjusted death rates for the leading chronic diseases — United States, 1960–2007



Source: National Center for Health Statistics. Health, United States, 2010. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2011. Available at [www.cdc.gov/nchs/data/health/health10.pdf](http://www.cdc.gov/nchs/data/health/health10.pdf).

# Current Status of the War on Cancer

Although we have won some battles, we have not won the war on cancer. Despite remarkable progress in our understanding of the disease and in treatment of some forms of it, some observers have passionately argued that we are losing this war,<sup>7,8</sup> suggesting radical prescriptions for change in how the war is fought. However, most would agree that we have not lost the war. Historic progress has been made, and remarkable opportunities exist to turn the tide. Refined and potentially more-effective tactical strategies are being developed and tested.<sup>9</sup> With respect to regrouping of and improvement

From: [Rethinking the war on cancer, \(Douglas Hanahan, 2014\)](#)

In view of the current status of the war on cancer, it would be worthwhile exploring alternative approaches to conquering cancer.

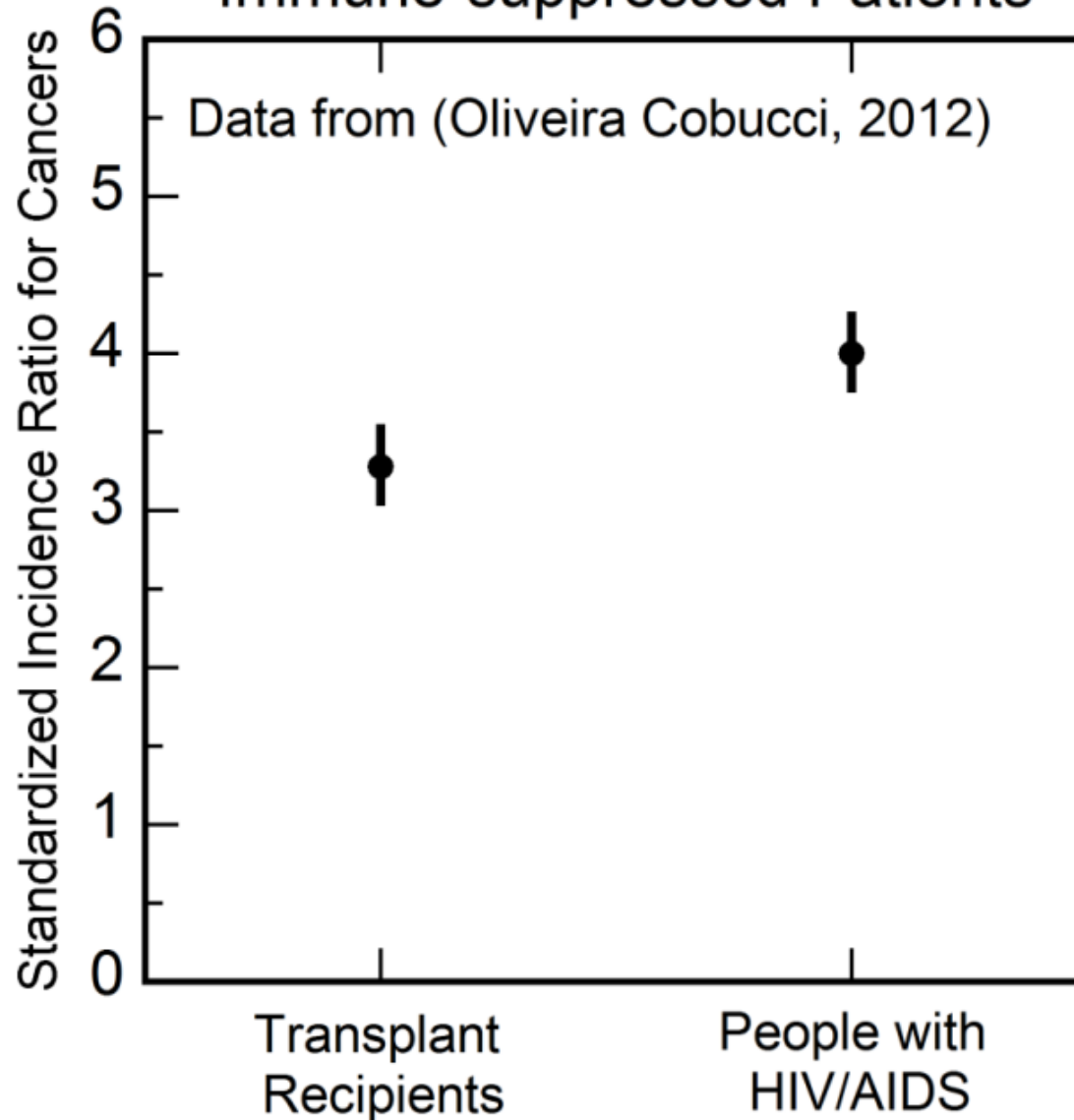
An alternative model of cancer is the  
**Immune Suppression Model of Cancer**  
based on the large increase in cancers observed when the  
immune system is suppressed.

In this model:

A normal cell, with the accumulation of mutations, can transform into a cancer cell. However, its uncontrolled growth is prevented by the immune system.

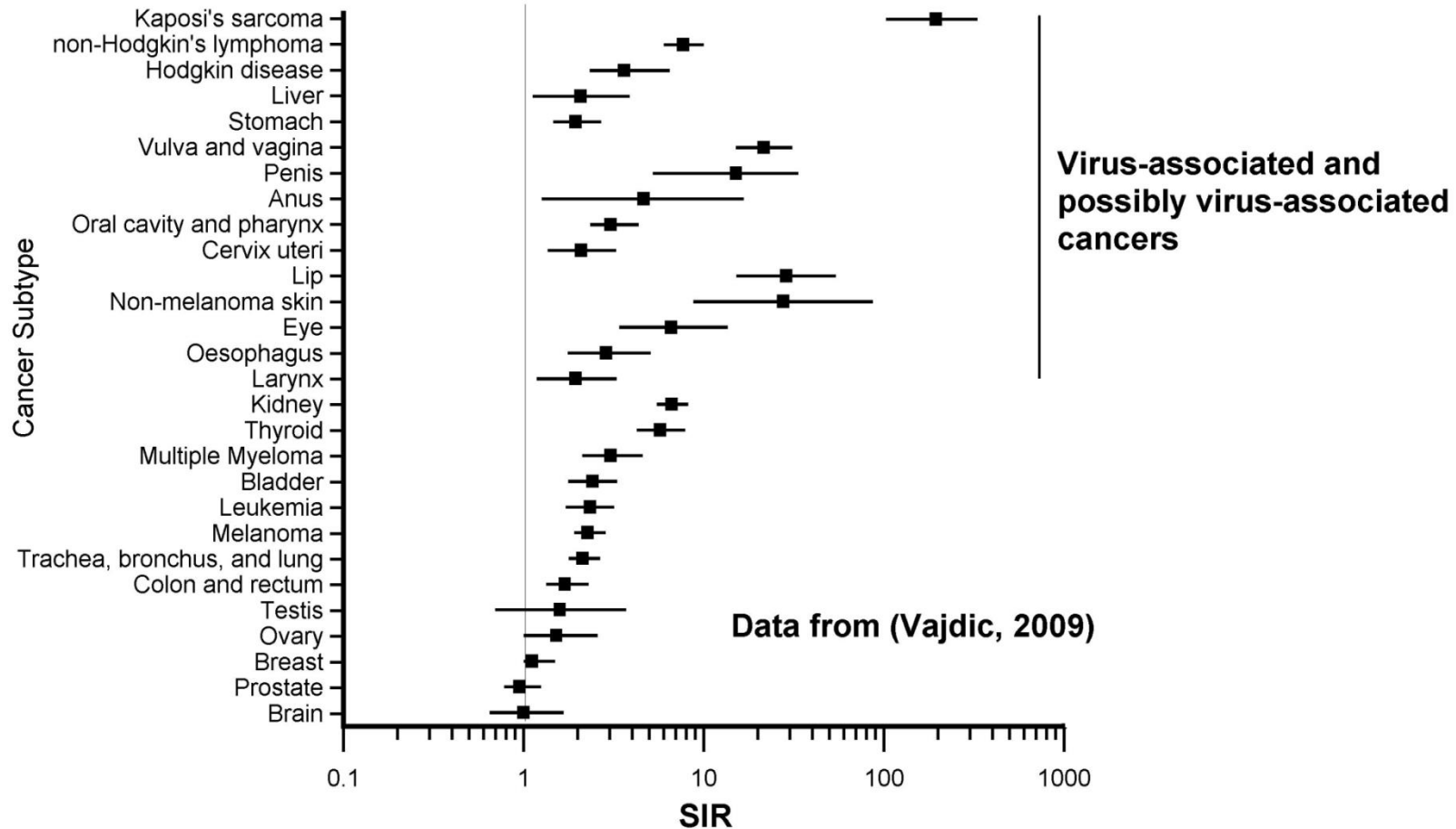
When the immune system is suppressed, clinical cancers occur.

## Cancer risk in Immune-suppressed Patients



Suppression of the immune system increases cancer risk drastically.

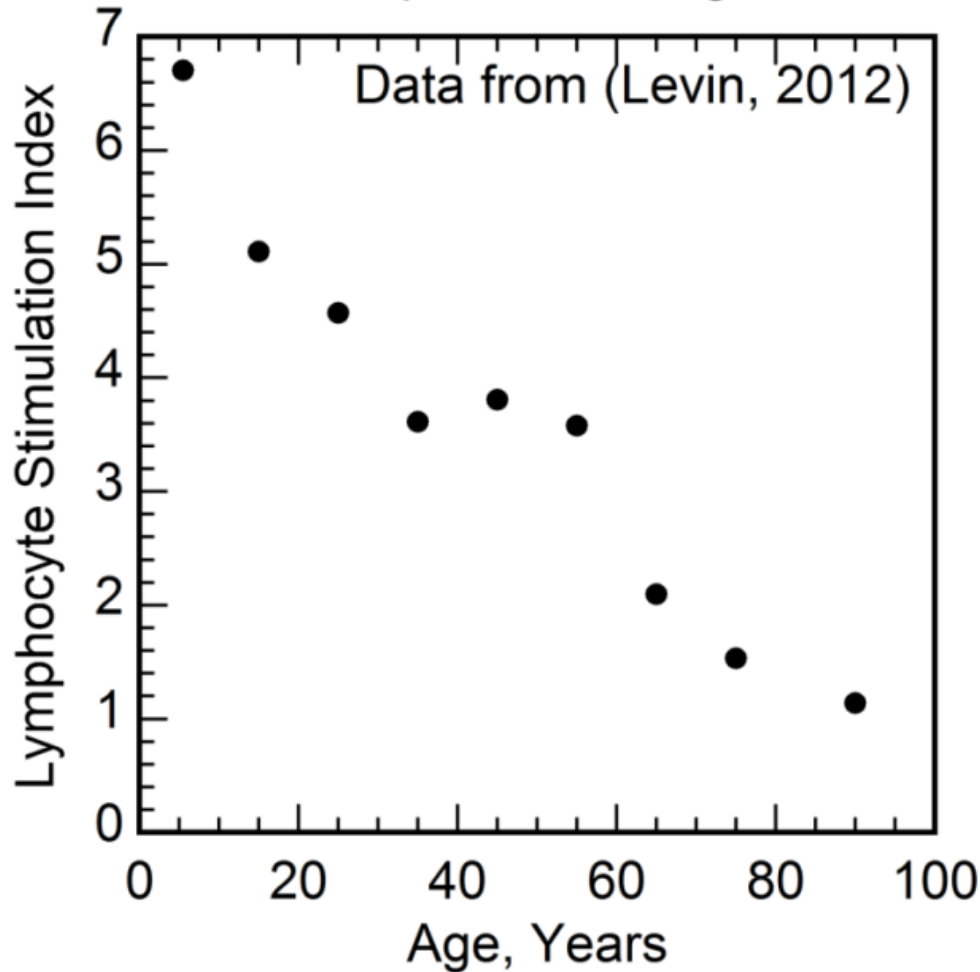
# Cancer incidence in Organ Transplant patients



Increased cancer incidence is observed not only for cancers known to be associated with viruses but also other cancers not known to be associated with viruses.



## Variation of Immune System Response with Age



The reduction in immune system response with age can qualitatively account for the well-known age-related increase in cancers.

# Prevention of cancer

under the Immune Suppression Model of Cancer

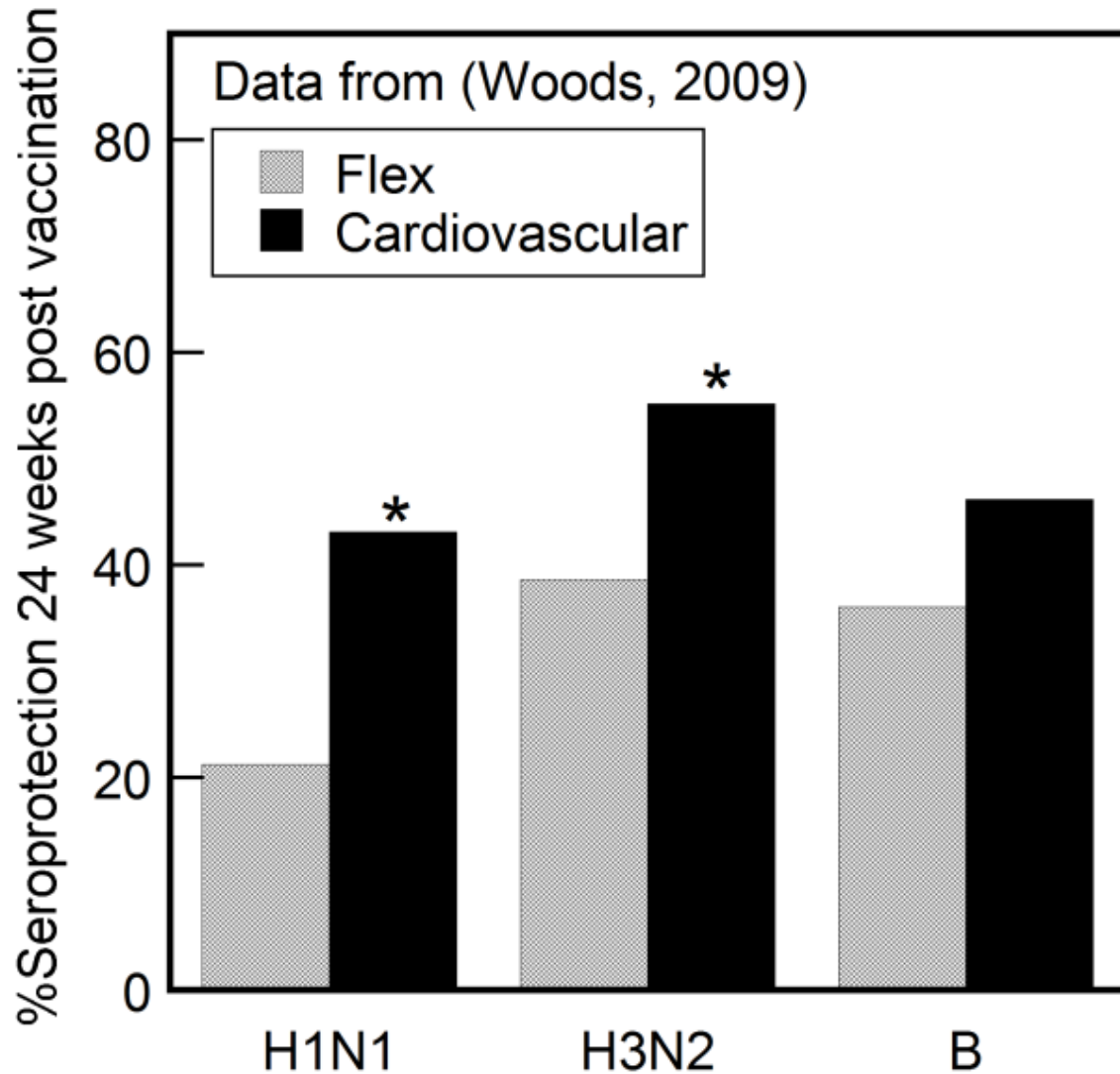
To prevent cancer,

we need to improve the immune system

How to boost the immune system?

A simple method – vigorous exercise

## Effect of exercise on the Immune System Response



\*Significant treatment difference ( $P < 0.05$ )

# Exercise induces adaptive response

## Adaptive Response following exercise:

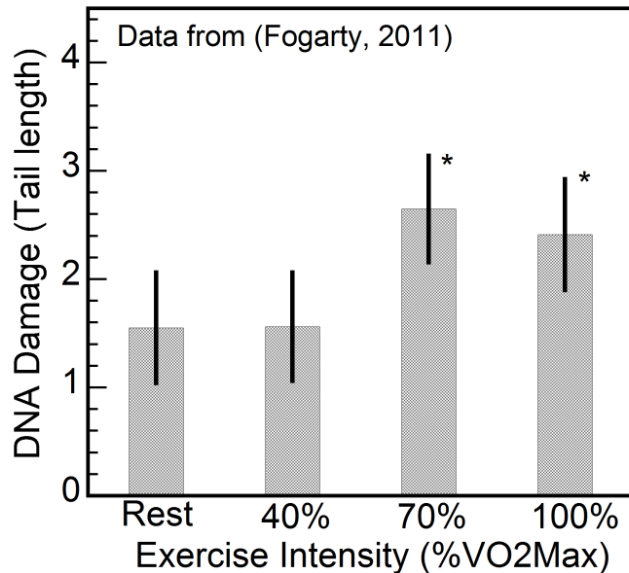
### Increased

- Antioxidants
  - DNA repair enzymes
  - Apoptosis
  - Immune System Response
- etc.

The increased defenses (antioxidants, DNA repair enzymes, etc.) would reduce the endogenous DNA damage that would have occurred in the subsequent period in the absence of exercise.

# Exercise Causes DNA damage

DNA Damage during incremental exercise



\* Significant increase compared to Rest ( $P < 0.05$ )

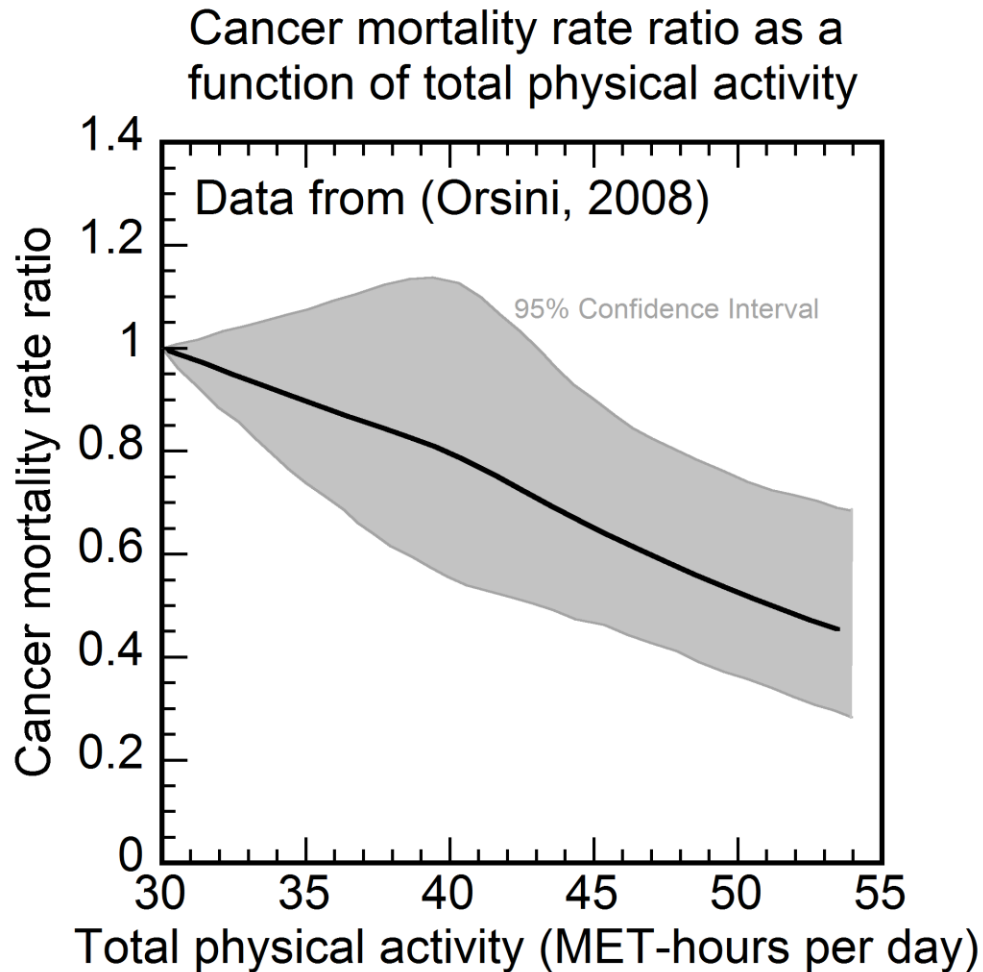
Concerns about DNA damage in the publication:

**“a novel finding of this investigation is that a short bout of exercise at moderate and high intensity (5 min) can cause an increase in alkoxyl free radicals, lipid peroxidation, and DNA damage”**

**“the fact that a very short bout of high-intensity exercise can cause an increase in damage to DNA is a cause for concern. Excessive damage to DNA is associated with a number of human pathologies including carcinogenesis and age-associated degenerative diseases”**

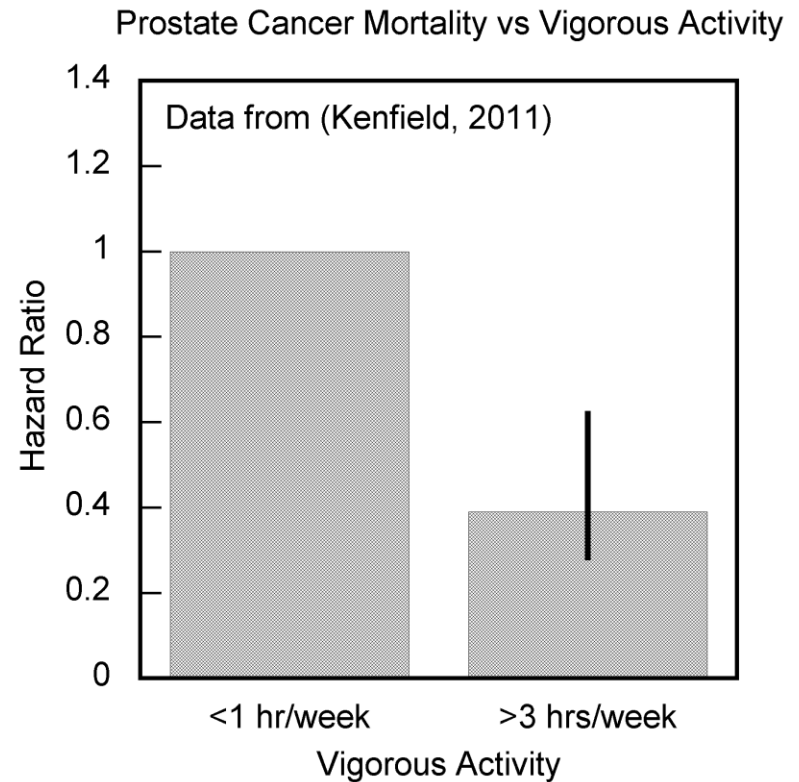
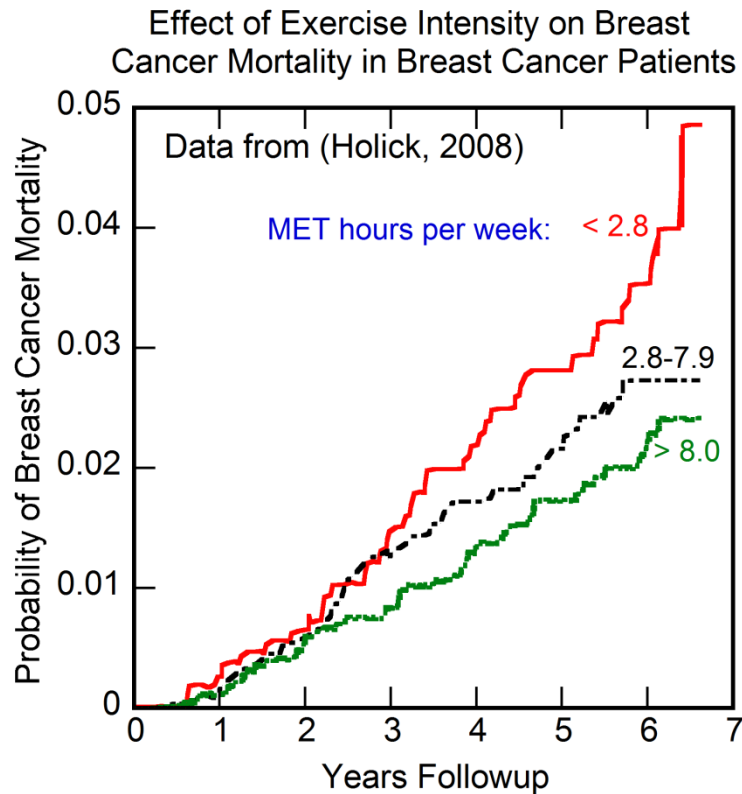
These concerns ignore adaptive response of the body to exercise, which would reduce the overall DNA damage in the subsequent period because of the enhanced defenses.

# Effect of Exercise on Cancers

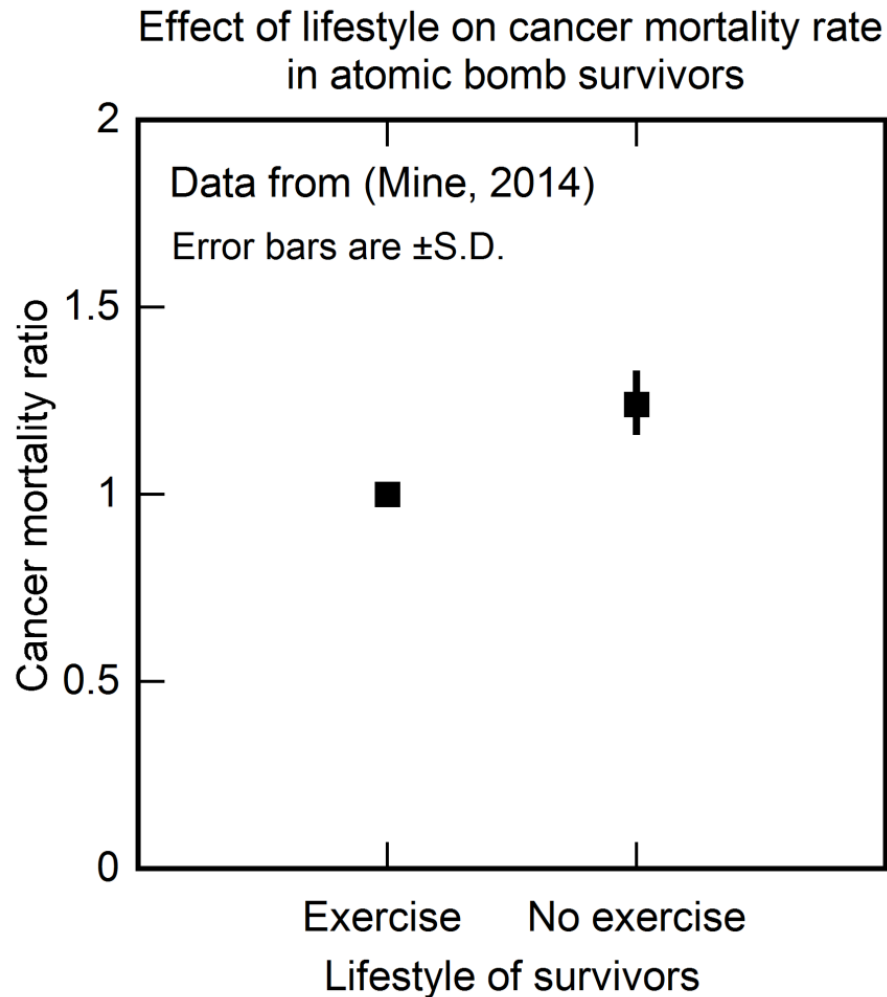


**Vigorous exercise needed for most effectiveness.  
Not just a walk in the park!**

# Vigorous Exercise Reduces Cancer Mortality in Cancer Patients



# Effect of Exercise on Cancer Mortality Rate in Atomic Bomb Survivors



Exercise resulted in reduced cancer mortality rate among the survivors.



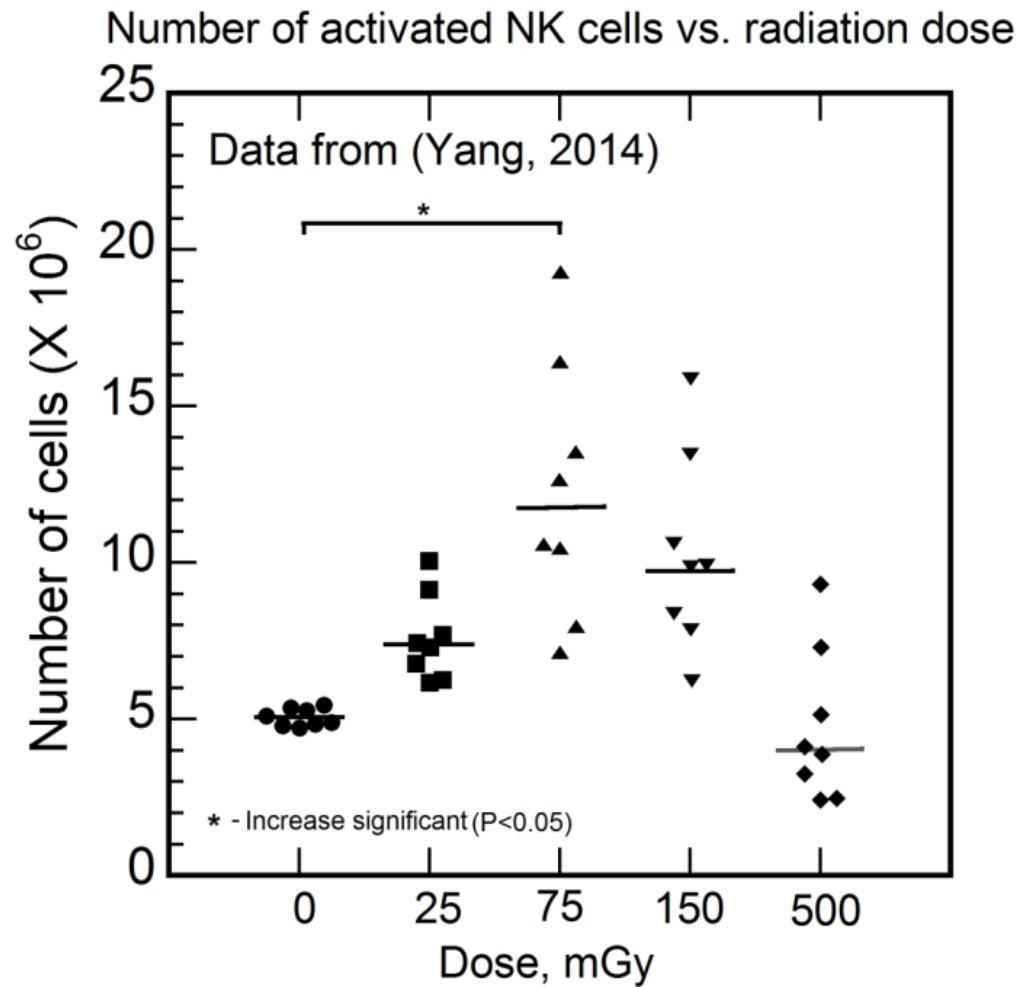
In view of all the evidence, we would be justified in utilizing the adaptive response from exercise to prevent cancers.

Another way of boosting the  
immune system?

# Another way of boosting the immune system?

Low-dose radiation

# Low-dose radiation boosts the immune system



# Low-dose radiation induces adaptive response

Adaptive Response following low-dose radiation exposure:

Increased

- Antioxidants
- DNA repair enzymes
- Apoptosis
- Immune System Response

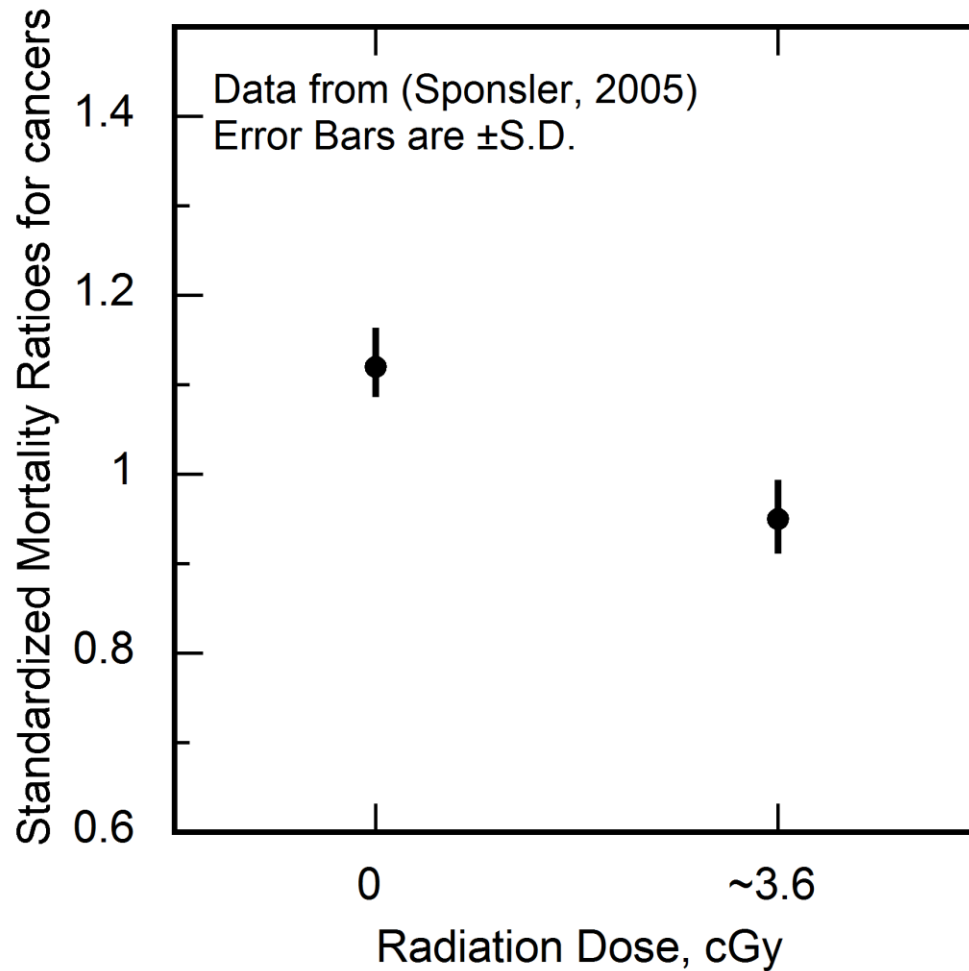
etc.

Referred to as Adaptive Protection ([Feinendegen, 2013](#))

The increased defenses (antioxidants, DNA repair enzymes, etc.) would reduce the endogenous DNA damage that would have occurred in the subsequent period in the absence of low-dose radiation exposure.

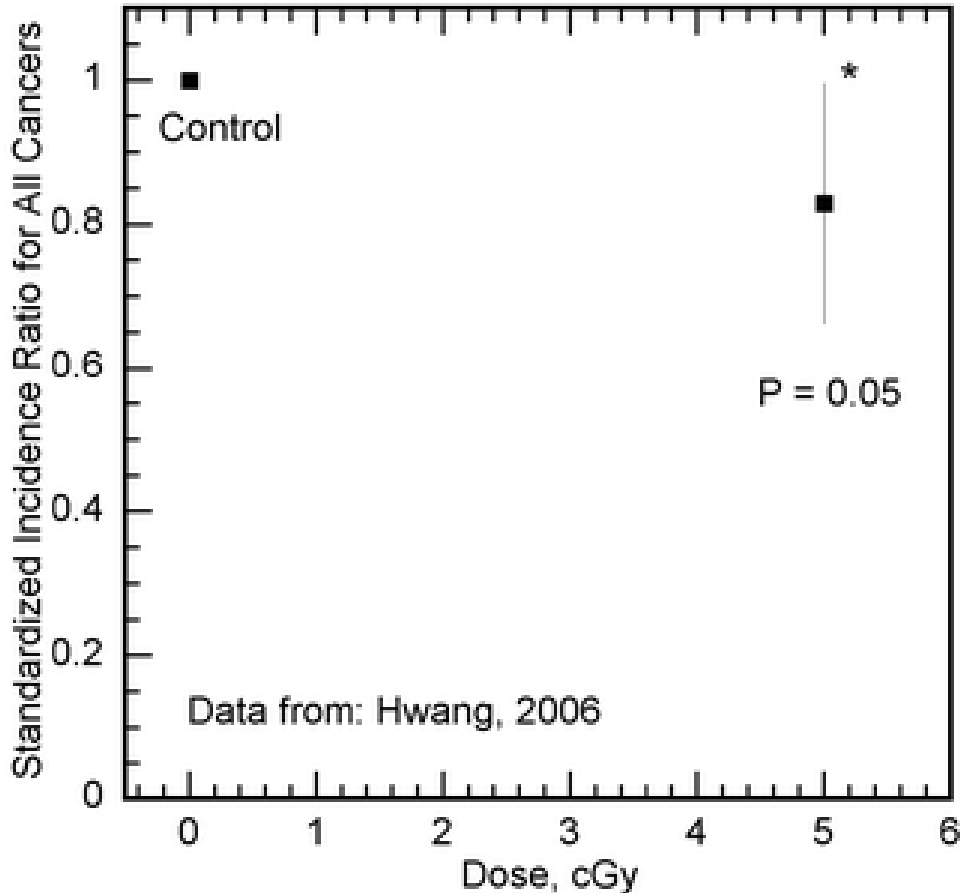
Low-dose radiation prevents cancers

## Standardized Mortality Ratios for cancers in Nuclear Shipyard Worker Study



Significantly reduced cancer mortality in the workers subjected to ~3,6 cGy in comparison to non-radiation workers.

## Incidence of All Cancers in Irradiated Taiwan Apartment Residents

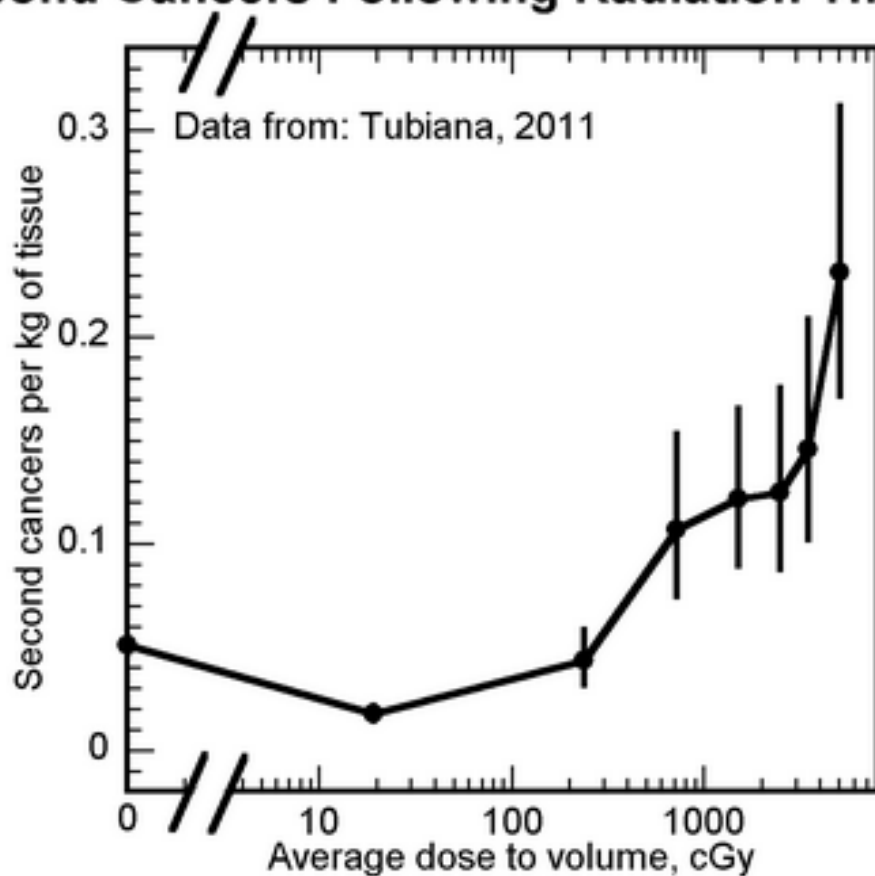


Reduction of all cancers in the apartment residents in Taiwan subjected to an average dose of ~5 cGy due to contaminated building materials.

This reduction continued in the 2008 follow-up report, as discussed [here](#).

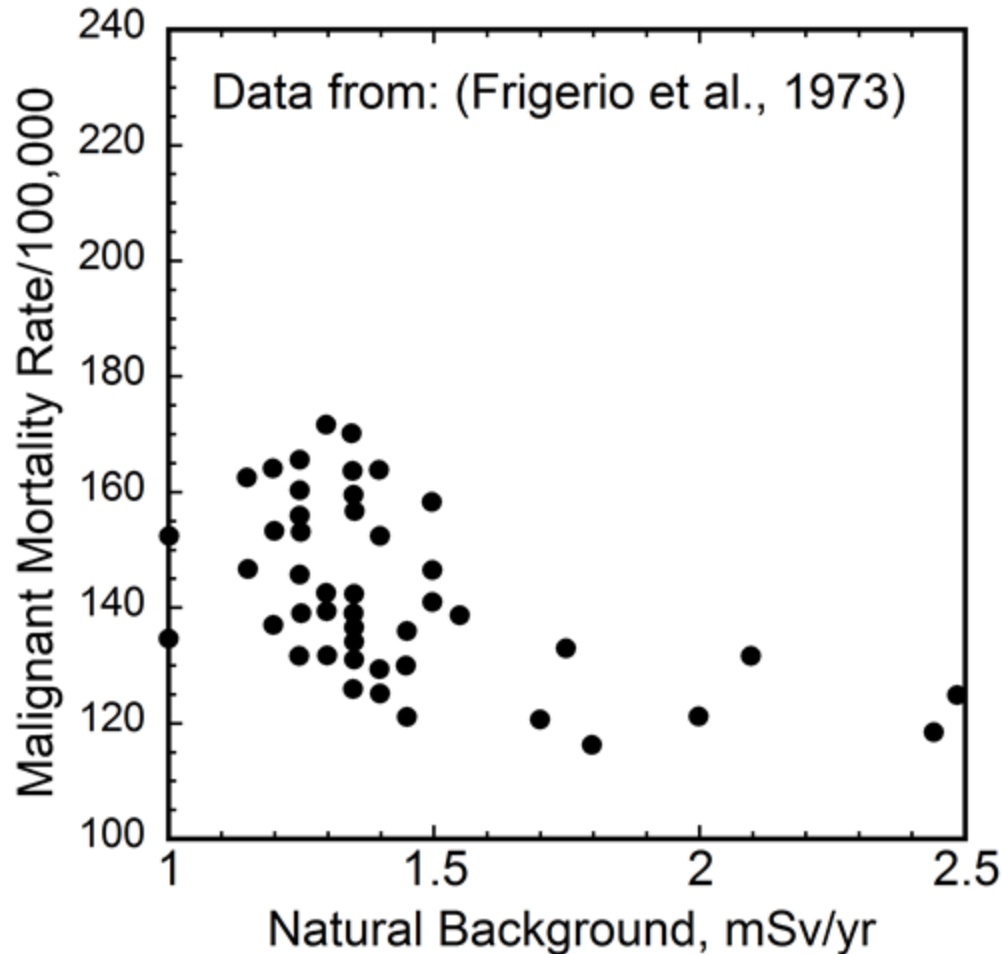


## Second Cancers Following Radiation Therapy



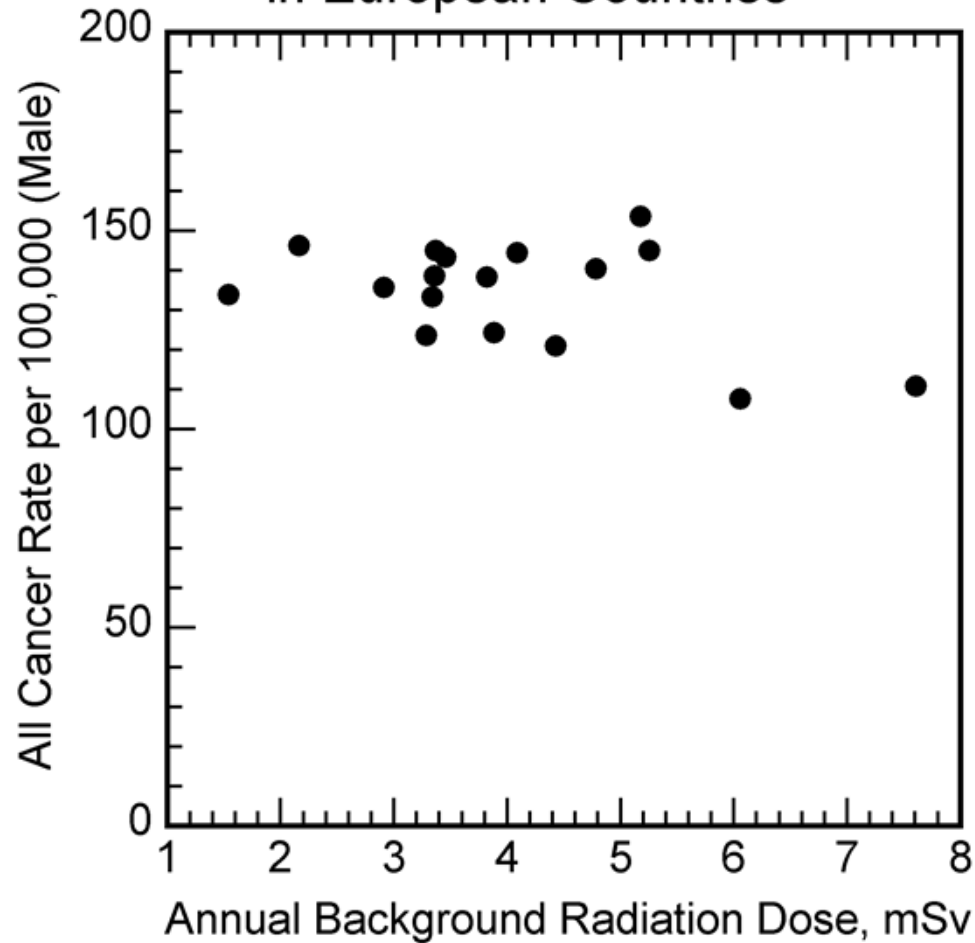
Reduction of second cancers per kg of tissue in regions of body subjected to radiation dose of ~20 cGy during radiation therapy, in comparison to regions not subjected to any radiation dose.

# Cancer Mortality Rates (1950-67) vs. background radiation in the USA



Trend of lower cancer mortality rates associated with higher background radiation levels in the different states of USA

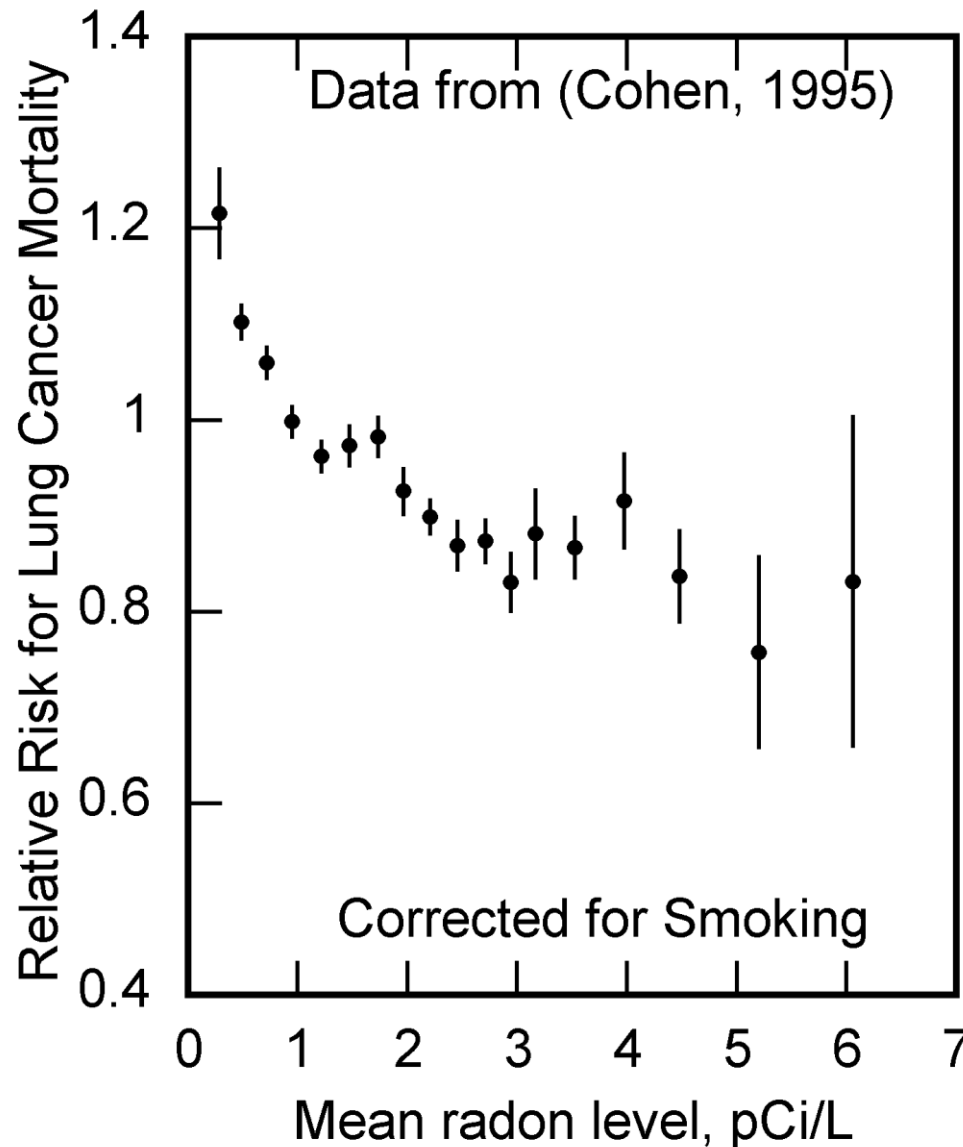
## Cancer Rate (in 2008) vs. Background Radiation in European Countries



Reduced cancer rates in the European countries with the highest background radiation levels

Radiation Levels from:  
[world-nuclear.org](http://world-nuclear.org)  
Cancer rates from:  
[WHO Mortality Database](http://WHO Mortality Database)

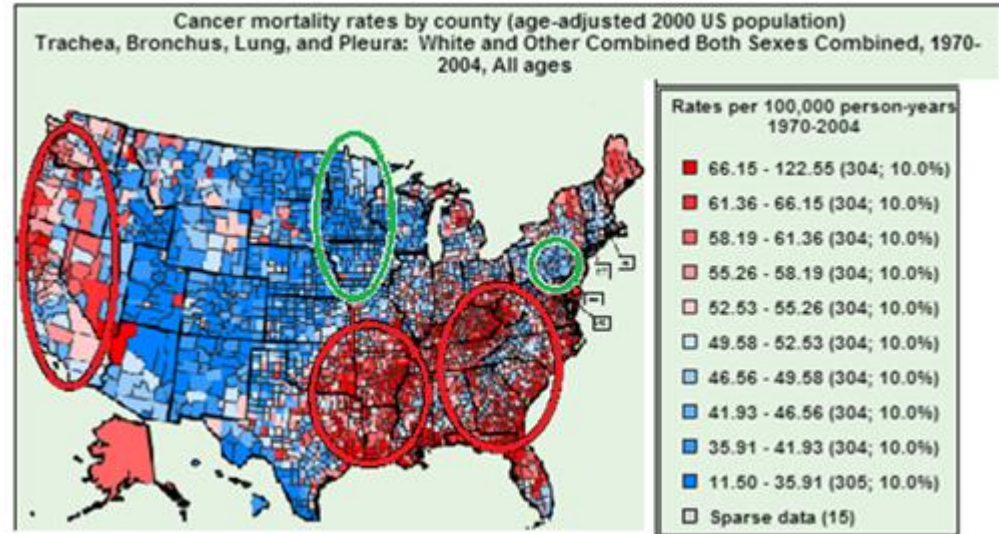
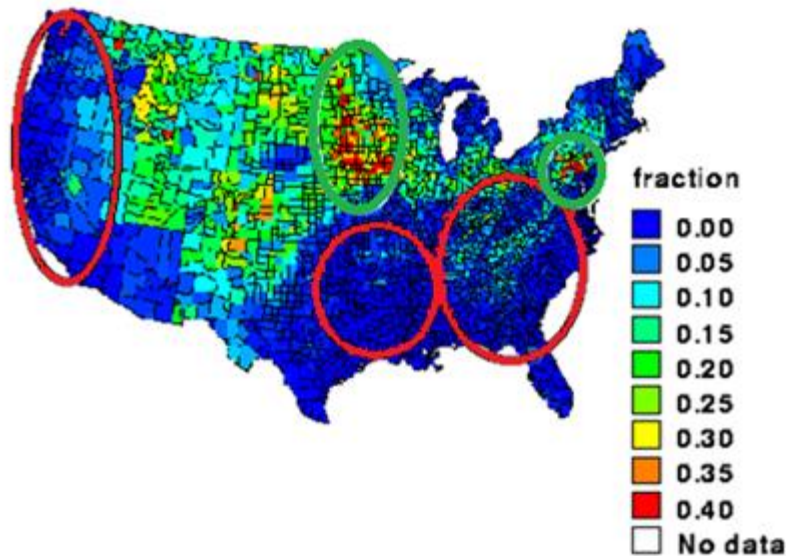
## Lung Cancer vs. Residential Radon Levels



Reduced lung cancer mortality rates with increased residential radon levels in USA counties

# Radon Levels and Lung Cancer in USA

Predicted fraction of homes over 4 pCi/L



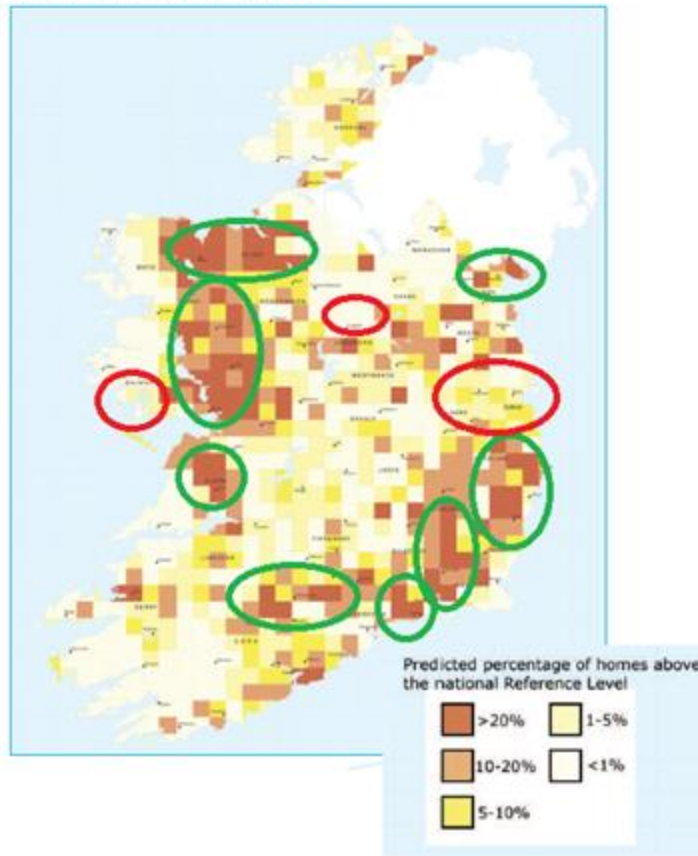
The regions of the country having higher radon levels (red color) marked in green ovals are seen to have generally lower levels of lung cancer (blue color) in the map on the right. The areas that have higher levels of lung cancer (red color) marked in red ovals are generally seen to correspond to lower levels of radon (dark blue color) in the map on the left.

**Green ovals** enclose high radon level areas; **Red ovals** enclose areas having high lung cancer rates. There is little overlap between **red ovals** and **green ovals**.

# IRELAND

## RADON LEVELS

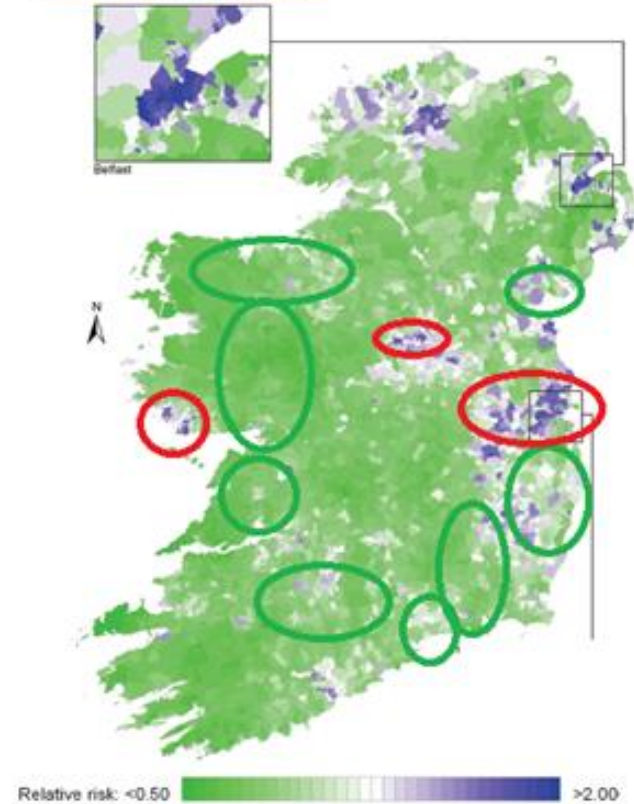
Figure 4. Map of Ireland showing predicted high radon areas.



## LUNG CANCERS

LUNG CANCER

Map 4.1 Lung cancer, smoothed relative risks: both sexes



**Green ovals** enclose highest radon level areas; **Red ovals** enclose areas having highest lung cancer rates. There is little overlap between **red** and **green ovals**.

# Maps of radon and lung cancer have been compared for many other regions

Similar pattern – highest radon level areas having lower lung cancer rates, and highest lung cancer rates corresponding to lower radon levels - is observed for different states of the USA, for different countries in Europe, etc. [See the unpublished report.](#)

Smoking is an important confounder for lung cancers. However, it is highly unlikely that smoking prevalence would always be correlated with radon levels to explain the observed correlation in so many different regions around the world. Therefore, the effect we have observed is likely a real effect, and is consistent with other observations of reduced cancers from low-dose radiation exposures.

In view of all the evidence, we would be justified in utilizing the adaptive response from Low-dose radiation to prevent cancers.



In view of all the data, why have we not utilized low-dose radiation to prevent cancers?

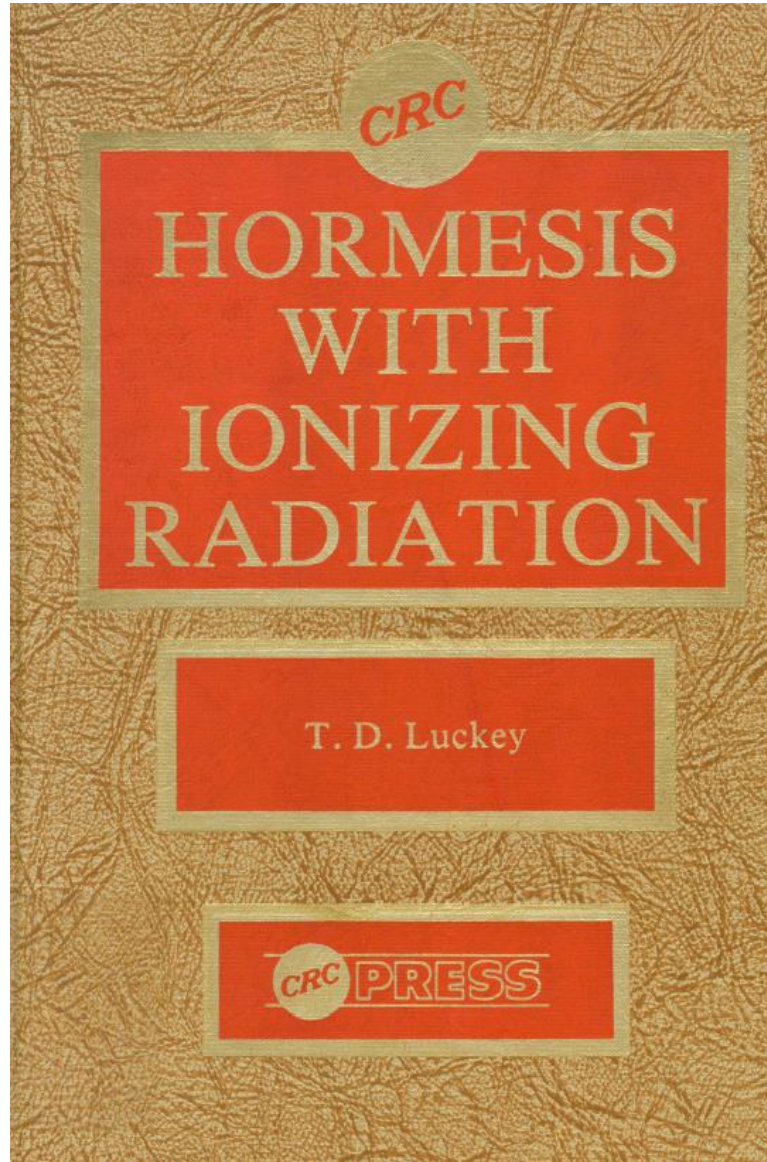
Current radiation safety paradigm and regulations based on the linear no-threshold (LNT) model.

**No threshold means:** slightest increase in radiation dose increases cancer risk

**Results in policies and regulations:**  
Keep radiation doses  
as low as reasonably achievable (ALARA)

**Cannot conduct cancer prevention studies.**

# T.D. Luckey's Book Published in 1980



# What was the Impact of not studying Radiation Hormesis for cancer prevention in the 1980s?

- Current worldwide cancer mortality rate:  
~7.6 M per year
- Assume 10% reduction in cancer mortality from the use of radiation hormesis
- Estimate 760K reduction of cancer deaths per year
- Preventable cancer death toll over last 20 years from not using radiation hormesis ~15M
- Cancer deaths occurring now which could have been prevented using radiation hormesis: >2000 per day

More than 2000 preventable cancer deaths are likely occurring presently every day in the world because of not studying radiation hormesis in the 1980s.

# What is the origin of the LNT hypothesis?

NAS BEAR I Committee was the first advisory body to recommend the use of the LNT hypothesis (1956)

The leading proponent of LNT hypothesis and genetic harm from low-dose radiation was

**Hermann J. Muller.**

He was a member of the Genetics Panel of the BEAR I Committee of NAS

Was there evidence to justify the adoption of the LNT hypothesis by the BEAR I Genetics Panel?

# Muller's Claim of No Threshold Dose Was Not Justifiable

## Herman J. Muller's Nobel Prize Lecture (Muller, 1946)

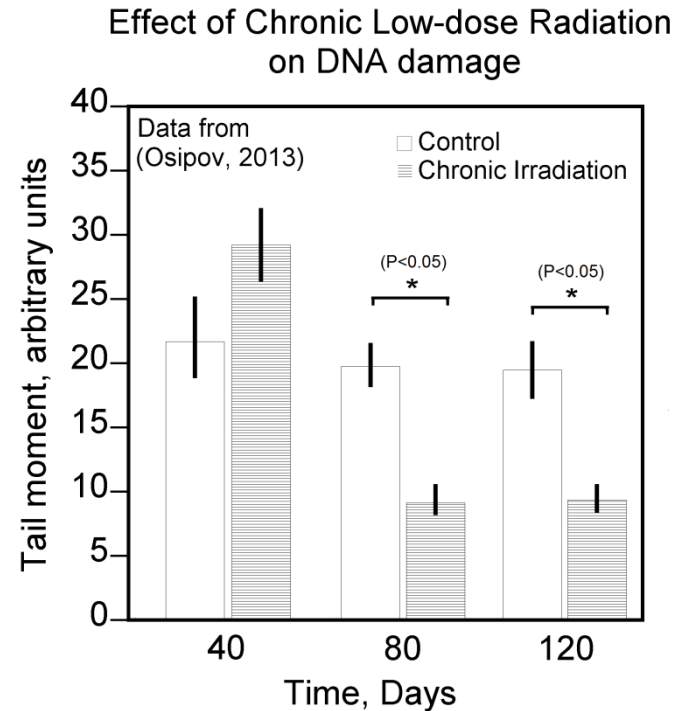
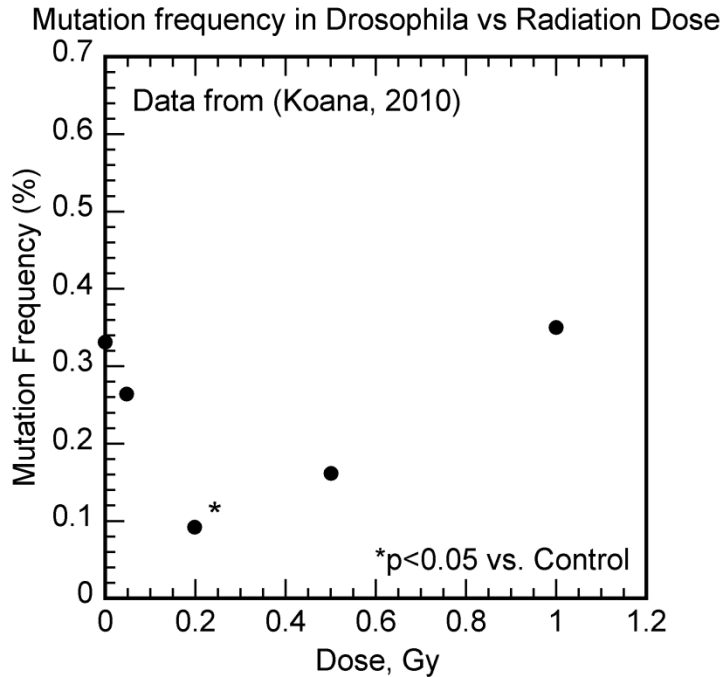
Both earlier and later work by collaborators (Oliver, Hanson, etc.) showed definitely that the frequency of the gene mutations is directly and simply proportional to the dose of irradiation applied, and this despite the wavelength used, whether X- or gamma- or even beta-rays, and despite the timing of the irradiation. These facts have since been established with great exactitude and detail, more especially by Timoféeff and his co-workers. In our more recent work with Raychaudhuri (1939, 1940) these principles have been extended to total doses as low as 400 r, and rates as low as 0.01 r per minute, with gamma rays. They leave, we believe, no escape from the conclusion that there is no threshold dose, and that the individual mutations result from individual "hits", producing genetic effects in their immediate neighborhood.

Note: 400 r is not low dose, and conclusion of no threshold dose is not justifiable based on this observation.

# Additional Reason Why Muller's Conclusion of No Threshold Dose was not Justified

Muller was aware of data – not yet published – that showed presence of a threshold dose for radiation-induced genetic mutations. In spite of this, he made the statement “no escape from the conclusion that there is no threshold dose” in his Nobel Lecture. [\(Calabrese, 2013\)](#)

# Recent studies have shown there is no linearity of dose-response at low doses



Reduction of DNA damage at low doses is due to activation of adaptive protection.



# Recent Findings on the origin of the LNT model

Self-interest by committee members may have motivated the initial adoption of the LNT model by the BEAR I committee in 1956.

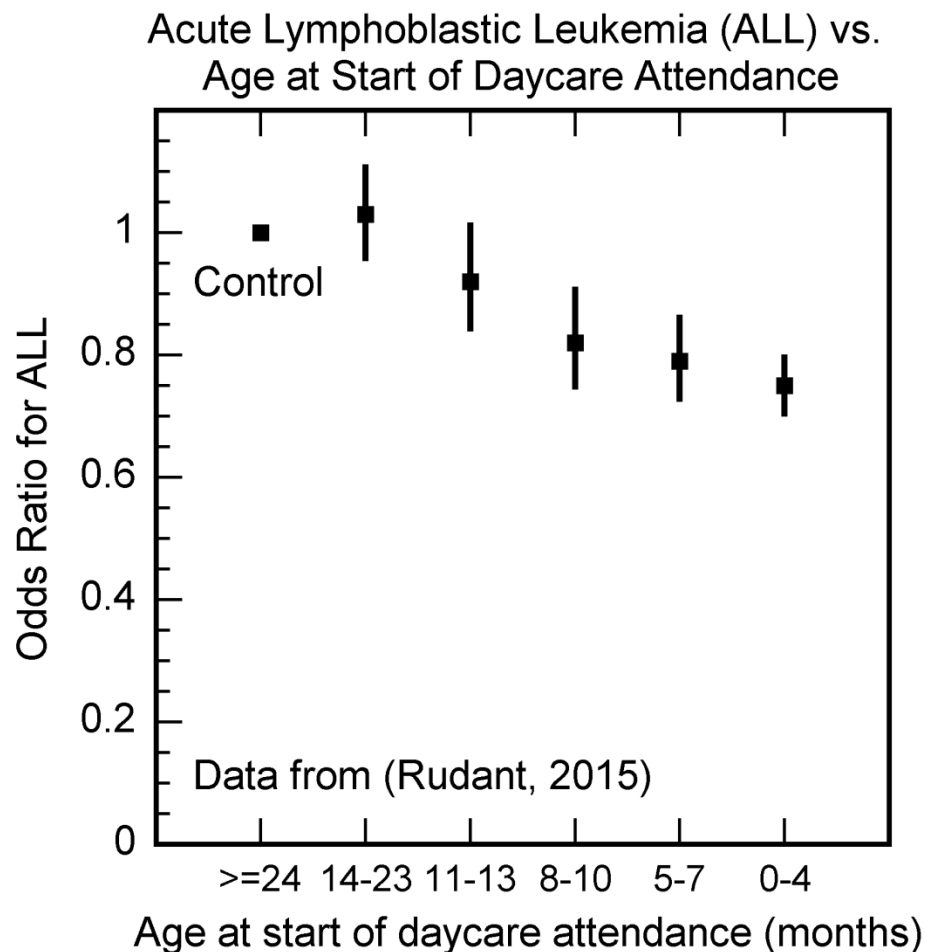
[See: \(Calabrese, 2014\)](#) The Genetics Panel of the NAS BEAR I Committee (1956): epistolary evidence suggests self-interest may have prompted an exaggeration of radiation risks that led to the adoption of the LNT cancer risk assessment model.

The LNT model should be abandoned and a fresh assessment should be performed on the proper approach to radiation safety.

Another way of boosting the  
immune system?

Infection

# Infections stimulate the immune system and reduce leukemias in children



Earlier attendance in daycares, where infants get exposed to more infections resulting in higher stimulation of the immune system, was correlated with reduced leukemias (ALL).

In view of such evidence, we would be justified in exploring the possibility of utilizing the adaptive response from infections to prevent cancers.

# Cancer Treatments using Adaptive Response

# Cancer Treatment using Infection to induce adaptive response

# Century-old Technology to Treat Cancer

## Coley's Vaccine (1890s)

- Killed bacteria vaccine injected into tumor/patient
- Induced immune system response/fever
- tumor regression observed, sometimes complete
- success rate similar to modern therapies
- with advent of radiation therapy and chemotherapy, went out of style

See (Cann, et al., 2003)

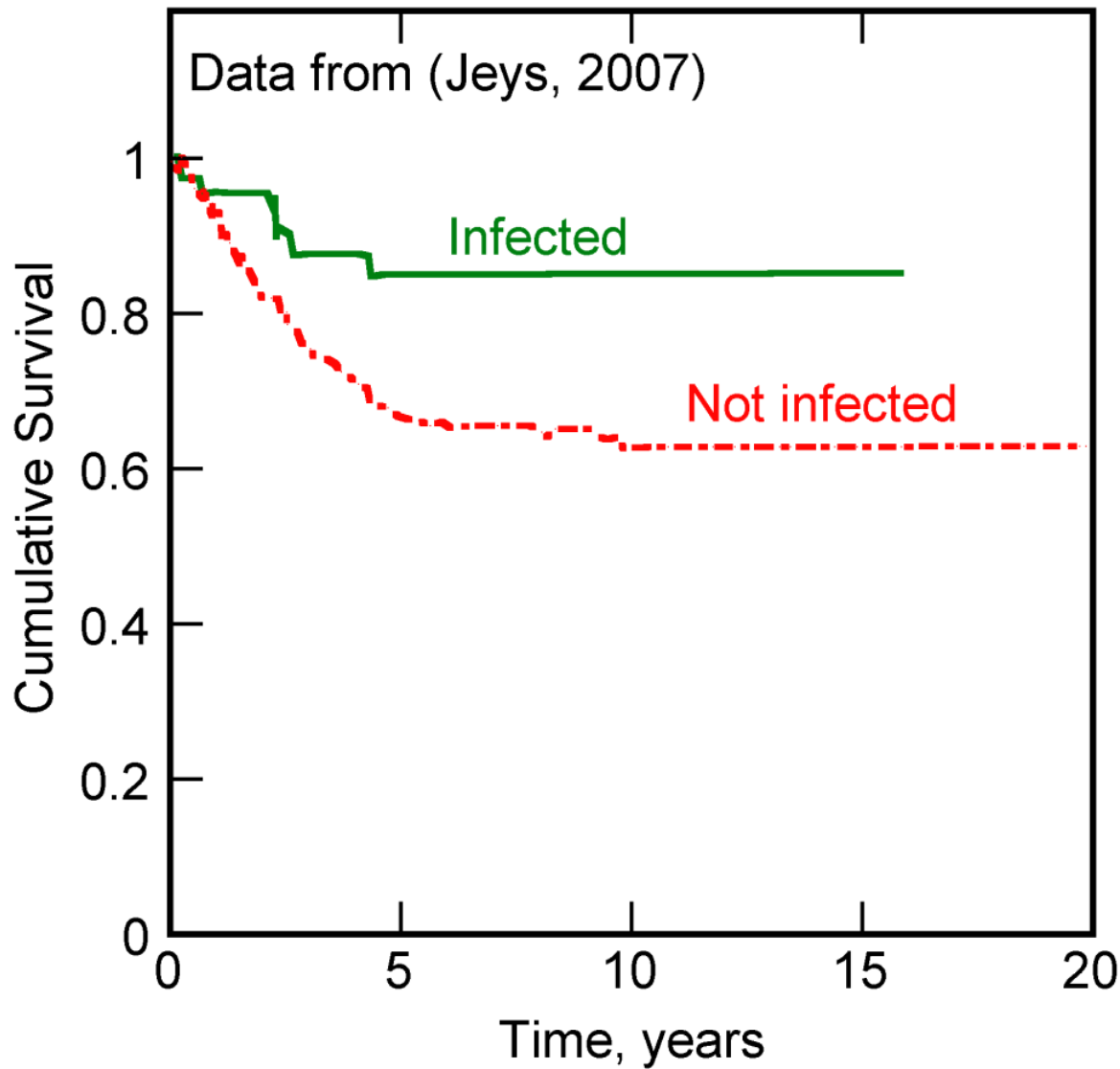
# Century-old Technology to Treat Cancer

- Coley's vaccine was assigned "new drug" status in 1963 by the US Food and Drug Administration, effectively preventing its use on patients.
  - Coley's treatment cannot be used on cancer patients in the USA.
  - Coley's vaccine treatment should be investigated and improved, with modern analytical techniques

See [Cann, et al., 2003](#))



# Survival of Osteosarcoma Patients with and without infections



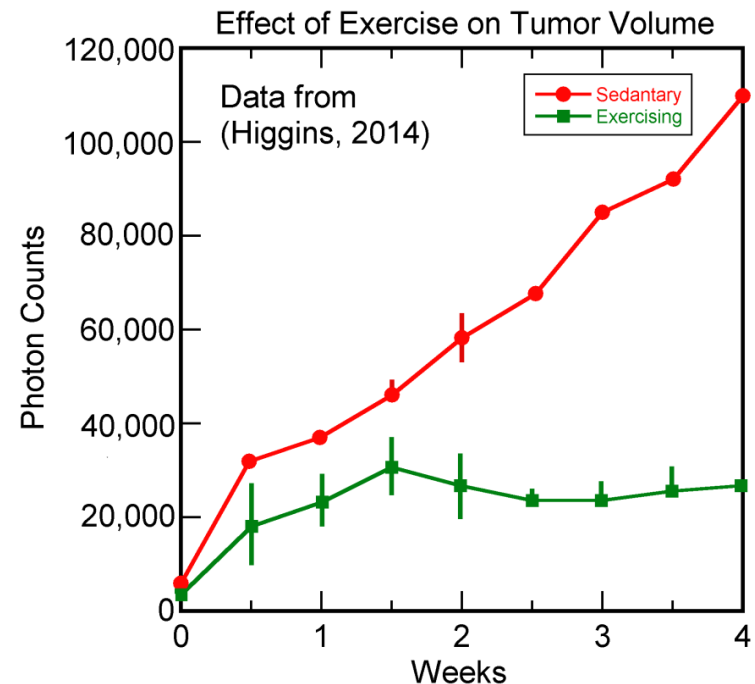
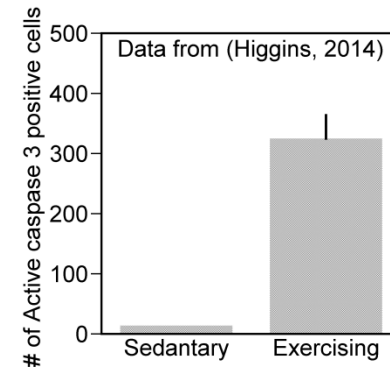
***Infected patients  
had better survival.***

# Cancer Treatment using Exercise to induce adaptive response

# Exercise increased apoptosis and reduced tumor growth in murine lung cancer model

## Methods:

- **Luciferase-tagged A549 lung adenocarcinoma cells – injected in tail vein of nude mice**
- **Bioluminescent imaging - tumor volume proportional to photon counts**
- **Daily wheel running (500-1000 meters/day) after tumors are visualized in optical imaging**
- **4-week study**
- **Western blot and immunohistochemical analyses**

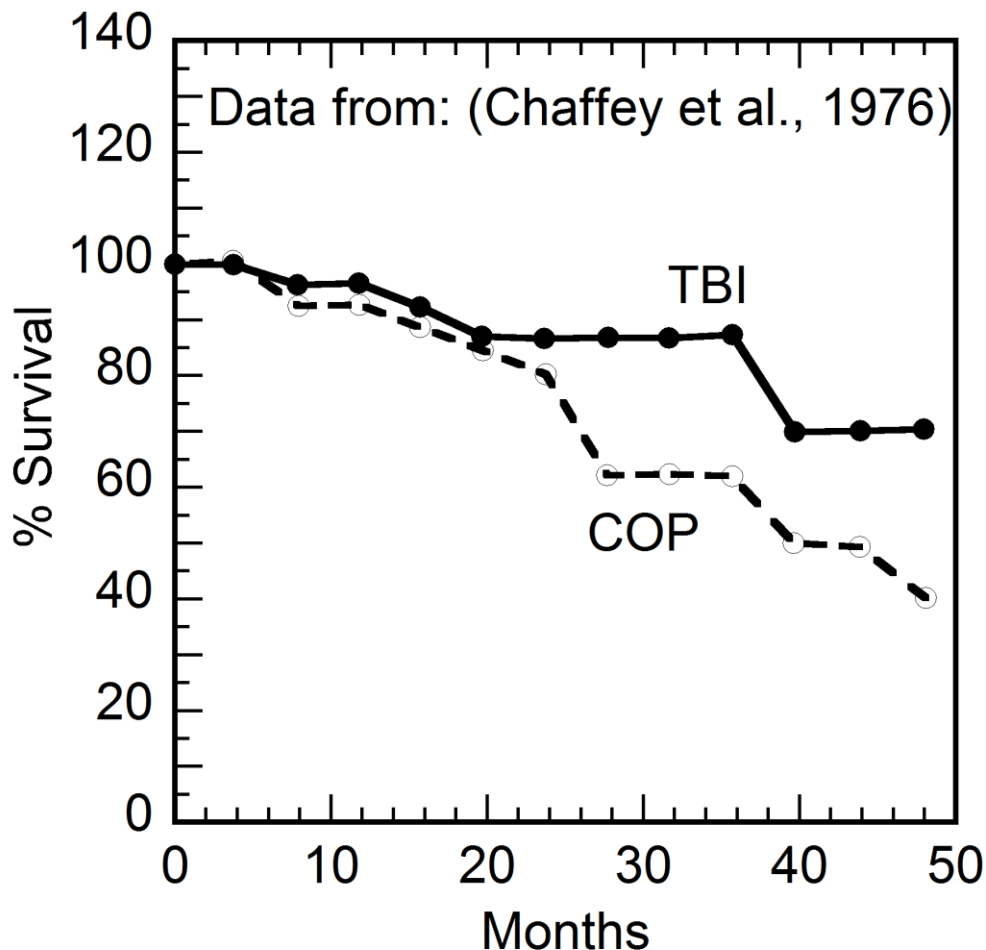


# Exercise to treat early-stage cancers

- Animal studies have shown tumor regression from vigorous exercise
- Human studies of adjuvant exercise have resulted in improved outcomes in cancer patients.
- Exercise alone needs to be investigated as a treatment for early stage cancers, in patients who have not been exercising prior to cancer diagnosis.

# Cancer Treatment using Low-dose radiation to induce adaptive response

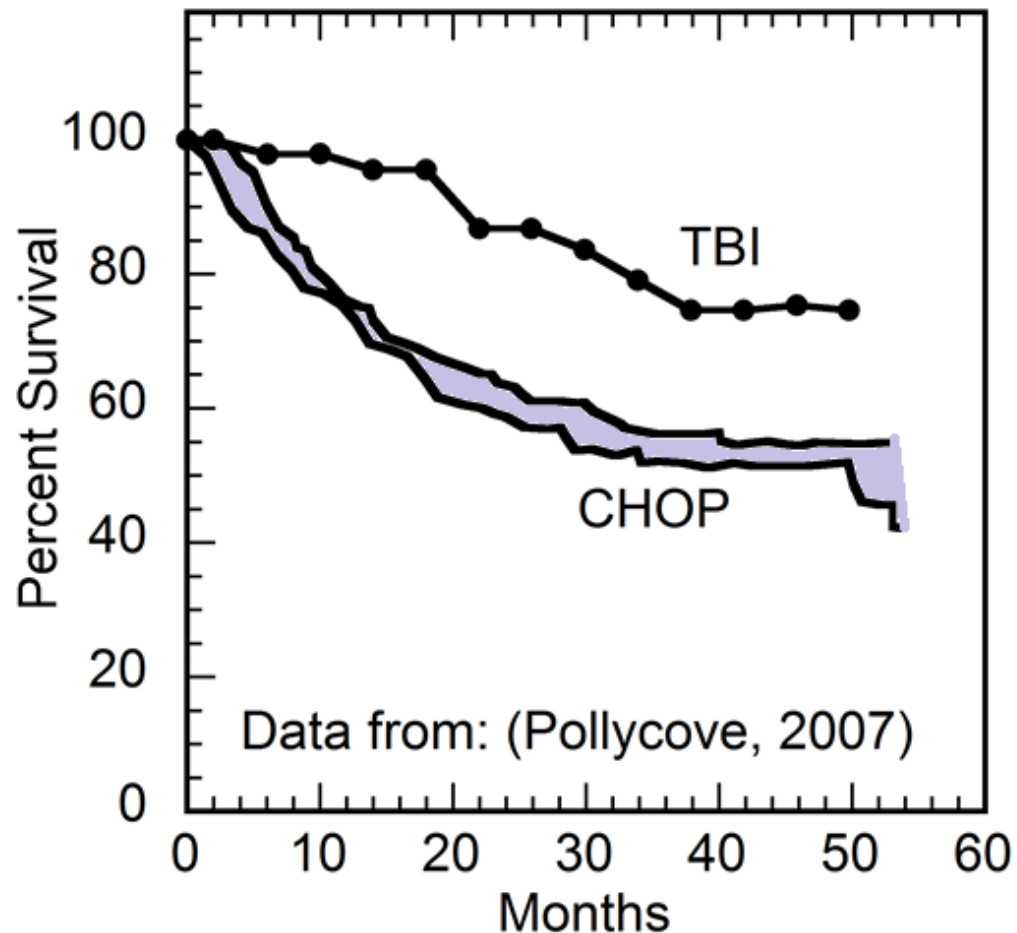
# Survival of Lymphosarcoma Patients Treated with TBI and COP



Low-dose radiation (15 cGy) applied 10 times during 5 weeks (Total dose 1.5 Gy) had a cancer therapeutic effect, performing as well as chemotherapy

TBI – whole body irradiation, 15 cGy, 10 times during 5 weeks. COP - Chemotherapy

## Survival of non-Hodgkin's Lymphoma Patients Treated with TBI or CHOP



Total body irradiation (TBI) (15 cGy) applied 10 times during 5 weeks (Total dose 1.5 Gy) for non-Hodgkin lymphoma patients had a cancer therapeutic effect, performing better than chemotherapy

TBI data from [\(Choi, 1979\)](#)

TBI – whole body irradiation, 15 cGy x 10 over 5 weeks. CHOP - Chemotherapy

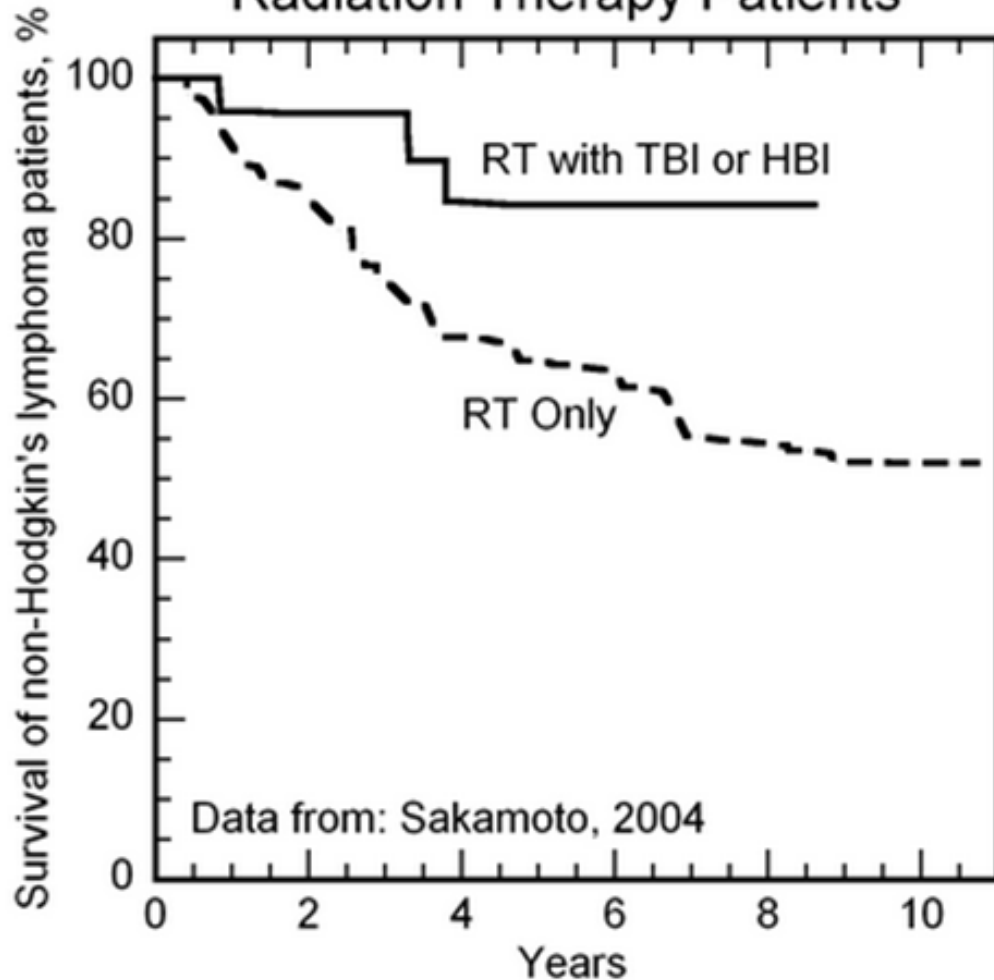
# Concern regarding low-dose radiation total body irradiation for treating cancer

One concern regarding low-dose radiation treatments such as described above is the increased risk of leukemias when the total dose from low-dose radiation treatments exceeded  $\sim 2$  Gy ([Travis, 1996](#)).

In view of this, smaller dose of radiation (less than 1.5 Gy total dose) should be tested to determine its effectiveness in treating cancers, to reduce the chance for increased leukemias.



## Survival of Non-Hodgkin's Lymphoma Radiation Therapy Patients



Improved survival of non-Hodgkin's Lymphoma patients when subjected to 10 or 15 cGy total-body or half-body irradiation (TBI or HBI) interspersed between radiation treatments to the tumor (Total dose=1.5 Gy).

Tumors outside the HBI field also regressed in response to the repeated LDR ([Pollycove 2007](#)), indicating it is likely the systemic adaptive response (e.g. immune enhancement), not tumor cell-killing from the total dose of 1.5 Gy that led to the cancer preventive effect.

# Summary and Conclusions

- Current approaches for prevention and treatment of cancer focusing on cancerous mutations are not satisfactory. Need to try alternative approaches.
- Suppression of the immune system increases cancer risk by a factor of  $\sim 3$ , suggesting immune suppression may be a primary cause of clinical cancers. Using the immune suppression model of cancer, boosting the immune system would reduce cancers.
- Stress from exercise, infection, and low-dose radiation evoke adaptive response including boosted immune system and so would reduce cancers.
- Evidence indicates this approach would be helpful both for cancer prevention and therapy.
- Use of low-dose radiation for cancer prevention and treatment cannot be tested in humans until radiation safety paradigm is changed from the reliance on the LNT model.