Challenges Identifying Radiogenic Cancers at Low Dose & Low Dose Rate
(<100 mGy & <5–10 mGy/h)

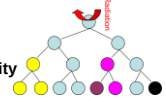
- Weak carcinogen at low doses
- No unique effects (type, latency, pathology)
- High incidence (~44%) & Mortality (24%)
- Limitations of cellular, animal, and radiopidemiological investigations
- Genetic predisposition (influence of oncogenes & tumor suppressor)
- Other potential mediators radiocarcinogensis
- Exposure to other carcinogens
- Incomplete Knowledge of Tumorigenesis & Biological Filtration

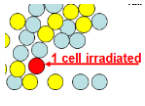
Radiation Induced Cancer: Mechanisms

- Prevailing paradigm is that unrepaired or misrepaired radiation induced complex (cluster) damage to DNA is responsible for the subsequent detrimental effects.

Other potential mediators radiocarcinogensis:

Genomic instability

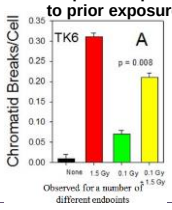




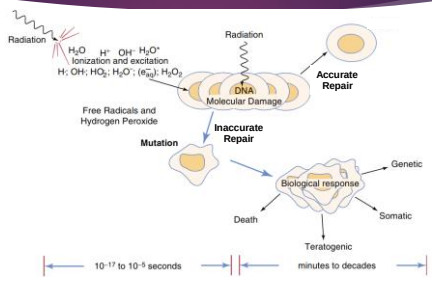
Bystander effects

The relationship of these cellular phenomena to disease outcomes, (if any), is not yet known.

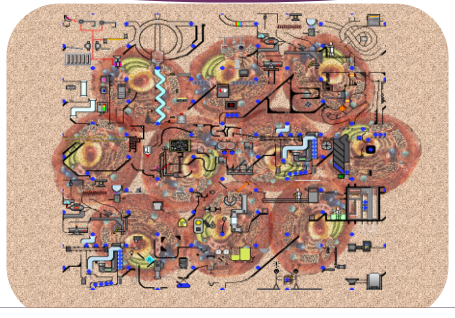
Adaptive response to prior exposure



Biological Effects of Ionizing Radiation

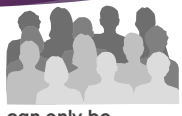


Complexity of Cellular Homeostasis



Radiation Induced Cancer

- Radiation induced cancer observed in animal experiments and in human populations

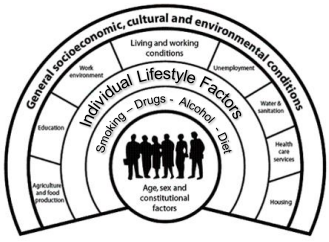


- Dose-response relationship for humans can only be studied via epidemiological investigation of exposed populations
- Dose-response relationship in low dose range (below ~100 mSv) is beyond the resolution of epidemiological investigations to date
- Linear extrapolation down to zero excess dose accepted for radiation protection purposes.

Epidemiology

- *"The best thing about epidemiology is that it studies the organism of interest……..humans"*
- *"But from there it's downhill in a hurry!"*

Potential Confounding Variables



Risk Terminology
Relative Risk & ExcessRelative Risk

- **Relative Risk (RR):** The incidence of disease (i.e., rate) in an exposed population (I_{ep}) divided by the incidence of disease in the population that was not exposed (I_{np})

$$RR = \frac{I_{ep}}{I_{np}}$$

"Relative" to the spontaneous cancer incidence in the population

Expressed in RR/Gy or RR/Sv

- **Excess relative risk (ERR):** RR-1(the background risk)
- A RR of 2 or a ERR of 1 means a doubling of the risk

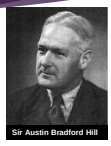
Risk Terminology
Excess Absolute Risk (EAR):

- Expressed as the number of excess cases **(incidence or mortality)** per population size (typically 10^5 or 10^6) per unit of time (typically per yr) and dose
- Also referred to as **"Attributable Risk"**
- Independent on spontaneous cancer incidence
- EAR= Can be express as:

$$\mathbf{EAR} = I_{ep} - I_{np}$$

  - **Annual Attributable Risk** (e.g., #cases/10^5/yr/Sv) or
  - **Lifetime Attributable Risk** (e.g., #cases/10^5/Sv)

Determination of Causality? The "Hill Criteria"


Sir Austin Bradford Hill

Professor Hill developed his list of 9 "criteria" for evaluating the question of causality that continues to be used in epidemiology today. When using them, don't forget Hill's own advice:

"None of these nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis...

What they can do, with greater or less strength, is to help answer the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Cited in Doll, 1991. "Sir Austin Bradford Hill and the progress of medical science." *BJR* 305, 1521-1526.

Evaluating Epidemiological Studies The Hill Criteria

1) **Consistency**
2) **Strength of Association**
3) **Temporality**
4) **Theoretical Plausibility**
5) **Coherence**
6) **Specificity in the Causes**
7) **Dose-Response Relationship**
8) **Experimental Evidence**
9) **Analogy**

#1 Consistency

- **Multiple observations of an association with different populations under different circumstances and similar results for similar exposure scenarios increase the credibility of a causal finding.**
  - **Different methods for assigning dose**
  - **Different study methods (e.g., ecological, cohort & case-control studies)**
  - **Similar RR for a given dose**
  - **Similar cancers from exposed regions**

Examples of Well Established Epidemiological Investigations of Radiation Induced Cancer—The Good

Group Effected	Cancer
Radium Dial Painters	Osteogenic Sarcoma
Early Angiography (Thorotrast)	Liver Cancer & Leukemia
Thymic Irradiation in Children	Leukemia
Multiple Fluoroscopy Women TB & Scoliosis	Breast Cancer
Chernobyl (In Children)	Thyroid Cancer
Uranium Miners	Lung Cancer
Mayak Plutonium production facility workers	Lung, Liver and Bone Cancer
Japanese Survivors (LSS)	Many Solid Cancers & Leukemia (not CLL)

United Kingdom CT Study

(Pearce et al., Lancet 2012)

- Retrospective Cohort record linkage study of leukemia and brain cancer incidence following CT scans to 178,000 persons at ages 0–21.
- Collection of scan data for individual patients was not possible. Average CT machine settings from two national surveys were used.
- Significant dose responses reported

Leukemia & MDS

LSS: Excess relative risk= ~3

excess relative risk per Gy = 36.

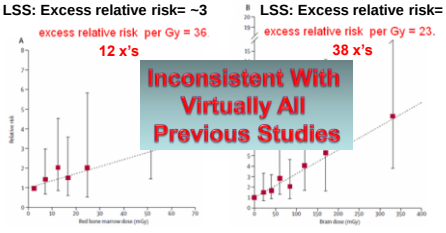
12 x's

Brain

LSS: Excess relative risk= ~0.6

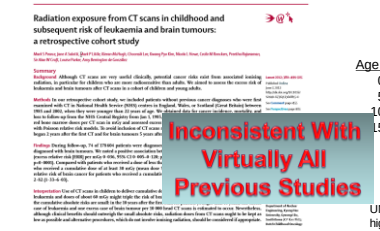
excess relative risk per Gy = 23.

38 x's



Age at Exposure Effect in UK Study Implausible – Risk increased with Age

Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study



Age at exam	ERR/Gy
0-	5
5-	28
10-	37
15-	41

Israeli tinea capitis [SS] – Malignant brain tumours	Average ERR*at 1 Sv
Age at exposure 0–4 years	3.6 (1.0, 9.9)
5–9 years	2.2 (0.8, 5.5)
10–15 years	0.5 (<0, n.a.)

UNSCEAR 2013: "The risk of glioma is highest at < 5 years at irradiation and seems to largely disappear at the age of 20 years or more after irradiation, suggesting that **susceptibility decreases as brain development nears completion**."

Australian CT Study

(Mathews et al., BMJ 2013)

- Data Linkages study of 680,000 children (0-19 y) who received CT scans and 10,000,000 with no record of such exposures.
- Excesses reported for practically all cancers:
  - Digestive organs
  - **Melanoma**
  - Soft tissue
  - Female genita
  - Urinary tract
  - Brain
  - Thyroid
  - Leukaemia (m
  - **Hodgkins lymphoma**

Cancers *not known* to be increased after radiation
are increased:
ma?
s lymphoma?

Inconsistent With Virtually All Previous Studies

Australian CT Study

(Mathews et al., BMJ 2013)

- Data Linkages study of 680,000 children (0-19 y) who received CT scans and 10,000,000 with no record of such exposures.
- Excesses report ers:
  - Digestive orga
  - Melanoma
  - Soft tissue
  - Female genital
  - Urinary tract
  - Brain
  - Thyroid
  - Leukaemia (myeloid)
  - Hodgkins lymphoma

Inconsistent With Virtually All Previous Studies

increased after radiation –
***are not*:**

- **Breast Cancer ?**
- **Lymphoid Leukaemia ?**

Australian CT Study

(Mathews et al., BMJ 2013)

Risks Too High

- "*The risk estimate for all cancers, excluding brain cancer after brain CT is **statistically incompatible** with the Japanese study on atomic bomb survivors"*

ERR/Sv	
A-Bomb Data-RERF	Mathews et al., BMJ 2013
~3	~27 ?

UNSCEAR

Inconsistent With Virtually All Previous Studies

#2 Strength of Association

The stronger the relationship between the risk factor and the disease the less likely it is that the relationship is due to confounding variables

Smoking and Carcinoma of the Lung.

R Doll and A B Hill
British Medical Journal (1950)

BRITISH MEDICAL JOURNAL
LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG
PRELIMINARY REPORT

RICHARD DOLL, M.D., M.R.C.P.
Member of the Statistical Research Unit of the Medical Research Council

A. BRADFORD HILL, Ph.D., D.Sc.
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical

Very Strong Association

TABLE IV.—*Proportion of Smokers and Non-smokers in Lung-carcinoma Patients and in Control Patients with Diseases Other Than Cancer*

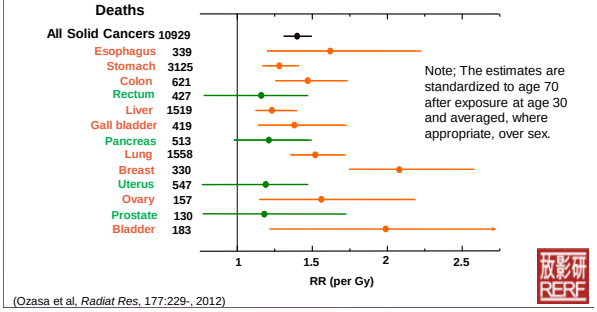
Disease Group	No. of Non-smokers	No. of Smokers	Probability Test
Males: Lung-carcinoma patients (649)	2 (0·3%)	647	P (exact method) = 0·00000064
Control patients with diseases other than cancer (649)	27 (4·2%)	622	

Relative Risk For Smoking & Lung Cancer ~10-30

"We therefore conclude if smoking is a factor, and an important factor, in the production of carcinoma of the lung."

Weak ------Association------Moderate

Relative Risk (RR) per Gy Solid Cancers (LSS Mortality, 1950-2003)



Note; The estimates are standardized to age 70 after exposure at age 30 and averaged, where appropriate, over sex.

(Ozasa et al, *Radiat Res*, 177:229-, 2012)

放影研 RERF

Radiation is a Weak Carcinogen

Hypothetical Study
Statistical Power Calculation

- Baseline cancer mortality risk is known to be 10%
- Estimated radiation-related excess risk is 10% at 1 Gy and proportional to dose between 0 and 1

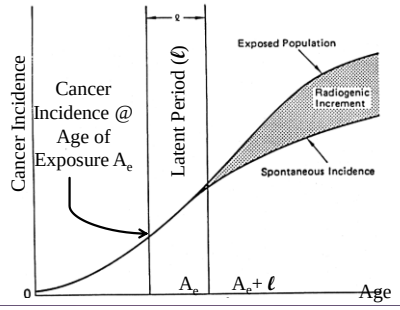
Radiation Dose	Excess Risk	Total Risk	Population size (N) needed for 80% power to detect the excess risk at the 5% significance level
1 Gy	10%	20%	80
100 mGy	1%	11%	6390
10 mGy	0.1%	10.1%	620,000
1 mGy	0.01%	10.01%	61,800,000

#3 Temporality

The exposure must precede the disease by a reasonable amount of time, i.e., a cause must precede an effect in time.

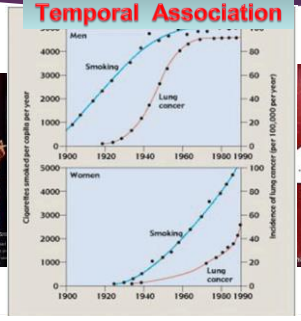
Longitudinal studies have shown that a person must smoke for years (decades) before carcinogenesis and cell transformations lead to lung cancer.

Temporality



Smoking & Lung Cancer

Plausible & Consistent Temporal Association



Mean Latent Periods for Tumor Induction by Radiation

Tumor Type	*~Mean Latent Period (Yrs)	~Total Period of Expression*
Brain	27	>50
Colon	26	>50
Skin & Lung	25	>50
Breast	22	>50
Stomach	14	>50
Salivary & Thyroid	20	>50
Bone	14	30
Leukemia	9	30

*** Varies with dose and age @ exposure**

Latent Period

-- Interval between initiation & transformation to unrestrained cell growth

+

-- Interval of progression to clinical diagnosis or presentation

Minimum Latent Period
-Solid Cancers ~7-10 yrs
-Leukemia ~2-3

Australian CT Study

(Mathews et al., BMJ 2013)

Temporal Association Not Plausible or Consistent

- "**Minimum** **tumors**, ranging from **10 years** to many years after the initial radiation exposure." *Linet et al. CA CANCER J CLIN 2012;62:75–100*

- *The appearance within 5 years of first CT scan of a significant excess of solid cancers is **implausibly early**."*

UNSCEAR

UNSCEAR 2013: EFFECTS OF RADIATION EXPOSURE OF CHILDREN
(Fred Mettler – Former ICRP C3 Chair)

#4 Theoretical Plausibility

- It is easier to accept an association as causal when there is a rational and theoretical basis for such a conclusion supported by known biological and other facts.
  - ❖DNA Damage from Ionization of Tissue Irradiated
  - ❖Complex Cluster Damage
  - ❖DSB Repaired Primarily by Error Prone NHEJ
  - ❖Biological Filtration (e.g., cell cycle check points) Not 100% Effective

Australian CT Study

(Mathews et al., BMJ 2013)

- Data Linkages study of 680,000 children (0-19 y) who received CT ... and 10,000,000 with ... record of such exp...
- Excesses ... :
  - Digestive organs
  - Melanoma
  - Soft tissue
  - Female genital
  - Urinary tract
  - Brain
  - Thyroid
  - Leukaemia (myeloid)
  - Hodgkins lymphoma

Not Plausible or Consistent Established Relationships

Brain cancers increased –

❖ *whether or not the brain was exposed ?*

#5 Coherence

❖A cause-and-effect interpretation for an association is clearest when it does not conflict with what is known about the variables under study and when there are no plausible competing theories or rival hypotheses. In other words, the association must be coherent with other knowledge.

United Kingdom CT Study

(Pearce et al., Lancet 2012)

Not Coherent – A Plausible Alternative Explanation Exists

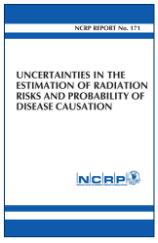
Major Epider

No Information on Why Scans Performed

See NCRP Report 171 (2012) (Chair: Julian Preston)

" **Children who receive frequent examinations** may have some underlying disability related to the outcome of interest. That is, a child who receives multiple CT exams of the head may have a central nervous system disorder that is prompting such examinations that eventually results in a cancer diagnosis." – **Reverse Causation** –

X-rays aren't causing cancers, cancers are causing X-rays.



How Much an Impact Could It Have Had?

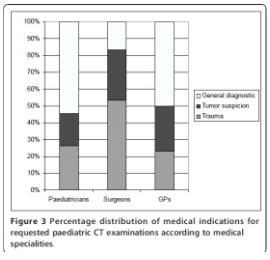
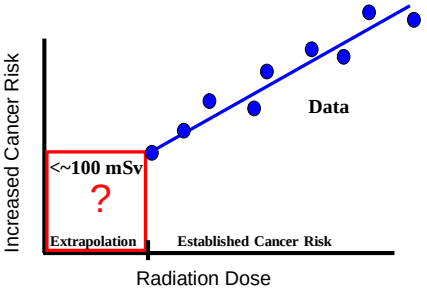


Figure 3 Percentage distribution of medical indications for requested paediatric CT examinations according to medical specialities.

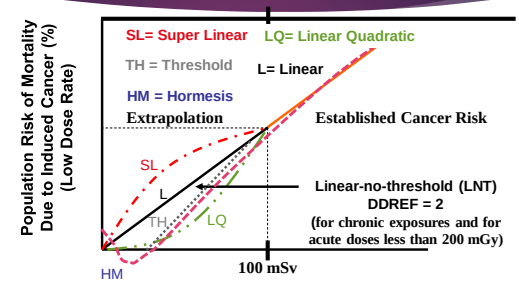
Referral for Tumor Suspicion 20-30%

Merzenich et al. BMC Health Services Research 2012, 12:47 http://www.biomedcentral.com/1472-6963/12/47

Radiation Induced Cancer Risk

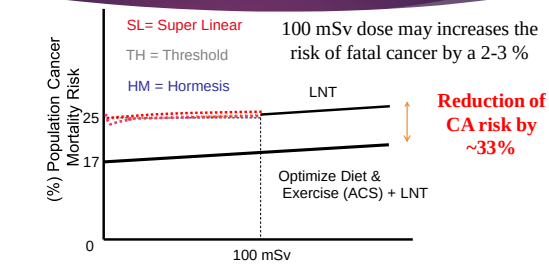


Models of Radiation Induced Excess Cancer Risk



✓ Risk of fatal cancer ~ 5% per 1 Sv --100 mSv dose Theoretical Increase ~22% to 22.5%

Perspective on Radiation Induced Cancer



✓ According to the American Cancer Society Optimization of Diet & Exercise would lower cancer mortality by ~1/3 in the US Population.

Questions to Ask when Reviewing an Epidemiologic Study

- Are there any methodological flaws in the study that should be considered when making conclusions?
- Does the research design fit the stated purpose of the study?
- What are the inherent limitations of this type of study?
- Are the study's results generalizable to other groups?
- How do these results compare with the body of research on the subject?

Questions to Ask when Reviewing an Epidemiologic Study

- What is the magnitude of statistical significance of the results presented?
- Could the study be interpreted to say something else?
- Are the conclusions supported by the data and what would be the real world implications if they are true?

Summary

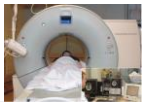
- The notion of cause has become more complex, with most health outcomes having multiple component causes.
- Distinguishing which of these are necessary or sufficient and their relative importance is central to preventive efforts.
- Bradford Hill's criteria provide a framework against which exposures can be tested as component causes, but they are not absolute.
- As with statistical p-tests, the criteria of causality must be viewed as aids to judgment, not as arbiters of reality.

Summary

- ***Cumulative exposure*** to high doses of diagnostic radiation ***may cause cancer*** later in life
- We'll likely never detect cancer increases following a single CT. It may be tiny, it may be zero. But multiple CTs are a concern – thus medical benefit should be clear and dose ***ALADA*** (As Low As Diagnostically Acceptable)
- Several current studies of CT & Cancer are not interpretable because of the potential for confounding by indication absence of individual dosimetry, and multiple inconsistencies.
- Good epidemiology could address the reasons for examination, provide individual dosimetry, and attempt to capture "missing doses".
- Meanwhile, it would seem prudent to assume that the low doses of radiation received during a CT scan may produce a small additional risk of cancer, and clinical practice might be guided by this assumption.

Summary

- **Radiation protection in medical imaging is based on two principles:**
  - *(i)* ***justification*** *of the procedures*
  - *(ii)* ***optimization*** *of the procedure to manage the radiation dose commensurate with the medical objective.*
- CT remains a powerful tool in the diagnosis of illness and there is little doubt that the benefits of its use vastly outweigh potential risks **when** it is **appropriately prescribed and properly performed** (i.e. justified and optimized).



The Ugly

The New York Times http://nyti.ms/1hUyUlq

Such Statements
– Unnecessarily Inflammatory
– Create Undo Anxiety in Patients
– Is a Violation of a Responsibility to do No Harm

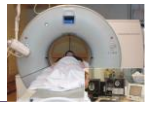
important culprit may be our own medical practices: We are silently irradiating ourselves to death.

Neither doctors nor patients want to return to the days before CT scans. But we need to find ways to use them without killing people in the process.

Summary

Is Medical Radiation Exposure Dangerous?

- ***This is not a scientific question***
- ***Answers will vary based on a number of factors***
- ***Two equally well informed individuals can rightly have different answers***
- ***Our responsibility is to:***
  - ***Communicate what we know as clearly and responsibly as possible***
  - ***Adhere the principals of optimization & justification***
  - ***Continue to improve upon our knowledge of effects at low dose***



Thank You For Your Attention