Correlation, Causation and the Assessment of Radiation Risk From Epidemiological Investigations: The Good, the Bad & the Ugly

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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 radiocarcinogenesis
- 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 radiocarcinogenesis:
  - Genomic instability
  - Bystander effects

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

- Adaptive response to prior exposure

  ![Graph showing adaptive response to prior exposure](attachment:image.png)
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.
“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 & Excess Relative 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

\[
EAR = I_{ep} - I_{np}
\]

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”**

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?"


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**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

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**#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

<table>
<thead>
<tr>
<th>Group Effected</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium Dial Painters</td>
<td>Osteogenic Sarcoma</td>
</tr>
<tr>
<td>Early Angiography (Thorotrast)</td>
<td>Liver Cancer &amp; Leukemia</td>
</tr>
<tr>
<td>Thyroid Irradiation in Children</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Multiple Fluoroscopy Women TB &amp; Scoliosis</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>Chernobyl (in Children)</td>
<td>Thyroid Cancer</td>
</tr>
<tr>
<td>Uranium Miners</td>
<td>Lung Cancer</td>
</tr>
<tr>
<td>Mayak Plutonium production facility workers</td>
<td>Lung, Liver and Bone Cancer</td>
</tr>
<tr>
<td>Japanese Survivors (LSS)</td>
<td>Many Solid Cancers &amp; Leukemia (not CLL)</td>
</tr>
</tbody>
</table>

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 risks ~ 3
excess relative risk per Gy = 36
~12 x's

Brain
LSS: Excess relative risks ~ 0.6
excess relative risk per Gy = 23.
~38 x's

Inconsistent With Virtually All Previous Studies

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

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."
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 genital
- Urinary tract
- Brain
- Thyroid
- Leukaemia (myeloid)
- Hodgkins lymphoma

Inconsistent With
Previously All
Previous Studies

Cancers not known to be increased after radiation
Melanoma?
Hodgkins lymphoma?

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Excesses reported for practically all cancers:
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- Brain
- Thyroid
- Leukaemia (myeloid)
- Hodgkins lymphoma

Inconsistent With
Previously All
Previous Studies

Increased after radiation –
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"
The stronger the relationship between the risk factor and the disease the less likely it is that the relationship is due to confounding variables.

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.”

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

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

#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.
Smoking & Lung Cancer
Plausible & Consistent Temporal Association

Mean Latent Periods for Tumor Induction by Radiation

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>~Mean Latent Period (Yrs)</th>
<th>~Total Period of Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>27</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Colon</td>
<td>26</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Skin &amp; Lung</td>
<td>25</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Breast</td>
<td>22</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Stomach</td>
<td>14</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Salivary &amp; Thyroid</td>
<td>20</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Bone</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Leukemia</td>
<td>9</td>
<td>30</td>
</tr>
</tbody>
</table>

* 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 latency periods are longer for solid 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 2013: EFFECTS OF RADIATION EXPOSURE OF CHILDREN (Fred Mettler – Former ICRP C3 Chair)
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 scans and 10,000,000 with no record of such exposure.
- Excesses of Not Plausible or Consistent Established Relationships:
  - Digestive organs
  - Melanoma
  - Soft tissue
  - Female genital
  - Urinary tract
  - Brain
  - Thyroid
  - Leukaemia (myeloid)
  - Hodgkin's lymphoma

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.
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.

United Kingdom CT Study
(Pearce et al., Lancet 2012)

How Much an Impact Could It Have Had?

Referral for Tumor Suspicion
20-30%

Radiation Induced Cancer Risk

Increased Cancer Risk

Data

Radiation Dose

<-100 mSv

Extrapolation

Established 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

100 mSv dose may increases the risk of fatal cancer by a 2-3 %

Reduction of CA risk by ~33%

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

Such Statements:
- Unnecessarily Inflammatory
- Create Undue Anxiety in Patients
- Is a Violation of a Responsibility to do No Harm

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