

### An analysis of recent literature regarding radiation risk

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### An analysis of recent literature regarding radiation risk

Goals:  
Examine adequacy of peer review process  
regarding scientific articles on radiation effects

Learning objectives:  
" To gain insight into the critical evaluation of  
scientific literature on bioeffects  
" To understand how to distinguish causation  
from correlation or association

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### Steven J. Gould

Natural History 95, 1986, p 22



" ...most interesting errors in the history of  
science reflect just a few common fallacies of  
reasoning.  
" My primary candidate is the confusion of  
correlation with a causality.  
" ...we often make the false inference and  
advocate a causal link from correlation alone.

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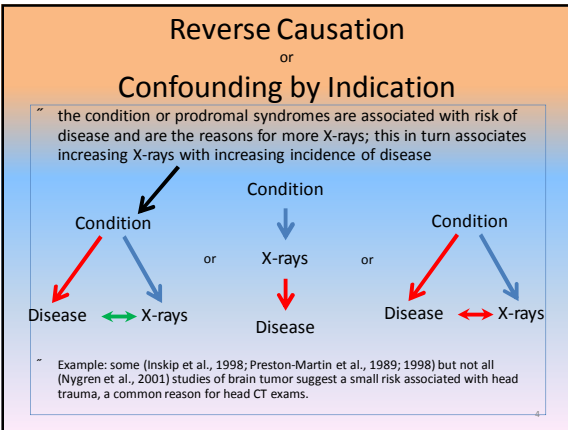
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**RESEARCH** CMAJ

**Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction**

Mark J. Eisenberg MD MPH, Jonathan Afialo MD MSc, Patrick R. Lawler MD, Michal Abrahamowicz PhD, Hugues Richard MSc, Louise Pilote MD MPH PhD

See related commentary by Mercuri and colleagues, page 413

**ABSTRACT**

low-dose ionizing radiation in the first year after acute myocardial infarction. The cumulative exposure to radiation from cardiac procedures was 5.3 millisieverts (mSv) per patient-year, of which 84% occurred during the first

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**Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction**

- ~ Retrospective review of 82,861 pts
- ~ 77% (~63,803) had at least one cardiac imaging or therapeutic procedure in first year after MI
- ~ Dose from studies estimated as **effective dose**
- ~ 12, 020 cancers diagnosed in follow-up period of 1 – 5 years after MI
- ~ Dose-response relationship found (excess of relative risk of cancer increased at rate of 3% per 10 mSv)
- ~ Data corrected for age and sex of subjects in database

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Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction

Interpretation:

“ Exposure to low-dose ionizing radiation from cardiac imaging and therapeutic procedures after acute myocardial infarction is **associated** with an increased risk of cancer.

Issue:

“ Is association causal or result of other associated factor not taken into account?

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Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction

Critique:

“**Percutaneous coronary intervention is a high dose procedure.**

“**Skin doses from such procedures are in the Gray range even though effective dose is 15 mSv.**

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Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction

Critique:

**Effective dose not applicable for risk research**

**Organ doses needed to study correlation with cancer sites. Data available but not used.**

**Were cancers located in areas receiving highest doses from procedures?**

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Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction

**Critique:**  
Minimum latent period 5 years for solid cancers and 2 years for leukemia (UNSCEAR, BEIR, ICRP, NCRP)  
Short follow-up period negates possible causal link to cancers other than leukemia

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Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction

**Critique:**  
Risk factors known to be correlated with heart disease and cancer not considered: smoking, diet, body mass index, exercise.  
These factors could cause conditions that increase number of imaging procedures or imaging procedures might increase likelihood of earlier diagnosis of existing cancer.  
Discussion warranted.  
Note: ACS predicts 1,600,000 new cancer cases and 580,000 deaths from cancer in U.S. in 2012. A third will stem from tobacco use and another third will result from excessive weight, poor nutrition or physical inactivity.

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

Mark S Pearce, Jane A Salotti, Mark P Little, Kiran M D'Augh, Choansik Lee, Kwang Pyo Kim, Nicola J Howe, Cecile M Ronckens, Preetha Rajaraman, Sir Alan W Craft, Louise Parker, Amy Berrington de Gonzalez

www.thelancet.com Published online June 7, 2012

Figure A: Relative risk vs. Red bone marrow dose (mSv). The y-axis ranges from 0 to 8, and the x-axis ranges from 0 to 250. Data points are shown with error bars and a linear regression line. The relative risk increases from approximately 1.0 at 0 mSv to about 3.5 at 250 mSv.

Figure B: Relative risk vs. Brain dose (mSv). The y-axis ranges from 0 to 20, and the x-axis ranges from 0 to 400. Data points are shown with error bars and a linear regression line. The relative risk increases from approximately 1.0 at 0 mSv to about 15.0 at 400 mSv.

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### What they did

- ❑ Retrospective cohort study of leukemia and brain cancers each in ~180,000 pts under 22 yo at time of CT scan
- ❑ Doses to brain and red bone marrow estimated based on national data
- ❑ Excluded first 2 years after exposure for Leuk and first 5 years for Brain Ca.
- ❑ Analyzed trends with multiple factors

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### Results and conclusions

- ❑ Doses of 50 mGy to RBM might almost triple risk of leukemia
- ❑ Dose of 60 mGy might triple risk of brain cancer
- ❑ Absolute risks are small ~1/10000 each of leukemia and brain tumor per head CT in first 10 years

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### Context

- ❑ Good discussion of results and comparisons with other studies
- ❑ Clinical symptoms leading to CT not available in data
- ❑ Performed sensitivity test to try to see if there was bias for reverse confounding - none detected
- ❑ Placed findings in rational perspective on benefit/risk

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## Things to be considered

- ❑ Techniques and doses were not available, used generalized information to assess dose. Effects of this omission not discussed in paper.
- ❑ Trend of risk of brain tumor with age opposite that of Atomic bomb survivors and not discussed
- ❑ Trend of leukemia in ABS was non-linear, discrepancy not discussed
- ❑ Reverse confounding might involve long latent periods, not discussed

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## Conclusion

- ❑ Overall paper gets high marks for quality but assertions that relationship is causal and not a case of reverse confounding still questionable
- ❑ Paper not definitive - multiple unanswered questions like effect of generalized dosimetry on results
- ❑ Message to practice same as before: don't use radiation in medicine without assessing the real need and potential benefit/risk - eliminate unnecessary use

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Radiology

### The Information Imperative: Is It Time for an Informed Consent Process Explaining the Risks of Medical Radiation?!

Richard C. Gosselin, MD  
Jose M. Alvarez, MD  
Jorge Ellis, Jr, MD, PhD  
Eugene Pomeroy, MD

Providing information to patients about their choices processes and the expanded medical procedures to remedy them are a constant requirement in all of medicine. This forms the

ions in the early 1970s, one in California (1) and one in Washington, District of Columbia (2), that hold that there is a duty owed to patients by health care providers to obtain their informed con-

It is our contention that risks of medical radiation should be conveyed in an active manner.

The seventh assembly of the Committee on Biologic Effects of Ionizing Radiation (BEIR) report of the National Academy of Sciences describes that 10 mSv of radiation exposure carries with it a 1 in 1000 chance of future malignancy in a 40-year-old adult (8). This risk is considerably greater in children, approaching 1 in 100 in a 1-year-old infant girl (9).

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**There is controversy over the certitude of radiation risk estimates.... The core of this controversy is the linear no-threshold risk model ... which is endorsed by ...**

- International Commission on Radiological Protection,
- National Academy of Sciences BEIR committee,
- United Nations Scientific Committee on the Effects of Atomic Radiation,
- U.S. Food and Drug Administration.

**Question:**

**For what purpose or use is it endorsed?**

- a. To determine the true risk for patients
- b. As inaccurate gauge to provide guidance for prudent use in medicine
- c. As inaccurate gauge to provide guidance on regulation of exposures to workers and public

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The BEIR VII executive summary states that “the risk of cancer proceeds in a linear fashion at lower doses without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans”. Low-dose is defined by the BEIR VII committee as doses in the range of near zero up to about 100 mSv (0.01 Sv).

**Observation:**

- BEIR VII also tells us to view estimates of LAR with a great deal of skepticism.
- In absence of direct information, idea that low doses induce cancer remains hypothetical.

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**Moreover, the great majority of published articles that directly examine medical radiation ... suggest a noninsignificant risk.**

*A recent article (CMAJ Cardiac Study) described a dose-dependent relationship between exposure to ionizing radiation from cardiac procedures, with a 3% increase in risk for cancer development over a mean follow-up period of 5 years for every additional 10 mSv experienced among a cohort of 82 861 patients.*

**The cited article is same article on cancer and MI that was reviewed previously:**

- 1. uses effective dose, not organ dose
- 2. involves a very short latent period
- 3. neglects smoking, diet, obesity, exercise as factors

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Antepartum Dental Radiography and Infant Low Birth Weight  
 Philippe P. Hujuel, PhD; Anne-Marie Bollen, PhD; Carolyn J. Noonan, MS; Michael A. del Aguila, PhD; JAMA, April 28, 2004—Vol 291, No. 16 1987

**Hypothesis:**

**Dental x-rays during pregnancy deliver doses to the thyroid, hypothalamus, or pituitary gland that cause low-birth-weight.**

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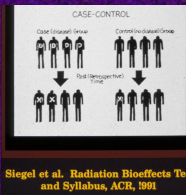
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Antepartum Dental Radiography and Infant Low Birth Weight

- ❑ A population-based case-control study.
- ❑ Cases: 1117 women with low-birth-weight infants (2500 g)
- ❑ 4468 control pregnancies resulting in normal-birth-weight infants (2500 g) randomly selected
- ❑ Doses estimated at ~1 mGy to thyroid. **No account made for use of thyroid shields. Doses possibly lower.**



Sligel et al. Radiation Bioeffects Test and Syllabus, ACR, 1991

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Antepartum Dental Radiography and Infant Low Birth Weight

**Fourteen potential confounding factors investigated, including:**

- ❑ **Self-reported maternal smoking during pregnancy\*** (X)
- ❑ **Kessner Adequacy of Prenatal Care Index (X)** (more x-rays for inadequate care)
- ❑ **Ethnicity (asian, black, white, other)\*** (X)

\*Confounding factor correlated with LBW  
 X = correlated with dental x-rays

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**Antepartum Dental Radiography and Infant Low Birth Weight**  
Philippe P. Hujoel, PhD; Anne-Marie Bollen, PhD; Carolyn J. Noonan, MS; Michael A. del Aguila, PhD; JAMA, April 28, 2004—Vol 291, No. 16 1987

- Exposure higher than 0.4 mGy (mean 1.2 mGy) during gestation rendered a statistically significant excess of low-birth-weight infants
- There was evidence of a dose-response relationship
- No effect was observed for doses less than 0.4 mGy (mean 0.2 mGy).

*In other words, only patients with higher dose studies demonstrate the effect, a difference in means of 1 mGy.*

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**Antepartum Dental Radiography and Infant Low Birth Weight**

Authors' notes and answers to letters:

- ~ Potentially incomplete accounting for smoking due to bias in recording this habit
- ~ Potentially incomplete correction for ethnicity and its associated risk factors
- ~ Potential uncertainty in relationship of severity of disease or trauma that is correlated with both x-rays and LBW - but they imply this not likely

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**Antepartum Dental Radiography and Infant Low Birth Weight**  
Philippe P. Hujoel, PhD; Anne-Marie Bollen, PhD; Carolyn J. Noonan, MS; Michael A. del Aguila, PhD; JAMA, April 28, 2004—Vol 291, No. 16 1987

Conclusion:

Dental radiography during pregnancy is **associated** with low birth weight, specifically with term low birth weight.

the observation that both orthodontic and endodontic therapies were associated with TLBW (10 cases) is more suggestive of dental radiography being **associated** with LBW than dental diseases or procedures.

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Antepartum Dental Radiography and Infant Low Birth Weight

Authors' notes and answers to letters:

~ Poor oral health might indicate poor nutrition – but they “doubt” this because used only well-off individuals and correction for care index led to higher correlation for X rays.

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Antepartum Dental Radiography and Infant Low Birth Weight

Philippe P. Hujuel, PhD; Anne-Marie Bollen, PhD; Carolyn J. Noonan, MS; Michael A. del Aguila, PhD; JAMA, April 28, 2004—Vol 291, No. 16 1987

Factors not discussed:

- ❑ Importance of diet, nutrition and hygiene
- ❑ Self reported smoking and alcohol use unreliable
- ❑ Contradicts large body of animal studies (e.g., Brent)
- ❑ Observation in organ other than that where effect is tested – lack of supporting data
- ❑ Unusually low-dose (mean 1.2 mGy) for effect not observed in other studies.

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Antepartum Dental Radiography and Infant Low Birth Weight  
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LETTERS TO THE EDITOR  
Dental x-rays and low birth weight

John D Boice, Jr    John J Mulvihill  
Marilyn Stovall    Daniel M Green

- ❑ periodontal disease has been linked to preterm births and low birth weight

Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R and Beck J 1996 Periodontal infection as a possible risk factor for preterm low birth weight. *J. Periodontol.* 67 (Suppl) 1103-13  
JeffcoatMK, GeursNC, ReddyMS, GoldenbergRL and HauthJC 2001 Current evidence regarding periodontal disease as a risk factor in preterm birth *Ann. Periodontol.* 6 183-8  
Jeffcoat M K, Geurs N C, Reddy M S, Cliver S P, Goldenberg R L and Hauth J C 2001 Periodontal infection and preterm birth: results of a prospective study *J. Am. Dent. Assoc.* 132 875-80

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Cataracts among Chernobyl Clean-up Workers: Implications Regarding Permissible Eye Exposures  
 Worgul BV, Kundiyeu YI, Sergiyenko NM, Chumak VV, Vitte PM, Medvedovsky C, Bakhanova EV, Junk AK, Kyrychenko OY, Musijachenko NV, Shylo SA, Vitte OP, Xu S, Xue X, Shore RE  
 Radiation Research 167, 233-243, 2007

~Prospective study of 8607 Chernobyl clean-up workers assessed at 12 and 14 years after exposure  
 ~Cohort young and prevalence of cataracts prior to clean-up assumed similar to prevalence of age-dependent cataract in non-cleanup cohorts.  
 ~Baseline reference was individuals exposed to less than 100 mGy.  
 ~Dose response effect found  
 ~Threshold for induction of Stage 1 opacities ~350 mGy, perhaps less, and not in excess of 700 mGy.

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 Radiation Research 167, 233-243, 2007

~Dose evaluation techniques extensively discussed  
 ~methods to test for potential for falsified data presented—no evidence of falsification found  
 ~Tests for confounding factors well delineated  
 ~age most important  
 ~Methods used to test for and stage radiation-related cataract well discussed  
 ~slit lamp microscopy and trained ophthalmologists blinded from dosimetry results).  
 ~Statistical analysis appropriately revealed  
 ~Methods used to test stability of results when various possible factors might render bias in certain conclusions appropriately discussed.  
 ~Results consistent with other more recent research on cataractogenesis.

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 Radiation Research 167, 233-243, 2007

**Conclusion:**

**Dose threshold for radiation-induced ocular changes resulting in stable cataract formation is much lower than previously believed.**

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## Conclusions

- ▣ Peer review of proffered papers only first step in scientific review
- ▣ Performing quality research requires tedious examination and critical analysis to rule out or admit bias or confounding in the data
- ▣ Discovering the truth behind radiation effects is a long and arduous road, requiring researchers to examine whether their results affirm or deny the plethora of research produced over the past century
- ▣ In epidemiology and causal judgment, consistency with other studies conducted by other investigators using other methods in different countries is important.

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