## 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

## Part 1: 1965 (not recent)

BRITISH JOURNAL OF CANCER

VOL. XIX MARCH, 1965 NO. 1

BREAST CANCER FOLLOWING MULTIPLE FLUOROSCOPIES

I. MACKENZIE

*From the Department of Surgery, Dalhousie University, and the Nova Scotia Tumour Clinic, Victoria General Hospital, Halifax, Nova Scotia, Canada*

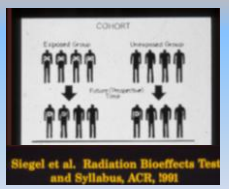
**"The following facts are presented to substantiate the possibility that, in certain circumstances, it *[ionizing radiation]* may play a part in the development of mammary carcinoma."**

**Patients were treated for TB by fluoroscopically guided artificial pneumothorax**


BRITISH JOURNAL OF CANCER
VOL. XIX MARCH, 1965 NO. 1
BREAST CANCER FOLLOWING MULTIPLE FLUOROSCOPIES

## The "facts": Incidence was high

- 13 of 271 patients with AP fluoroscopy treatment between 1940-49, developed breast cancer.
- only 1 of 510 patients at same clinic not treated with AP developed breast cancer.
- Incidence was at least 4 times higher than in 3 other provinces.
- Finding statistically significant.



Siegel et al. Radiation Bioeffects Test and Syllabus, ACR, 1991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## The facts: Breast cancer correlated with high radiation doses

- Over half of cancer cases had at least 100 fluoroscopies
- Radiation dermititis and skin cancers were found in 4 cases
- In all cases of BC, patient faced the x-ray source
- Women who faced opposite way did not develop BC.
- Beams were unfiltered for most part.


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## The facts: Supporting evidence of site & age

- Site of BC correlated with treated lung, but not statistically significant (numbers small)
- >70% of BC inner or central –
  - **correlating** with fluoroscoped area
  - **anti-correlating** with prevalence of breast cancer
- onset in 33% of BC cases occurred at < 40 years
  - **significantly different** from general incidence of ~10% <40 (P< 0.001)


BRITISH JOURNAL OF CANCER
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## The facts: Supporting evidence from other research

- Radiation implicated in BC by animal studies.


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## Confounding factors:

- Lifestyle habits (smoking, diet, ethnicity) not mentioned as possible factors in results. Populations assumed similar.
- Reproductive history not studied
- Age at treatment only implied by latent period and age of onset
- Undocumented AP fluoroscopies & other irradiations noted as unknown contributors to results.
- Possibility of agent related to tuberculosis discussed, but discarded due to no identifiable relation of potential factor to AP therapy.
- Findings possibly spurious, but deemed unlikely.


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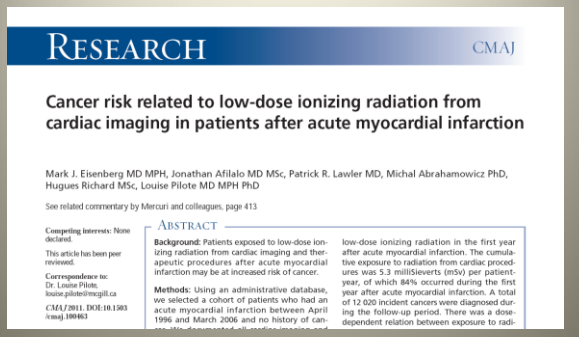
## Conclusion

Irradiation contributed to development of mammary cancers based on:

- Correlation between cancer site and site of radiation delivery
- Correlation with delivery of high radiation dose
- Unusual younger age of onset and
- Support from animal studies.
- Causal confirmation requires more studies and dose-response relationship.

## Part 2: 2011


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 Afilalo 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

Competing interests: None declared.

This article has been peer reviewed.

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CMAJ 2011. DOI:10.1503/cmaj.100463

ABSTRACT

Background: Patients exposed to low-dose ionizing radiation from cardiac imaging and therapeutic procedures after acute myocardial infarction may be at increased risk of cancer.

Methods: Using an administrative database, we selected a cohort of patients who had an acute myocardial infarction between April 1996 and March 2006 and no history of can-

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 year after acute myocardial infarction. A total of 12 020 incident cancers were diagnosed during the follow-up period. There was a dose-dependent relation between exposure to radi-

### 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

### 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?

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?

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 (and skin?) (UNSCEAR, BEIR, ICRP, NCRP)

Short follow-up period negates possible causal link to cancers other than leukemia and skin

A-bomb data render quadratic and linear – quadratic response for these cancers further reducing likelihood of causal relationship

Benefit/Risk ignored (Pts had MI!).

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
- These factors could cause conditions that increase number of imaging procedures.
- Discussion warranted.

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.
- Do patients' cancers correlate to organ sites exposed in these patients?


Early release, published at www.cmaj.ca on February 7, 2011. Subject to revision.

CMAJ COMMENTARY

Radiation exposure from medical imaging: A silent harm?

Mathew Mercuri MSc, Tej Sheth MD, Madhu K. Natarajan MD MSc

See related research article by Eisenberg and colleagues

**Commentary failed to point out severe deficiencies in study.**

## Part 3: 2010

**Igor Shuryak, Rainer K. Sachs, and David J. Brenner**
**Cancer Risks After Radiation Exposure in Middle Age**
***JNCI J Natl Cancer Inst (2010) 102(21): 1628-1636***

Igor Shuryak, Rainer K. Sachs, and David J. Brenner
Cancer Risks After Radiation Exposure in Middle Age *JNCI J Natl Cancer Inst (2010) 102(21): 1628-1636*

**Authors assert this:**

**Relative risks of radiation-induced cancer in Japanese atomic bomb survivors generally do not decrease monotonically with increasing age of adult exposure.**

**These observations are inconsistent with most standard models of radiation-induced cancer, which predict that relative risks decrease monotonically with increasing age at exposure, at all ages.**

Igor Shuryak, Rainer K. Sachs, and David J. Brenner
Cancer Risks After Radiation Exposure in Middle Age *JNCI J Natl Cancer Inst (2010) 102(21): 1628-1636*

**How do they reconcile these statements with those of Preston 2007?**

**Preston 2007: "For all solid cancers as a group, the excess relative risk (ERR per Gy) decreases by about 17% per decade increase in age at exposure after allowing for attained age effects"**

Shuryak I, Sachs RK, Brenner DJ.**Cancer risks after radiation exposure in middle age.** J Natl Cancer Inst. 2010 Nov 3;102(21):1628-36.

**What authors reported they did:**

- **Analyzed age-at-exposure cancer risk patterns in Japanese A-bomb survivors using biologically based model of radiation carcinogenesis incorporating both a) initiation and b) radiation-induced promotion of premalignant damage.**
- **Emphasizes kinetics of radiation-induced initiation and promotion, and tracks yields of premalignant cells before, during, shortly after, and long after radiation exposure.**

Shuryak I, Sachs RK, Brenner DJ.**Cancer risks after radiation exposure in middle age.** J Natl Cancer Inst. 2010 Nov 3;102(21):1628-36.

**Models, Models Everywhere—Is There a Fit for Lifetime Risks?**
John D. Boice Jr
**Items not discussed:**

- **Apparent contradiction with statements of Preston regarding effects with age**
- **Contradictory evidence from medically exposed populations (e.g., Rx for rectal, genital, urinary bladder and colon in women showing decreased risk with age)**
- **BEIR VII did not assume ERR decreases for exposure in middle and older ages but that ERR is constant for exposures after age 30 years**

Shuryak I, Sachs RK, Brenner DJ.**Cancer risks after radiation exposure in middle age.** J Natl Cancer Inst. 2010 Nov 3;102(21):1628-36.

**Models, Models Everywhere—Is There a Fit for Lifetime Risks?**
John D. Boice Jr
**Items not discussed:**

- **factors associated with birth cohort such as smoking, diet, and viral infections could affect the pattern of risk with age at exposure. (Promoting agents change with birth cohort)**
- **limited evidence that risk increases at older exposure ages not as strong in Japanese mortality data as in Japanese incidence data. (Japanese mortality data more comprehensive)**

Shuryak I, Sachs RK, Brenner DJ.**Cancer risks after radiation exposure in middle age.** J Natl Cancer Inst. 2010 Nov 3;102(21):1628-36.

**Conclusion:**

**Paper discusses one perspective on risk modeling and does not incorporate full discussion of limitations and contradictory findings.**

# Part 4: 2004

**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**

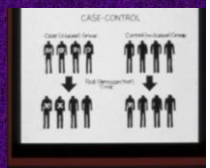
Hypothesis:

Doses from dental x-rays during pregnancy deliver doses to the thyroid, hypothalamus, or pituitary gland sufficient to alter function and result in low-birth-weight infants.

Doses were ~1.2 mGy to thyroid.

**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 page 1987**

- A population-based case-control study.
- Cases: 1117 women with low-birth-weight infants (2500 g)
- Four control pregnancies resulting in normal-birth-weight infants (2500 g) were randomly selected for each case (n=4468)

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Potential confounding factors available in data:

- Maternal age at the time of delivery* (NX)
- Ethnicity (white, black, asian, other)* (X)
- Education level (< or > 12 years)
- The duration of eligibility for dental insurance during pregnancy
- Marital status*
- Parity (categorized into 0, 1-2, and 3 prior pregnancies)*
- Self-reported maternal smoking during pregnancy* (X)
- Gestational or established diabetes* (NX)
- Kessner Adequacy of Prenatal Care Index (X) (more x-rays for inadequate care!)
- Self-reported 1 or more alcoholic drinks per week during pregnancy (NX)
- Prepregnancy weight*
- Weight gain during pregnancy*
- Preeclampsia* (NX)
- Chronic hypertension* (NX)

*Confounding factor correlated with LBW
NX = confounding factor not correlated with dental x-rays; X = correlated with dental x-rays

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- Exposure higher than 0.4 mGy (mean 1.2 mGy) during gestation occurred in 21 (1.9%) mothers of low-birth-weight infants (adjusted odds ratio 1.11-4.66 - 95% confidence interval , *P=.03).*
- Exposure higher than 0.4 mGy (mean 1.2 mGy) occurred in 10 (3%) term low-birth-weight pregnancies (adjusted OR for a term low-birth-weight infant of 1.46-8.92 - 95% CI, *P=.005).*
- 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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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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Factors not discussed:

- **Importance of diet, nutrition and hygiene**
- **Self reported smoking and alcohol use unreliable**
- **Contradicts large body of animal studies**
- **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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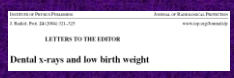
LETTERS TO THE EDITOR
Dental x-rays and low birth weight

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

- **Epidemiology is simply not capable of detecting radiation effects following such trivial doses**
- **Literature review misleading with little if any relevance to low-dose exposure of adult thyroid gland**
  - **High doses in childhood damage the infantile uterus – this is cause of lbw**
  - **spinal x-rays and low birth weight children are most likely due to effects of and severity of scoliosis, not radiation**
  - **A-bomb survivor studies do not support their findings**
  - **association between radiation exposure and autoimmune thyroid disease is far from established**

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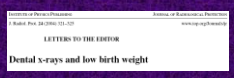
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- periodontal disease has been linked to preterm births and low birth weight

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, Goldenerg 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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Commentary by Robert L. Brent
Health Physics 88 (4):379-81;2005

- Medical literature cited to support their findings involved doses orders of magnitude higher and irradiated the conceptus directly
- Hundreds of animal studies results were not referenced and refute their findings
- No detailed clinical study of 31 growth retarded babies to determine if maternal disease, genetic or other factors would explain the results.

# PART 5

**Cataracts among Chernobyl Clean-up Workers: Implications Regarding Permissible Eye Exposures**
Worgul BV, Kundiyev 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.

## Conclusions

- Peer review of proffered papers only first step in scientific review
- Performing quality research requires tedious examination and critical analysis of bias in the data
- Researchers often biased toward "proving a hypothesis" and peer review should guard against bias
- Discovering the truth behind radiation effects is a long and arduous road, requiring that researchers examine how 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.