Epidemiology for Radiation Risk Assessment and Protection

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Scientific bases for radiation protection today

- Enormous amount of information on health effects (cancer, cataracts, hereditary effects) from:
  - Epidemiology
    - ✓ atomic bomb survivors
    - ✓ patients irradiated for therapeutic purposes
    - ✓ populations with occupational exposures (miners)
    - ✓ populations with environmental exposures (Radon, ^{131}I)
  - Animal experiments
  - Mechanistic studies

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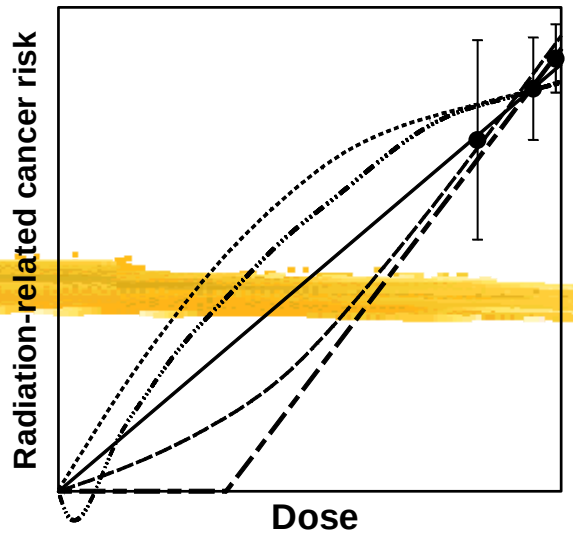
Current questions in radiation protection



- Cancer
  - Effects of low doses and dose-rates
  - Effects of different types of radiation and of mixtures
  - Effects of factors which might modify risks
    - ✓ Age
    - ✓ Sex
    - ✓ Environmental exposures
    - ✓ Host factors, including genetic polymorphisms, iodine deficiency
- Non-targeted effects
  - Cardiovascular effects at low doses and dose-rates
  - Cognitive effects

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Answers ???

- Very fast growing body of knowledge on molecular and cellular mechanisms, at lower and lower doses
  - Genomic instability
  - Adaptive response
  - Bystander effects
  - Know a lot about repair of different types of damage ...
- New paradigm of radiation biology

... but unknown significance in humans
(whole organisms, genetic and epigenetic heterogeneity, exposed to many other factors ...)

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HOW SHOULD WE GO AHEAD AND ANSWER THESE QUESTIONS TO ASSESS RISK

???

[redacted]

Health Risks From Exposure to Low Levels of Ionizing Radiation

BEIR VII–Phase 2

Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radia

Board on Radiation Effects Research

Division on Earth and Life Studies

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Based on a comprehensive review of the literature, the committee concluded that the risk would continue 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****.*

... magnitude of that increase is uncertain, however

COMMITTEE TO ASSESS HEALTH RISKS FROM EXPOSURE TO LOW LEVELS OF IONIZING RADIATION

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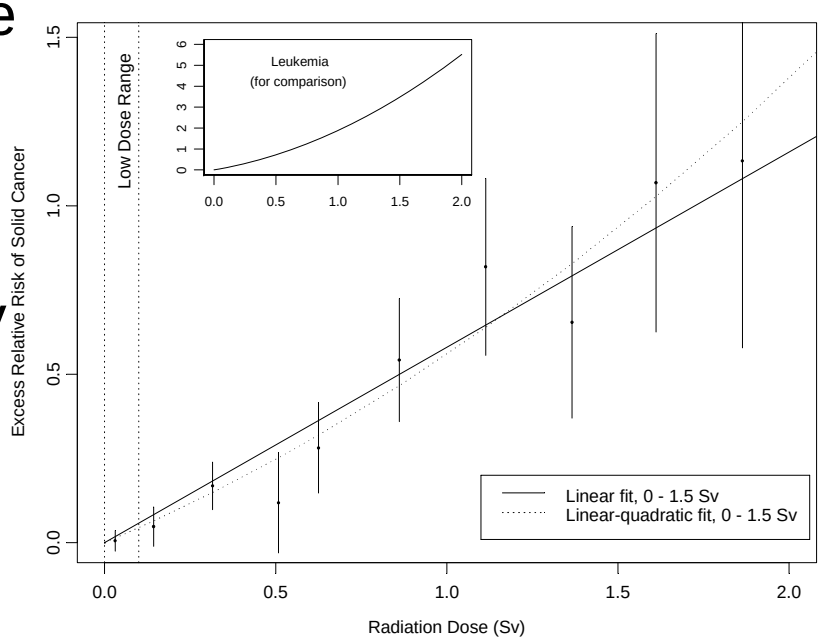
BEIR VII – reviewed dose responses for low doses and dose-rates

- Radiobiological data:
  - Linear-quadratic dose-response over the range 0-2 Gy with upward curvature
- A-bomb survivor solid cancer incidence :
  - Well described by linear model 0-1.5 Gy
  - Compatible with small amount of curvature
- Bayesian analyses



⇨ ***Models for risk predictions from low doses and dose-rates***

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From direct epidemiological observation

- Epidemiology is valuable for radiation protection
  - Direct observation of health effects of relevance in populations we want to protect

  … humans are the main relevant animal species for radiation protection
    - ✓ Each human has his/her own
      - Exposures and exposure circumstances
      - Hormonal status – which varies over time
      - Genetic and epigenetic make-up
- But need careful studies
  - Epidemiology subject to
    - ✓ Biases
    - ✓ Errors
    - ✓ Low power to study small effects

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Direct epidemiological evidence
- Requirements -

- Study population
  - Very large
  - Well-defined
  - No selection bias
- Follow-up / Case & control ascertainment
  - Complete, non-differential
  - Accurate diagnosis
- Dose-estimates
  - Individual
  - Accurate and precise

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Nuclear industry workers

- *Characteristics*
  - Very large, stable populations
  - Well characterized exposures
    - ✓ Generally low doses, protracted
    - ✓ Mainly external γ–radiation
  - Detailed individual annual dose estimates – *measured in real time with personal dosimeters* –

... Relevant population for radiation protection

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Mayak and the Techa River

Mayak Industrial Association

- ✓ Began operation in 1948 - production and separation of plutonium
- ✓ Releases of waste into the Techa River

... external γ exposure

... internal dose from ^{89}Sr & ^{90}Sr, ^{137}Cs, ^{103}Ru & ^{106}Ru, ^{95}Zr & ^{95}Nb

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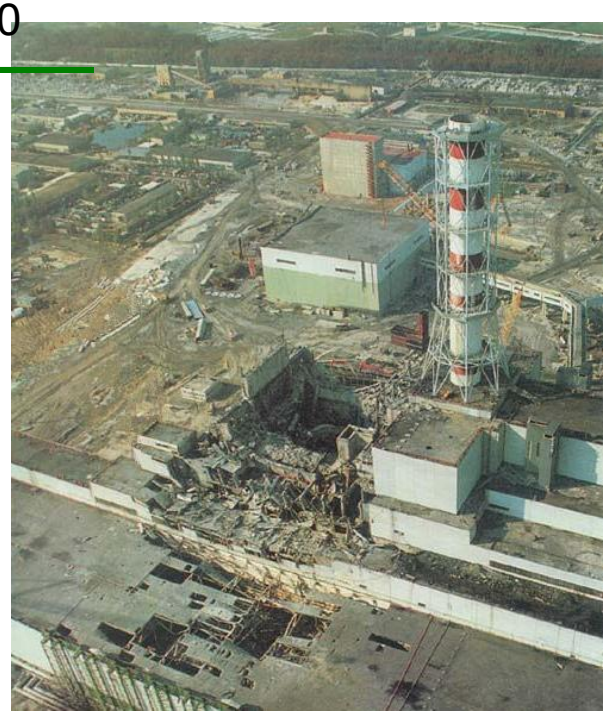
The Chernobyl accident

Population	Approximate size of population	Mean effective dose (mSv)♣
Liquidators (1986–1987, NPP + 30 km zone)	240,000	100
1986 evacuees	116,000	33
Persons living in contaminated areas:		
Cs^{137} deposition density >555 kBq/m^2 *	270,000	50
Cs^{137} deposition density >37.5 kBq/m^2	5,000,000	10

* Strict control zones

♣ Accumulated doses: 1986-2005



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Low dose protracted exposure studies

- Growing body of evidence from large scale low dose studies suggesting existence of a small risk at low doses

ERR/Gy (95% CI) for solid cancers

	Size of cohort	Average dose (mGy)	Average years of follow-up	Solid cancers	ERR/Gy (95% CI)
A-bomb survivors	~80,000	200	47	3,259	0.32[a] (0.01,0.5)
Techa River cohort					
Mortality follow	29,873	30	29	1,842	0.92 (0.2, 1.7)
Incidence follow-up[6]	17,433	40	25	1,836	1.0 (0.3, 1.9)
15-country Nuclear workers study	407,391	19	13	4,770	0.87 (0.03, 1.9)
Without Canada					0.58 (-0.2, 1.6)

[a] *Men – exposed 20-60 years of age*

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Low dose protracted exposure studies

ERR/Gy (95% CI) for leukaemia excluding CLL

	Size of cohort	Average dose (mGy)	Average years of follow-up	Leukaemia	ERR/100 mGy (95% CI)
A-bomb survivors					
Linear model	~80,000	200	47	83	0.32[a] (0.2, 0.6)
Linear-quadratic					0.15 (-0.1, 0.5)
Techa River cohort	29,873	30	29	60	0.46 (0.2, 1.1)
15-country Nuclear workers study	407,391	19	13	196	0.19 (<0[b], 0.8)
Chernobyl liquidators					
Baltic / Belarus/Russia	145,000	*median:*		19	0.50 (-0.4, 5.7)
All haematological malign.		*13*		70	0.60 (-0.02, 2.4)

[a] *Men – exposed 20-60 years of age*

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Low dose protracted exposure studies

- Recent studies suggest existence of a small risk at low doses for low LET radiation
  - Risk estimates higher than linear extrapolations from a-bomb survivors
  - But studies have some limitations:
    - ✓ 15-country study: exact magnitude of smoking confounding not clear
    - ✓ Techa river: uncertainties/errors in dose estimates
  - Risk estimates statistically compatible with extrapolations from a-bomb survivors

- And for high LET
  - Studies of environmental radon clearly show increased risks

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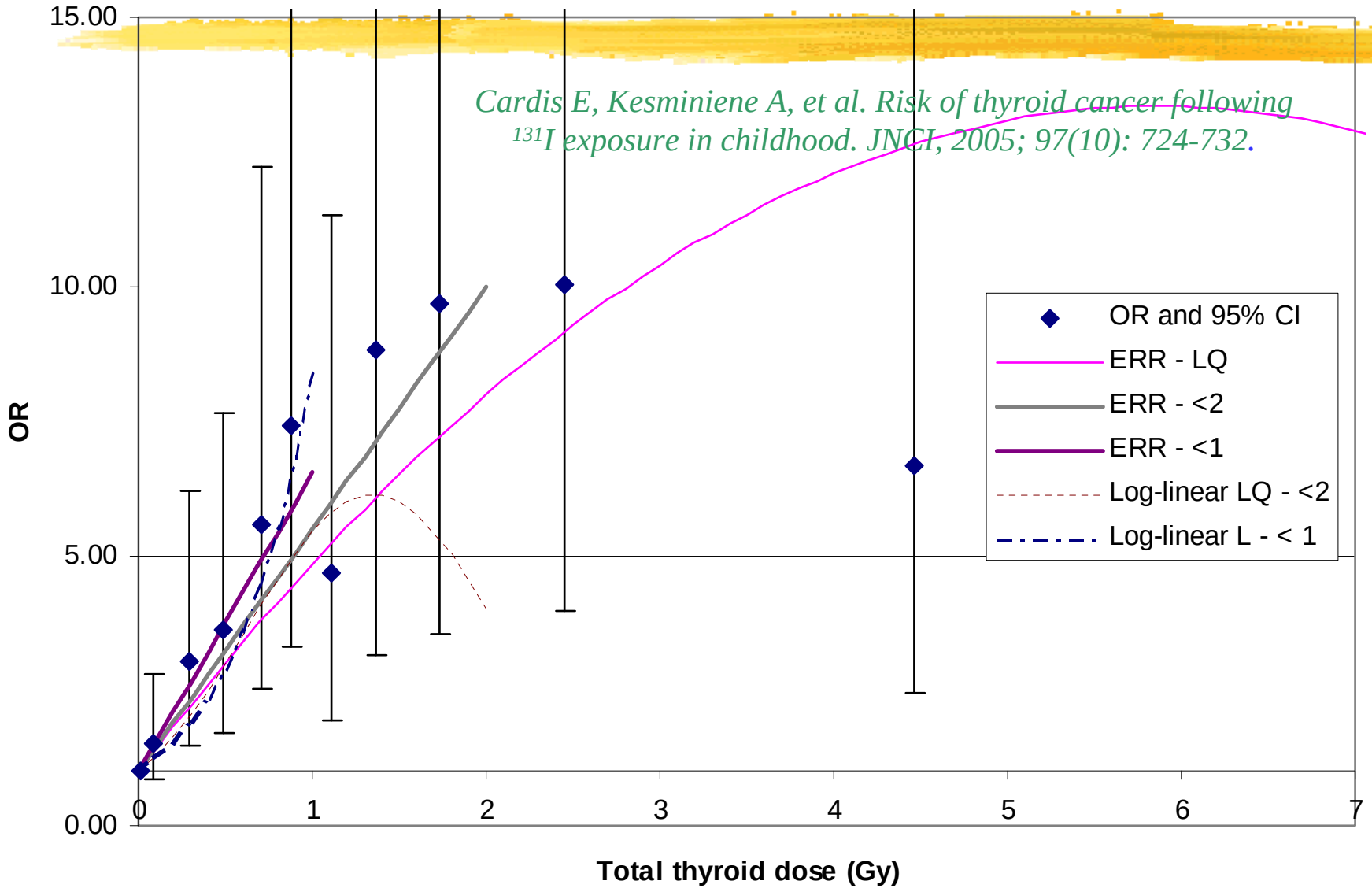
And epidemiology has taught us about risk modifiers

- Age at exposure ... *evidence that exposure at young ages entails greater risks*
  - Atomic bomb survivors
  - Thyroid cancer after exposure to ^{131}I from Chernobyl
  - Medically irradiated populations
  - In utero exposure at 6-10 mGy – increased childhood cancer risk
- Environmental factors
  - Smoking and radon
  - Iodine deficiency and ^{131}I

Thyroid cancer after Chernobyl



Cardis E, Kesminiene A, et al. Risk of thyroid cancer following ^{131}I exposure in childhood. JNCI, 2005; 97(10): 724-732.

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Estimated OR at 1 Gy
– by level of soil iodine and stable iodine consumption status –

Consumption of potassium iodide	OR at 1 Gy (95% CI)	
	Highest two tertiles of soil iodine	Lowest tertile of soil iodine
No	3.5 (1.8 to 7.0)	10.8 (5.6 to 20.8)
Yes	1.1 (0.3 to 3.6)	3.3 (1.0 to 10.6)

Cardis E, Kesminiene A, et al. Risk of thyroid cancer following ^{131}I exposure in childhood. JNCI, 2005; 97(10): 724-732.

Gene-radiation interactions ?

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Effect of Chest X-Rays on the Risk of Breast Cancer Among *BRCA1/2* Mutation Carriers in the International *BRCA1/2* Carrier Cohort Study

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ABSTRACT

Purpose
Women who carry germline mutations in the *BRCA1* and *BRCA2* genes are at greatly increased risk of breast cancer (BC). Numerous studies have shown that moderate to high doses of ionizing radiation are a risk factor for BC. Because of the role of the BRCA proteins in DNA repair, we hypothesized that *BRCA* carriers might be more sensitive to ionizing radiation than women in the general population.

Patients and Methods
A retrospective cohort study of 1,601 female *BRCA1/2* carriers was performed. Risk of breast cancer from exposure to chest x-rays, as assessed by questionnaire data, was analyzed using a weighted Cox proportional hazards model.

Results
In this cohort, any reported exposure to chest x-rays was associated with an increased risk of BC (hazard ratio [HR] = 1.54; $P = .007$). This risk was increased in carrier women aged 40 years and younger (HR = 1.97; $P < .001$) and in women born after 1949 (HR = 2.56; $P < .001$), particularly those exposed only before the age of 20 years (HR = 4.64; $P < .001$).

Conclusion
In our series of *BRCA* carriers, we detected a relatively large effect on BC risk with a level of radiation exposure that is at least an order of magnitude lower than in previously studied medical radiation–exposed cohorts. Although part of this increase may be attributable to recall bias, the observed patterns of risk in terms of age at exposure and attained age are consistent with those found in previous studies. If confirmed, the results have important implications for the use of x-ray imaging in young *BRCA1/2* carriers.

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INTRODUCTION

Exposure to ionizing radiation has been shown to be associated with a significant, but at low doses, usually modest increase in breast cancer (BC) risk (reviewed recently in Ronckers et al[1]). Epidemiologic studies of atomic bomb survivors, such as the Life Span Study, and of medically irradiated populations show increased risks of female BC, with relative risks ranging from 1.0 to 4.3 per Gy.[2-11] Most of the information about patterns of risk over time comes from studies of populations who received relatively moderate to high doses of radiation to the breast. The relative risks of BC for women exposed to external doses of ionizing radiation in childhood and adolescence are substantially higher than the risks for women exposed as adults.[3-9] Results of a recent combined analysis of data from atomic bomb survivors and seven medically exposed cohorts[7] indicate clearly that, although radiation exposure at any age increases BC risk, the relative and absolute excess risks tend to decrease with increasing age at exposure.[3,5,7] The increased risk of BC starts to be observed 10 to 15 years after exposure, with relative risks decreasing as a function of attained age after reaching a peak, usually between age 30 and 40 years.[3,5,7] A study of children exposed repeatedly to x-rays for monitoring of the curvature of the spine for scoliosis has suggested that adolescence, when breast tissue is developing, is a vulnerable time for carcinogenic exposures.[11] However, little, if any, data are available on the risks because of routine, occasional x-rays in the general population.

From L'Institut National de la Santé et de la Recherche Médicale (Inserm) U-946 et Service de Biostatistique de l'Institut Curie, Paris; International Agency for Research on Cancer, Lyon; Centre Paul Strauss, Strasbourg; Centre René Huguenin, Saint Cloud, France; Cancer Research UK, Genetic Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge; Department of Genetics, St Mary's Hospital, Manchester, United Kingdom; Division of Clinical Epidemiology, German Cancer Research Center, Heidelberg, Germany; Departments of Epidemiology and Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, the Netherlands; Division of Senology, Medical University of Vienna and Private Trust for Breast Health, Vienna, Austria; Laboratoire de Génomique des Cancers, Laval University, Québec City, Québec, Canada; and Department of Medical Informatics, University of Utah, Salt Lake City, UT; and the Gene Étude Prospective Sein Ovaire (GENEPSO), Gen en Omgeving studie van de werkgroep Hereditair Borstkanker Onderzoek Nederland (GE04-HEBON), and the International BRCA1/2 Carrier Cohort Study (IBCCS) Collaborators' Group.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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Breast Cancer Research

Breast Cancer RESEARCH

Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study

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PRECLINICAL STUDY

The spectrum of *ATM* missense variants and their contribution to contralateral breast cancer

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Abstract Heterozygous carriers of *ATM* mutations are at increased risk of breast cancer. In this case-control study, we evaluated the significance of germline *ATM* missense variants to the risk of contralateral breast cancer (CBC). We have determined the spectrum and frequency of *ATM* missense variants in 443 breast cancer patients diagnosed before age 50, including 247 patients who subsequently developed CBC. Twenty-one per cent of the women with unilateral breast cancer and 17% of the women with CBC had at least one *ATM* germline missense variant, indicating no significant difference in variant frequency between these two groups. We have found that carriers of an ATM missense mutation, who were treated with radiotherapy for the first breast tumour, developed their second tumour on average in a 92-month interval compared to a 136-month mean interval for those CBC patients who neither received RT nor carried a germline variant, ($p = 0.029$). Our results indicate that the presence of *ATM* variants does not have a major impact on the overall risk of CBC. However, the combination of RT and (certain) *ATM* missense variants seems to accelerate tumour development.

Keywords Breast cancer · ATM · Missense variants · Radiotherapy

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Introduction

Homozygous or compound heterozygous germline mutations in the *ATM* gene cause the autosomal recessive disorder ataxia-telangiectasia (A-T). This progressive neurological childhood disease is characterized by cerebellar degeneration, immunological defects, extreme sensitivity for ionising radiation and increased risk for cancers, particularly lymphomas [1]. *ATM* mutations identified in A-T families can be classified in three categories; truncating mutations, mutations that lead to some expression of mutant protein that lacks kinase activity and missense mutations with reduced kinase activity (http://chromium.liacs.nl/lovd/).

Heterozygous pathogenic *ATM* mutation carriers, ~0.5–1% of the general population, do not display the symptoms observed in A-T patients. Several epidemiological studies have consistently shown elevated rates of

The *CHEK2*1100delC* Allelic Variant and Risk of Breast Cancer: Screening Results from the Breast Cancer Family Registry

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Abstract

CHEK2, a serine-threonine kinase, is activated in response to agents, such as ionizing radiation, which induce DNA double-strand breaks. Activation of CHEK2 can result in cell cycle checkpoint arrest or apoptosis. One specific variant, *CHEK2*1100delC*, has been associated with an increased risk of breast cancer. In this population-based study, we screened 2,311 female breast cancer cases and 496 general population controls enrolled in the Ontario and Northern California Breast Cancer Family Registries for this variant (all controls were Canadian). Overall, 30 cases and one control carried the *1100delC* allele. In Ontario, the weighted mutation carrier frequency among cases and controls was 1.34% and 0.20%, respectively [odds ratio (OR), 6.65; 95% confidence interval (95% CI), 2.37-18.68]. In California, the weighted population mutation carrier frequency in cases was 0.40%. Across all cases, 1 of 524 non-Caucasians (0.19%) and 29 of 1,775 Caucasians (1.63%) were mutation carriers (OR, 0.12; 95% CI, 0.02-0.89). Among Caucasian cases >45 years age at diagnosis, carrier status was associated with history of benign breast disease (OR, 3.18; 95% CI, 1.30-7.80) and exposure to diagnostic ionizing radiation (excluding mammography; OR, 3.21; 95% CI, 1.13-9.14); compared with women without exposure to ionizing radiation, the association was strongest among women exposed >15 years before diagnosis (OR, 4.28; 95% CI, 1.50-12.20) and among those who received two or more chest X-rays (OR, 3.63; 95% CI, 1.25-10.52). These data supporting the biological relevance of CHEK2 in breast carcinogenesis suggest that further studies examining the joint roles of *CHEK2*1100delC* carrier status and radiation exposure may be warranted. (Cancer Epidemiol Biomarkers Prev 2006;15(2):348–52)

Introduction

Ionizing radiation is a known carcinogen in both animals and humans and has been implicated in breast carcinogenesis in particular. Exposure to ionizing radiation can cause a variety of types of damage to the DNA, of which the most serious are double-strand breaks. When unrepaired, DNA double-strand breaks can result in the loss of genetic material whereas incorrectly repaired double-strand breaks can result in damage ranging from localized mutations at the site of the original lesion to large-scale genomic rearrangements. The products of genes for which identified variants or mutations increase risk for breast cancer act predominantly within a common cellular pathway used by human cells to sense, signal, and repair such damage from DNA double-strand breaks (1). Stimulation of this pathway by exposure to ionizing radiation or other DNA double-strand break–inducing agents activates the ATM protein, a serine-threonine kinase, which phosphorylates a wide array of substrates including BRCA1 and CHEK2 (2, 3). Phosphorylation of CHEK2 on T68 is essential for its activation and all of its known functions. On activation, CHEK2 acquires the ability to carry out the following functions: (*a*) Activated CHEK2 regulates the S-phase cell cycle checkpoint, presumably by phosphorylating CDC25A (4, 5). (*b*) CHEK2 modulates p53 activity either by direct phosphorylation of p53 or by phosphorylation of murine double minute-2 and this interaction serves to both regulate the G_1-S cell cycle checkpoint and activate p53-dependent apoptotic pathways (6, 7). (*c*) CHEK2 also activates DNA damage–responsive, but p53-independent, apoptotic pathways through its phosphorylation of promyelocytic leukaemia protein and E2F1 (8, 9). (*d*) CHEK2 phosphor-

Genetic predisposition for the development of radiation-associated meningioma: an epidemiological study

Pazit Flint-Richter, Siegal Sadetzki

Summary

Background Ionising radiation is an established risk factor for meningioma, yet less than 1% of irradiated individuals develop this tumour. Familial aggregation of meningioma is rare. We aimed to assess whether genetic factors can modify the risk for meningioma formation after the initiating effect of radiation, by comparison of the frequency of meningiomas in families that included irradiated and unirradiated siblings.

Methods This study was based on a larger epidemiological, genetic case-control study, and included 525 families that were divided according to irradiation and disease status of each of the family's index participant: 160 had radiation-associated meningioma (RAM); 145 were irradiated and did not develop meningioma; 85 had meningioma with no previous history of irradiation; and 135 were unirradiated and did not develop meningioma. Data were collected by questionnaires.

Findings We found additional first-degree relatives with meningioma in 17 families (11%) in the RAM group, whereas only between one and two such families (1%) were found in the other groups ($p<0·0001$). All meningiomas seen in the families of the RAM group were in irradiated participants. Also, 22 families (10%) in the RAM group had members with cancers in irradiated sites (including head, neck, and chest) compared with 9 (5%) of irradiated controls ($p=0·04$).

Interpretation This dataset of families, which included irradiated and unirradiated, and also affected and unaffected family members, created a natural experiment. Our results support the idea that genetic susceptibility increases the risk of developing meningioma after exposure to radiation. Further studies are needed to identify the specific genes involved in this familial sensitivity to ionising radiation. DNA repair and cell-cycle control genes, such as the ataxia-telangiectasia gene, could be plausible candidates for investigation.

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See Reflection and Reaction page 369

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Introduction

Meningiomas are solid tumours arising from the meninges that cover the central nervous system.[1] Most meningiomas are sporadic, and genetic conditions with high-penetrance genes account for only a small fraction of cases.[2] Consequently, familial aggregation of meningioma is rare and is usually associated with type-2 neurofibromatosis (NF2).[3] Aggregations of meningiomas have also been reported in families without any stigmata of neurofibromatosis, suggesting the existence of additional unknown genes that have a role in the development of the inherited form of the disease.[4–6] A population-based Swedish study found that out of 1845 meningioma cases, 19 (1%) had parents with meningiomas (standardised incidence rate [SIR] 3·06 [95% CI 1·84–4·79]) and 10 (54%) had siblings with

unirradiated individuals and sibling controls (the tinea capitis cohort) is now being followed for almost 40 years for radiation sequelae.[14] One of the most prominent findings in terms of risk assessment found in the tinea capitis studies was a significantly increased risk for meningiomas in the exposed population (relative risk [RR] 9·5 [95% CI 3·5–25·7]).[11,13] Yet, less than 1% of the irradiated individuals developed the tumour. This observation supports the notion that other factors probably modify the risk for meningioma formation after the initiating effect of ionising radiation.

Our hypothesis was that individuals who develop meningioma after irradiation are more susceptible to the carcinogenic effect of ionising radiation. Such genetic susceptibility might lead to aggregation of meningiomas in the family if several family members are exposed to the

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Role of epidemiology in radiation research and radiation protection

- Careful studies of well targeted populations
  - Can provide direct information on effects of low-dose protracted exposures
    - ✓ Uncertainties – but at least provide a check on extrapolations from higher dose studies
  - Provide important information about factors that modify risk
    - ✓ Suggest that some of us are more sensitive to radiation induced health effects than others

    … *extremely important in assessing risk at low doses*

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The future ?

- Essectial to continue follow-up of informative epidemiological studies
  - As study participants age, the statistical power of the studies (nuclear workers, Techa, liquidators) will increase considerably
- Set-up specific new cohorts that are relevant and informative
  - ✓ Children with higher dose paediatric exposures
  - ✓ Cohorts with particular risk profiles (AT heterozygotes, …)

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Limitations

- "Standard" epidemiology has its limitations
  - Statistical power
  - "Black box" – limited information on intermediate factors and outcomes
  - ...

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Limitations

- But so do *in vitro* and *in vivo* studies
  - Separate studies of bystander effect, genomic instability, induction of DSBs, etc ...
    - ✓ don't tell you what the resulting dose-response is at low doses …
      - *particularly in populations that may be very heterogeneous with respect to their risk*
    - ✓ can model, but the predictions will only be as good as the very complex model
  - Knock-out/ knock-in mice are not humans
    - ✓ in terms of their disease
    - ✓ in terms of the multitude of genetic variants and concomitant exposures

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Solution ?

- Continue as is done currently, i.e.
  - Study genetic and epigenetic factors in vitro and in vivo
  - Develop models that integrate all relevant aspects and predict risks to humans
  - Test adequacy of the model by comparing predictions with epidemiological observation?

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Solution ?

- Better integrated epi/biology project?
  i.e. careful, large-scale epidemiological studies
  - With all important “epidemiological variables”
    - ✓age, sex
    - ✓*dose* and dosimetric uncertainties
    - ✓important risk factors for the disease
  - With biological samples to measure relevant genetic, epigenetic and other relevant biological parameters

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Integrated epi/biology

- Careful consideration
  - Study population
  - Study design and conduct
    - ✓Pure “record linkage studies” not suitable, many occupational cohorts also
    - ✓“Opportunistic designs”, relying on existing biological repositories also not necessarily suitable
    - ✓Studies of medically exposed subjects may be particularly suitable for such integration
    - ✓Cohorts of mutation carriers may be particularly informative

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Integrated epi/biology

- Approach is timely
  - Availability of biological methods
  - “New” mechanistic ideas and hypotheses
- Approach is urgent
  - Improving the relevance of our approaches to address critical issues in radiation protection
  - *Make the most of the tax payers’ money*
- Joint planning essential
  - Are we ready ?