Diagnostic Radiation Exposure and Cancer Risk

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DCEG Radiation Epidemiology and Dosimetry Course 2019
Why Study Cancer Risks from Medical Diagnostic Radiation?

Exposures increasing & evolving
- Quantify risks from current exposures
- Emerging exposures eg PET-CT
- Public health concern – is it safe?
Why Study Cancer Risks from Medical Diagnostic Radiation?

Exposures increasing & evolving
• Quantify risks from current exposures
• Emerging exposures eg PET-CT
• Public health concern – is it safe?

Inform low-dose radiation carcinogenesis
• Understand risks from low-dose, fractionated, non-uniform exposure
• Risk in women & children (complement worker studies)
## Diagnostic Imaging Procedures for Selected Years in the United States

<table>
<thead>
<tr>
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<tr>
<td>Radiologic procedures#</td>
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<td>Dental radiographic examinations</td>
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Number of procedures in millions

Mettler, 2009 (Radiology)
### Diagnostic Imaging Procedures for Selected Years in the United States

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Number of procedures in millions

Mettler, 2009 (Radiology)
Dramatic Increase in Medical Exposures in the U.S.

1980

- <0.1mSv: 15%
- 0.5mSv: 83%
- 3mSv: 15%

- CT scans: 3 million
- Nuclear medicine: 6 million

2006

- <0.1mSv: 50%
- 3mSv: 48%
- 3.2mSv: 2%

- CT scans: 70 million
- Nuclear medicine: 18 million

NCRP report 160 (2009)
International Trends in Diagnostic Imaging

Mettler et al. (Radiology 2009)

United States
Well developed countries

Per 1000 pop/yr

CT scans
Nuclear medicine

# Diagnostic Imaging - Effective & Organ Doses

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<tr>
<th>Procedure</th>
<th>X-ray</th>
<th>CT scan</th>
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<td>Skull</td>
<td>0.1 mSv</td>
<td>2 mSv</td>
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<td>Chest</td>
<td>0.1 mSv</td>
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Mettler et al (Radiology 2009)
## Diagnostic Imaging - Effective & Organ Doses

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<th>Stomach</th>
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<tr>
<td>Skull</td>
<td>40 mGy</td>
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<td>0 mGy</td>
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Mettler et al (Radiology 2009)
Radiation Protection Principles

- Justification
- Optimization
- Dose limit
Radiation Protection Principles (2)

- Justification ➔ Do more good than harm
- Optimization ➔ ALARA
- Dose limit ➔ Medical exposure
Radiation Protection Principles (3)

- **Justification** ➔ Do more good than harm
- **Optimization** ➔ ALARA

- **Dose limit** ➔ Not Applicable for medical exposure
  - Intentional and for the direct benefit of the patient.
  - Limit may compromise patient care.

- **Diagnostic Reference Level (DRL)** – investigation level
Optimization and Justification in medical diagnostic imaging

• Appropriateness use criteria
Optimization and Justification in medical diagnostic imaging (2)

• Appropriateness use criteria

Guidelines funded by the ACR to assist physicians on which imaging tests they should, or should not, order for different patient symptoms, medical histories, and health status
Optimization and Justification in medical diagnostic imaging (3)

• Appropriateness use criteria
• Campaigns to reduce unnecessary use
Optimization and Justification in medical diagnostic imaging (4)

- Appropriateness use criteria
- Campaigns to reduce unnecessary use
- Doses optimization

Part of the Image Gently campaign to reduce doses from pediatric CTs.
→ Adjust CT parameters to child size
Recent Trends in the United States

CT procedures (millions per year)

Nuclear medicine procedures (millions per year)

myocardial perfusion tests
Studies on Diagnostic Radiation and Cancer Risk

PUBLIC HEALTH CONCERN

LOW-DOSE RADIATION CARCINOGENESIS

CLINICAL DECISION MAKING
Studies on Diagnostic Radiation and Cancer Risk
Methodological Issues

- Case-control vs cohort design
- Sample size
- Exposure assessment
- Confounding by indication
Studies on Diagnostic Radiation and Cancer Risk
Methodological Issues (2)

- Case-control vs cohort design
- Sample size
- Exposure assessment
- Confounding by indication

• Recall bias in case-control studies.
• Loss to follow-up and incomplete ascertainment in cohort studies
Studies on Diagnostic Radiation and Cancer Risk
Methodological Issues (3)

- **Case-control vs cohort design**
  - Recall bias in case-control studies.
  - Loss to follow-up and incomplete ascertainment in cohort studies.

- **Sample size**
  - Maximize power by studying highly radiosensitive cancers & childhood exposure.

- **Exposure assessment**
  - Confounding by indication.
Studies on Diagnostic Radiation and Cancer Risk
Methodological Issues (4)

- Case-control vs cohort design
  - Recall bias in case-control studies.
  - Long follow-up for cohort studies.

- Sample size
  - Maximize power by studying highly radiosensitive cancers & childhood exposure.

- Exposure assessment
  - Medical records vs Self-reported.
  - Information for dose reconstruction.
  - Organ doses.

- Confounding by indication
## Studies on Diagnostic Radiation and Cancer Risk

### Methodological Issues (5)

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Evidences from Main Studies on Diagnostic Radiation and Cancer Risk

• Diagnostic X-rays
  ✓ In-utero exposure
  ✓ Adult and childhood exposure
  ✓ BRCA mutation carriers

• Pediatric CT

• Screening examinations
Oxford Survey of Childhood Cancer Mortality, 1953-1972

- Study on leukemia and childhood cancer mortality associated with radiation exposure due to abdominal and pelvis X-rays during pregnancy
- Nationwide survey - 15,300 deaths (cases), 1:1 paired controls (age, sex & local of residence)
- X-rays exposure - Self-reported from mother of cases and controls

Doll and Wakeford (Br J Radiology 1997); Wakeford (Radiat Prot Dosimetry 2008)
Diagnostic X-Ray and Cancer Risk

In Utero Exposures (2)

Oxford Survey of Childhood Cancer Mortality, 1953-1972

✓ OR=1.39 (1.30-1.49) childhood cancer
✓ OR=1.49 (1.33-1.67) childhood leukaemia
✓ Decline in risk by birth cohort
✓ Dose per film
  ▪ 15mGy 1940s
  ▪ 3mGy 1960s
✓ Recall bias?

Doll and Wakeford (Br J Radiology 1997); Wakeford (Radiat Prot Dosimetry 2008)
Diagnostic X-Ray and Cancer Risk
In Utero Exposures (3)

Other studies on leukaemia and in utero radiation exposure:
- Northeastern US case-control study (medical record-based)
  ✓ OR=1.48 (1.18-1.85)

(Monson & MacMahon, 1984, JNCI)
Other studies on leukaemia and in utero radiation exposure:

- Northeastern US case-control study (medical record-based)
  - OR=1.48 (1.18-1.85)

- Meta-analysis of 32 case-control studies
  - RR=1.32 (1.19-1.42)
Other studies on leukaemia and in utero radiation exposure:

- Northeastern US case-control study (medical record-based)
  - OR=1.48 (1.18-1.85)

- Meta-analysis of 32 case-control studies
  - RR=1.32 (1.19-1.42)

- UKCCS case-control study (medical-record-based)
  - All childhood cancers, OR=1.14 (0.90-1.45)
  - Leukemia, OR=1.36 (0.91-2.02)

(Monson & MacMahon, 1984, JNCI)
Breast cancer risk & Multiple Spine X-rays
US Scoliosis Cohort Study

- 3,010 Scoliosis patients
- Mean age: 12 (0-19) years
- 36 years follow-up, 78 breast cancer
- Repeated spine X-ray (medical records):
  - Mean: 27 (range: 0-332)
- Breast dose:
  - Mean: 120 mGy (range: 0-1110)
Breast cancer risk & Multiple Spine X-rays
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- Repeated spine X-ray:
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- Breast dose:
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ERR/Gy = 2.9 (-0.1 to 8.6)
Diagnostic X-Ray and Cancer Risk

Adult Exposures

Multiple fluoroscopies among Tuberculosis patients

Breast Cancer

- Massachusetts TB 4,940 women (1925-54)
- Canadian TB 31,710 women (1930-1952)

Diagnostic X-Ray and Cancer Risk
Adult Exposures (2)

Multiple fluoroscopies among Tuberculosis patients

Breast Cancer
- Massachusetts TB 4,940 women (1925-54)
  ✓ Mean breast dose 0.8Gy (88 exposures)
  ✓ 234 breast cancers cases
  ✓ RR=1.61 (1.30-2.01) at 1Gy
- Canadian TB 31,710 women (1930-1952)

Boice et al (Radiat Res 1991); Howe and McLaughlin (Radiat Res 1996); Howe (Radiat Res 1995);
Multiple fluoroscopies among Tuberculosis patients

**Breast Cancer**

- Massachusetts TB 4,940 women (1925-54)
  - Mean breast dose 0.8Gy (88 exposures)
  - 234 breast cancers cases
  - RR=1.61 (1.30-2.01) at 1Gy

- Canadian TB 31,710 women (1930-1952)
  - 688 breast cancer deaths
  - RR=1.36 (1.11-1.67) at 1Gy

Diagnostic X-Ray and Cancer Risk
Adult Exposures (4)

Multiple fluoroscopies among Tuberculosis patients

Lung Cancer

- Massachusetts 13,572 TB patients (Mean dose 0.8Gy)
- Canadian 64,172 TB (Mean dose 1Gy)

Howe (Radiat Res 1995); Davis et al (Cancer Research 1989)
Multiple fluoroscopies among Tuberculosis patients

Lung Cancer

- Massachusetts 13,572 TB patients (Mean dose 0.8 Gy)
  - 357 lung cancer deaths
  - RR at 1 Gy 0.96 (0.89 to 1.14)

- Canadian 64,172 TB (Mean dose 1 Gy)
Multiple fluoroscopies among Tuberculosis patients

Lung Cancer

- Massachusetts 13,572 TB patients (Mean dose 0.8Gy)
  - 357 lung cancer deaths
  - RR at 1 Gy 0.96 (0.89 to 1.14)

- Canadian 64,172 TB (Mean dose 1Gy)
  - 1,178 lung cancer deaths

- No excesses of lung cancer

Howe (Radiat Res 1995); Davis et al (Cancer Research 1989)
Lung Cancer

- Massachusetts 13,572 TB patients (Mean dose 0.8Gy)
  - 357 lung cancer deaths
  - RR at 1 Gy 0.96 (0.89 to 1.14)

- Canadian 64,172 TB (Mean dose 1Gy)
  - 1,178 lung cancer deaths
  - RR at 1 Gy 1.00 (0.94 to 1.07)

- No excesses of lung cancer

• Confounding by indication?
• TB risk factor for lung cancer
• Misclassification of cause of death (lung cancer vs tuberculosis)
Diagnostic X-Ray and Cancer Risk
Breast cancer & Chest X-rays among BRCA carriers

Ionizing radiation

Radiosensitive population – carries of BRCA 1/2 mutation
✓ greater risk of developing breast cancer

BRCA 1/2 genes → DNA repair process, including double-strand breaks caused by ionizing radiation

Diagnostic X-Ray and Cancer Risk

Breast cancer & Chest X-rays among BRCA carriers (2)

- Cohort study n=1993 BRCA 1/2 mutation carriers, 2006-2009
  - Three nationwide studies in France, UK and the Netherlands
  - Cumulative breast dose - self-reported diagnostic procedures

Diagnostic X-Ray and Cancer Risk
Breast cancer & Chest X-rays among BRCA carriers (3)

- Cohort study n=1993 BRCA 1/2 mutation carriers, 2006-2009
  - Three nationwide studies in France, UK and the Netherlands
  - Cumulative exposure - self-reported diagnostic procedures
  - Any diagnostic radiation, HR=1.65 (1.11-2.46)
  - Exposure <age 30
    - HR=1.90 (1.20-3.00), with dose–response pattern
    - Breast dose>17 mGy, HR=3.84 (1.67-8.79)
Diagnostic X-Ray and Cancer Risk
Breast cancer & Chest X-rays among BRCA carriers (4)

- Cohort study n=1993 BRCA 1/2 mutation carriers, 2006-2009
  - Three nationwide studies in France, UK and the Netherlands
  - Self-reported diagnostic procedures
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  - Exposure <age 30
    ✓ HR=1.90 (1.20-3.00), with dose–response pattern
    ✓ Breast dose>17 mGy, HR=3.84 (1.67-8.79)
  - Exposure >age 30
    ✓ HR=1.06 (0.66-1.71)
Increased risk in dose levels lower than other cohorts exposed to radiation

Recall bias?

- Two methodological studies in the Dutch cohort → extent of the misclassification was small and mainly non-differential by disease status.
Swedish medical records study

484 thyroid cancer cases and matched population controls (1980-1992)

Generic thyroid dose estimates

Inskip et al (JNCI 1995)
Swedish medical records study

484 thyroid cancer cases and matched population controls (1980-1992)

Generic thyroid dose estimates

No risk associated with past X-rays

Similar results < age 20 exposure

But small number of X-rays among children and adolescents.

<table>
<thead>
<tr>
<th>Cumulative thyroid dose (mGy)</th>
<th>Cases / Controls</th>
<th>RR</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>0</td>
<td>133/137</td>
<td>1.00</td>
<td>Ref.</td>
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<tr>
<td>&gt;0-1.6</td>
<td>116/114</td>
<td>1.05</td>
<td>(0.73-1.52)</td>
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<tr>
<td>1.7-6.8</td>
<td>114/114</td>
<td>1.04</td>
<td>(0.70-1.55)</td>
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<td>7.0-75.3</td>
<td>121/119</td>
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<td>P-trend</td>
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Inskip et al (JNCI 1995)
Diagnostic X-Ray and Cancer Risk
Thyroid Cancer & Diagnostic X-rays (3)

USRT Cohort study, n=76,415 and 414 thyroid cancer cases

- Self-reported personal medical diagnostic procedures
- Estimated radiation thyroid dose (questionnaire and literature review)
- Assuming Rad Technologists report their medical radiation more accurate than general population

Little et al (BMJ 2018)
Diagnostic X-Ray and Cancer Risk
Thyroid Cancer & Diagnostic X-rays (3)

USRT Cohort study, n=76,415 and 414 thyroid cancer cases

- Self-reported personal medical diagnostic procedures
- Estimated radiation thyroid dose (questionnaire and literature review)
- Assuming Rad Technologists report their medical radiation more accurate than general population
- Weak evidence of association of diagnostic X-rays and thyroid cancer

Little et al (BMJ 2018)
Comparison of documented and recalled histories of diagnostic X-rays

- 123 cases & controls - Sweden study
- 50 cases & controls - US Kaiser NW health plan
- Medical records vs Telephone interview
- Discrepancy score: N per interview - N per medical record
  - Negative → underreporting
  - Positive → overreporting

Berrington de Gonzalez et al (AJE 2003)
Diagnostic X-Ray and Cancer Risk
Thyroid Cancer & Diagnostic X-rays (5)

Comparison of documented and recalled histories of diagnostic X-rays

- 123 cases & controls - Sweden study
- 50 cases & controls - US Kaiser NW health plan
- Medical records vs Telephone interview
- Discrepancy score: N per interview - N per medical record
  ✓ Negative → underreporting
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Berrington de Gonzalez et al (AJE 2003)
Pediatric CT Scans & Cancer Risk

- Higher doses & risks for children

- Adult settings in past (<2000)

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<th>Chest CT</th>
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<td>Brain</td>
<td>Lung/Breast</td>
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<tr>
<td>&lt;1990</td>
<td>60mGy</td>
<td>30mGy</td>
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<td>2000+</td>
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<td>5mGy</td>
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- Children have a long life expectancy → increase risk over lifetime
NCI-UK Pediatric CT scan Cohort

- Record linkage study of brain and leukemia
  - Cancer incidence following CT scans to 178,000 persons (1985-2002) at ages 0-21
  - Historical data from RIS, paper of film records

Pearce et al (Lancet 2012); Kim et al (Radiat Prot Dosimetry 2012)
NCI-UK Pediatric CT scan Cohort (2)

- Record linkage study of brain and leukemia
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  - Generic dosimetry based on average machine settings.

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- Organ dose estimates
  - Generic dosimetry based on average machine settings.

- Avoid CT scans related to cancer diagnosis:
  - Leukemia - Follow-up begun 2 years after the first CT
  - Brain tumors - Follow-up begun 5 years after the first CT

Pearce et al (Lancet 2012); Kim et al (Radiat Prot Dosimetry 2012)
Leukaemia/MDS and brain tumors dose-response

Leukaemia & MDS (n=74)

Excess relative risk per mGy = 0.036

$p$-trend = 0.010

Pearce et al, Lancet 2012
Leukaemia/MDS and brain tumors dose-response (2)

Leukaemia & MDS (n=74)

Excess relative risk per mGy = 0.036

Brain (n=135)

Excess relative risk per mGy = 0.023

p-trend = 0.010

p-trend < 0.01

Pearce et al, Lancet 2012
Comparison with the Life Span Study*

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*Restricted to similar dose range, age at exposure and follow-up time

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<td>0.006 (0.0001-0.063)</td>
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*Restricted to similar dose range, age at exposure and follow-up time

Pearce et al, Lancet 2012
Brain tumors

CT scan may have been performed because of a preexisting or unreported brain cancer

Confounding by Indication?

Underlying condition related to cancer & the condition related to CT scan frequency
Impact of Underlying Conditions

Relevant clinical information were collected and reviewed:

• **Predisposing conditions for Leukemia and Brain tumors:**
  ✓ Down syndrome, LFS, Fanconi anemia, bone marrow transplants, neurofibromatosis type 1 and 2, and others.
Impact of Underlying Conditions (2)

Relevant clinical information were collected and reviewed:

• **Predisposing conditions for Leukemia and Brain tumors:**
  - Down syndrome, LFS, Fanconi anemia, bone marrow transplants, neurofibromatosis type 1 and 2, and others.

• **Previous cancer or possible previous cancer:**
  - Previous cancer not in the UK cancer registry
  - Possible previous cancer – Possible undiagnosed cancer or if the CT could have been performed due to cancer-related symptoms.
## Impact of Excluding Underlying Conditions and Possible Previous Cancer

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Berrington de Gonzalez et al (BJC 2016)
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<td>0.023 (0.010-0.049) (n=135)</td>
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Berrington de Gonzalez et al (BJC 2016)
NCI-UK Pediatric CT Scan Cohort study

- Extended cohort follow-up
- Case-control study (detailed dosimetry)
- Collection of CT films to improve dosimetry/uncertainty
Ongoing Pediatric CT Scans Cohorts

- Canada (n=400k)
- Israel (n=70k)
- French (n=60k)
- German (n=45k)
- Australian Cohort (n=680k)
- Taiwan (n=24k)
- The Netherlands (n=45k)
Statistically significant dose-response between brain dose and brain tumors

No statistically significant dose-response between bone marrow dose and leukemia

Canada (n=400k)

Israel (n=70k)

French (n=60)

German (n=45k)

Australian Cohort (n=680k)

Taiwan (n=24k)

The Netherlands (n=45k)

Journy et al (JRP 2016); Krille et al (Rad Envi Bioph 2015), Melleupas et al (JNCI 2019)
**European Study EPI-CT – 9 countries, ~ 1 million**

- Belgium, Denmark, France, Germany, The Netherlands, Norway, Spain, Sweden and UK.
- CT scans aged 0-22 yrs
- Organ dose reconstruction – RIS and PACS - NCICT
- Underlying diseases collected from various source (hospital database and rare disease registries)
- First results – SMR
- Dose-response analysis underway

(Bernier et al, IJE 2019)
EPI-CT study – First results

SMR according to the time since first CT (1-year exclusion period)

• **1-5 years since 1st CT**
  All causes of mortality → SMR=4.2 (4.1-4.3)
  All cancer mortality → SMR=3.3 (3.0-3.7)
  Non-cancer mortality → SMR=3.7 (3.6-3.8)

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• **5+ years since 1st CT**
  - All causes of mortality → SMR=2.2 (2.2-2.3)
  - All cancer mortality → SMR=1.1 (1.0-1.2)
  - Non-cancer mortality → SMR=2.3 (2.3-2.4)

(Bernier et al, IJE 2019)
EPI-CT study – First results (2)

SMR according to the time since first CT (1-year exclusion period)

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(Bernier et al, IJE 2019)
Diagnostic X-Ray and Cancer Risk

On-going studies

US Kaiser Pediatric Imaging Case-Control Study

In utero & childhood exposures

4 Kaiser HMOs

- 750 leukemias (estimated)
- Controls matched on age & time in health plan

Imaging data from PACs

PIs: Smith-Bindman, Miglioretti, Kwan

Kwan et al (JAMA 2019)
Pooled Analysis of 9 Cohorts and Thyroid Cancer/Leukemia

9 cohorts of childhood exposure

- 394 thyroid cancers
- 221 leukemias

Diagnostic/therapeutic radiation & A-bomb

- Restricted to <200 or <100mGy

Lubin,..., Veiga (JCEM 2017)  Little,...,Berrington (Lancet Haematology, 2018)
Pooled Analysis of 9 Cohorts and Thyroid Cancer/Leukemia (2)

9 cohorts of childhood exposure
- 394 thyroid cancers
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- Restricted to <200 or <100mGy

$\text{ERR/Gy} = 11.1 \text{ (95% CI: 6.6 to 19.7)}$

Lubin, ..., Veiga (JCEM 2017)  Little, ..., Berrington (Lancet Haematology, 2018)
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Diagnostic/therapeutic radiation & A-bomb

- Restricted to <200 or <100mGy

Significant dose-response for:
Acute myeloid leukemia (p-trend=0.03)
Acute lymphoblastic leukemia (p-trend=0.02)
Screening Tests & Cancer Risk

- Screening – Testing for a disease in a population with no symptoms
  - Doses lower than diagnostic
  - Large numbers of healthy individuals → will not develop the disease
  - Benefits (reducing mortality) >>>>> Risks
  - Very low doses → large sample size
  - Risk projection rather than direct studies
Screening Tests & Cancer Risk (2)

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  - Benefits (reducing mortality) $\gg\gg\gg$ Risks
  - Very low doses $\rightarrow$ large sample size
  - Risk projection rather than direct studies

• 2 mammograms at age 35 (10mGy)
• 20 years follow-up
• 60 million women for 50% power (Land, 1981)
Screening Examinations: Risk Projection

- Younger screening ages
  - Lower cancer incidence rates $\Rightarrow$ lower absolute mortality reduction
- Mortality reduction from screening $\gg$ radiation induced mortality
  - Mammography BRCA carriers $>$ age 35
  - Lung CT smokers $>$ age 50
  - CT colonography $>$ age 50

Repeated low-dose medical exposures related to increased cancer risk....but absolute risks generally small
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Absolute excess risk from CT:

1 Head CT before age 10 → 1 excess case of leukemia and one excess case of brain tumor per 10,000 patients
Repeated low-dose medical exposures related to increased cancer risk, but absolute risks generally small

Evidence of excess risks from cumulative doses <100mGy for childhood leukemia & thyroid cancer
Repeated low-dose medical exposures related to increased cancer risk… but absolute risks generally small

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Risk estimates for non-uniform exposures and children and women
Repeated low-dose medical exposures related to increased cancer risk….but absolute risks generally small

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Risk estimates for non-uniform exposures and children and women

ERR/Gy generally compatible with A-bomb Life Span Study (DDREF = 1?)
Diagnostic medical radiation exposure continues to expand and evolve
Diagnostic medical radiation exposure continues to expand and evolve

Expansion of electronic medical records and digital imaging facilitates studies
Future Opportunities (3)

Diagnostic medical radiation exposure continues to expand and evolve

Expansion of electronic medical records and digital imaging facilitates studies

Opportunities to study non-cancer outcomes from low doses eg CVD & cataracts
Why is it important to study diagnostic radiation exposure and cancer risk?

A. Public health concern
B. Implications for clinical decision making
C. Learn about radiation risk in low-dose fractionated exposure
D. All above
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A. Public health concern
B. Implications for clinical decision making
C. Learn about radiation risk in low-dose fractionated exposure
D. All above
Medical diagnostic radiation exposure should be clinically justified and dose optimized.

A. True

B. False
Medical diagnostic radiation exposure should be clinically justified and dose optimized.

A. True  
B. False