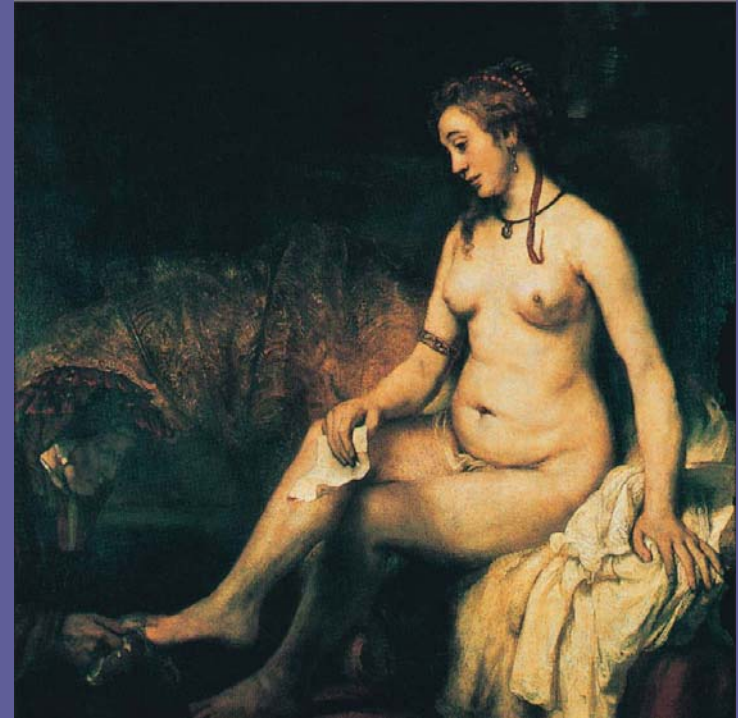


Radiation exposure and the risk of breast cancer in BRCA 1/2 mutation carriers



"Bathsheba bathing" by Rembrandt, 1654

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Radiation exposure and breast cancer risk in BRCA 1/2 carriers

- Background
- Diagnostic radiation in BRCA carriers
- Therapeutic radiation in BRCA carriers
- Radiation in women with a family history of breast cancer
- Conclusions

Ionizing radiation and breast cancer in BRCA1/2 mutation carriers

- **Hypothesis**

BRCA1/2 carriers have an increased risk of radiation-induced breast cancer

- **Mechanism**

function BRCA1/2 genes: DNA repair of double strand breaks caused by ionizing radiation

- **Concerns**

- Low dose: frequent (mammographic) screening of BRCA1/2 carriers, from a relatively young age onwards
- High dose: radiotherapy treatment for primary breast cancer

Early literature on risk of radiation-induced breast cancer in genetically predisposed women *prior to BRCA1/2 test*

- 1989 -1990, *Breast Cancer Research Treatment*
 - discussion on use of mammographic screening in genetically predisposed women (Lynch et al, BCRT 1989; comment Sluijter/Koten/Den Otter et al 1989; author reply Lynch et al 1990)
- Den Otter et al, *Anticancer research*
 - 1993: view-presenting paper: exclusion from mammographic screening of women genetically predisposed to breast cancer will probably eliminate mammographically-induced breast cancer
 - 1996: theoretical/mathematical study: calculations suggest that in women with an inherited gene for breast cancer one excess tumor in one out of 10 women will be induced by 20 mammograms

Diagnostic radiation and breast cancer risk in BRCA1/2 carriers

	Study design	N	Exposure	Association BC risk
Andrieu et al, JCO '06	Retrospective cohort	1601	Chest X-rays before and after age 20	+
Gronwald et al, BCRT '08	Case-case (BRCA+ vs BRCA-)	296	Chest X-rays before age 30	+
Narod et al, Lancet Onc '06	Case-control	3200	Age at 1 st screening mammography	-
Goldfrank et al, CEBP '06	Case-control	213	Number of mammograms	-

IBCCS Study of X-ray exposure and breast cancer risk in BRCA carriers, Andrieu et al, JCO 2006

International BRCA1/2 Carrier Cohort Study

Retrospective cohort, N=1,601 carriers (53% affected)

2 Analytic approaches:

- **Whole cohort**

Weighted vs. unweighted analysis

- Necessary since breast cancer dx may have led to genetic testing → oversampling of affected individuals in cohort

- **Incident cohort**

- Necessary to reduce survival bias (some women interviewed long after breast cancer dx → bias if exposure related to survival)
- Restriction to individuals diagnosed/ censored within 5 yrs prior to interview (n=969, 295 affected)

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Andrieu et al, JCO 2006

chest X-rays before and after age 20

- International BRCA1/2 Carrier Cohort Study
- Retrospective cohort, N=1,601 carriers (53% affected)

Chest X-ray exposure	Risk estimate
Ever/never	1.54 (1.1 - 2.1)
Ever/never (<i>pseudo-incident cohort</i>)	1.75 (1.1 – 2.8)
Ever/never < age 20	1.76 (0.9 - 3.4)
Exposed < age 20 only (<i>attained age<41</i>)	2.61 (1.3 - 5.4)
Exposed < age 20 only (<i>born>1949</i>)	4.64 (2.2 - 10.9)

Andrieu et al, JCO 2006

chest X-rays before and after age 20

Weighted Cox regression Analysis of combined X-ray exposure in the pseudo-incident cohort with follow-up beginning five years prior to interview

Exposure	Pyrs (BC)	HR ¹	95%CI
Combined X-ray vs.			
Never	773 (28)	1.00	
Before age 20 only	137 (12)	5.21	1.6-17.5
After age 20 only	256 (26)	1.91	0.9-4.1
Before and after age 20	978 (88)	1.98	1.1-3.7
1-4 X-rays before and after age 20	705 (50)	1.76	0.9-3.4
5+ X-rays before or after age 20	666 (76)	2.69	1.4-5.3

¹Adjusted for parity (ever/never), stratified by country group and birth cohort

Andrieu et al, JCO 2006

Mammograms not included in analysis

Why?

Concern about bias:

Family history of **early** breast cancer



Early start of mammographic screening

Confounding by indication might explain **more** mammographies at early ages in carriers with breast cancer at young ages

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Narod et al, Lancet Onc 2006

age 1st screening mammography

- Case-control study in 44 centers, six countries: North America, Europe and Israel
 - N=1,600/1,600 matched on BRCA, year of birth, and country
 - Only prediagnostic mammograms included
- 41% cases and 46% controls exposed
- Mean age 1st mammography: 35.3 ±7.8; 14% had 1st mammography < age 30
- *No association* between earlier start of mammography and breast cancer risk

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Goldfrank et al, CEBP 2006

number of mammograms

- 213 BRCA carriers from New York (US) and Barcelona (Spain); 85 affected
- Information on mammograms before enrollment/diagnosis (retrieved prior to test result)
- 89% exposed
- Median age 1st mammogram 35 years
- No association between prediagnostic mammograms (number and age at 1st) and breast cancer

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Gronwald et al, BCRT 2008

chest X-rays before age 30

- Case-case study; all drawn from national breast screening registry Poland
- 138 BRCA1+ vs. 158 BRCA1-
- BRCA1+:
 - More frequent chest X-ray < age 20
 - 1.8 chest X-rays < age 30 vs. 1.0 in BRCA1- (p<0.01)
 - Breastca risk associated with ever chest X-ray < age 30 for BRCA1+ vs. BRCA1- carriers: OR =1.8 (1.2 - 2.9)

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Limitations of 4 studies on diagnostic radiation in BRCA1/2 carriers

- Small sample size in 2/4 studies
- Incomplete exposure measurement
- Retrospective design
 - Self-reported exposure; no objective verification
 - Differential recall of exposure?
 - Literature: largely non-differential misclassification → attenuated risk estimates
 - Prevalent cases: potential survival bias
- Mammography exposure: self-selection for screening by family history? Would lead to spurious positive association and not to null finding.

Diagnostic radiation and breast cancer risk in BRCA1/2 carriers in the Netherlands

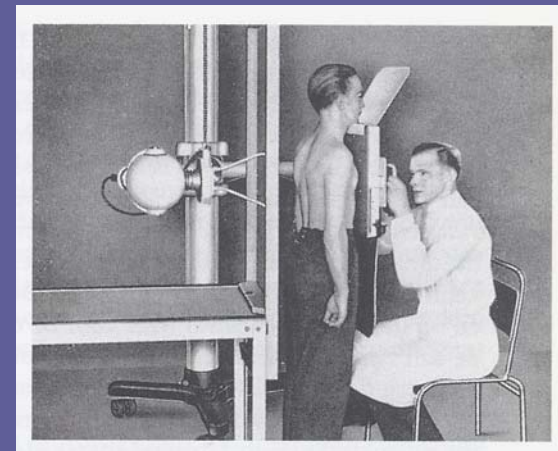
Pijpe et al, in preparation

- Retrospective cohort
- N=1,113 BRCA1/2 carriers
- Chest X-rays and fluoroscopies

Poster session
today at 3pm

Preliminary results

- Exposure to fluoroscopy *and* chest X-rays < age 20: 1.49 (0.98 – 2.25)
- Stronger risk increases in pseudo-incident cohort and subgroups



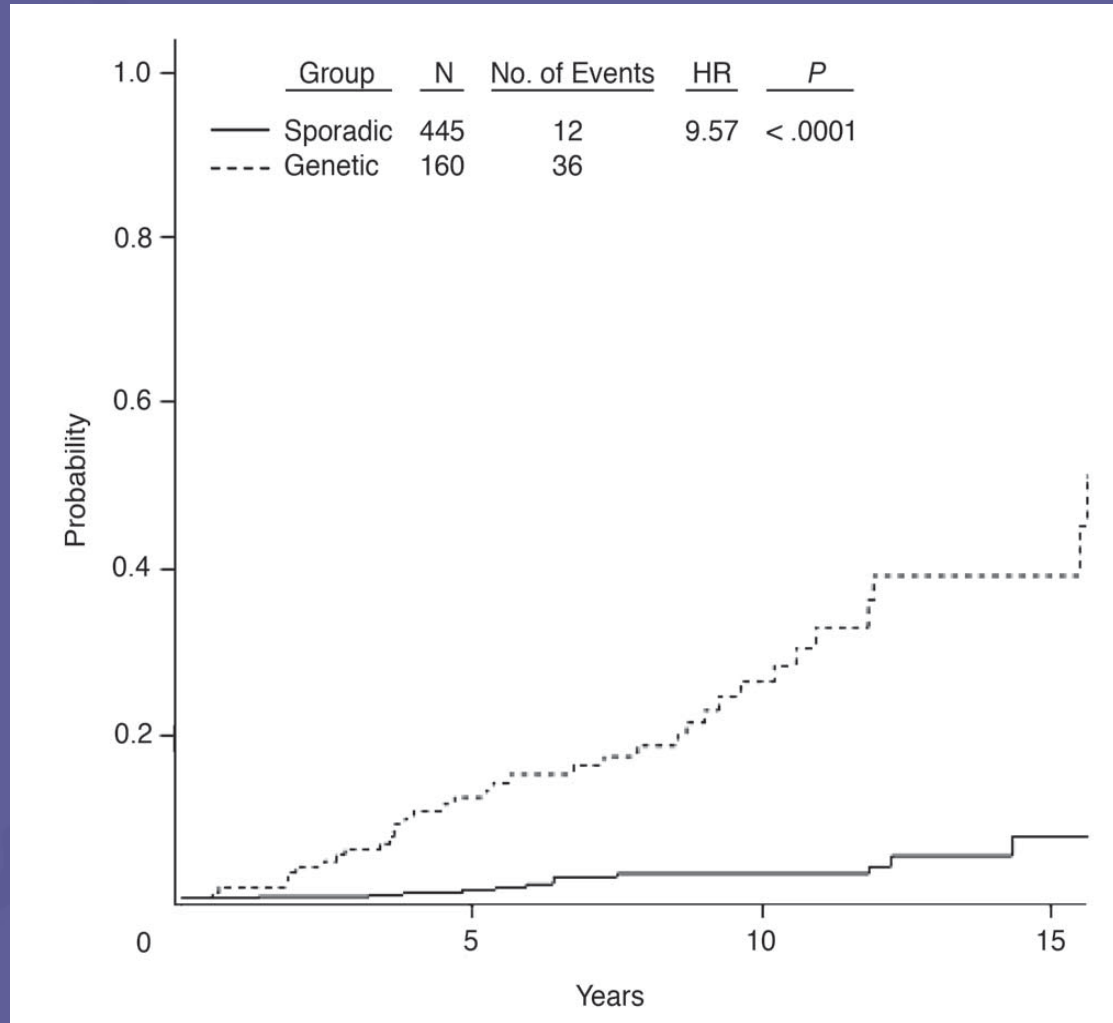
Funding: Dutch Cancer Society and EU Gene Rad Risk

Does benefit from early mammographic screening outweigh the radiation risk?

Estimated risk of radiation-induced breast cancer from mammographic screening in young BRCA mutation carriers (Berrington de Gonzalez et al, JNCI 2009)

- Annual mammographic screening of carriers at
 - age 25-29: no benefit
 - age 30-34: no or small benefit
 - Age 35 or older: some net benefit
- Results dependent on number of assumptions: e.g.
 - Mortality reduction mammography 15-25%
 - Lead time for breast cancer of 2 years
 - Survival probability carriers same as general population
 - Linear no-threshold model
 - Additive/(supra)multiplicative interaction BRCA and radiation

Overall contralateral breast cancers in BRCA1/2 mutation carriers and sporadic controls. HR, hazard ratio.



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Pierce et al JCO 2000

Radiotherapy for first breast cancer

- 71 BRCA 1/2 carriers with BC and 213 women with sporadic BC
- Median follow-up 5.3 years
- No increased risk of radiation-associated complications in carriers (skin, subcutaneous tissue, lung)
- No effect on CBC, but power very low (22 cases)
- Pierce 2006 with 160 carriers and 445 controls does not report on RT effect

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Metcalfe et al JCO 2004

Radiotherapy for first breast cancer

- 491 BRCA 1/2 carriers with breast cancer
- Mean follow-up 9.2 yrs
- 10-year actuarial risk of CBC: 29.5%
- 46% received RT
- Multivariate HR associated with RT: 0.86 (95%CI 0.56 – 1.34)
- Reduced HRs for oophorectomy and tamoxifen (n.s.)
- Testing and survival bias

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Broeks et al BCR 2007

Do DNA-damage repair pathway genes increase the risk of radiation-induced breast cancer?

- Case-only study of contralateral breast cancer (ideal for assessment of gene-environment interactions)
- 247 patients (80% response) with contralateral breast cancer after 1st breast cancer before age 50 (1966-2000)

Assumption: independence between genotype and exposure (RT)

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(Broeks et al. Breast Cancer Res 2007;9:R26)

Case-only study examining role of DNA damage repair pathway genes in radiation-induced contralateral breast cancer (CBC)

Mutations in	CBC after RT (n=169)	CBC after surgery only (n=78)	OR for CBC after RT
BRCA1/2	14.2%	10.3%	1.5 (0.6-3.4)
ATM	2.4%	0%	-
CHECK2	7.7%	2.6%	3.2 (0.7-14.4)
Any DDRP mutation	24.3%	12.8%	2.2 (1.1-4.6)

Carriers of germline mutations in DDRP genes have increased risk of RT-induced breast cancer, compared to non-carriers

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Radiotherapy and contralateral breast cancer risk in BRCA1/2 carriers

- BRCA carrier studies observed no association (Metcalfe et al, JCO 2004; Pierce et al, JCO 2000/2006), but low power

Recent Dutch Study:

- Among women with breast cancer, the risk of radiation-induced CBC ≥ 5 yrs after RT:
OR 2.5 (1.03 – 6.10) for carriers of mutations in DNA damage repair pathway genes* vs. non-carriers (Broeks et al BCR 2007)

Association due to BRCA 1/2?

* note: mutation in DNA damage repair pathway: BRCA1, BRCA2, CHEK2 and ATM

Radiation exposure and breast cancer in women with *positive family history*

- **Inconsistent findings!**
- **Diagnostic radiation:**
 - (Ronckers et al, CEBP 2008; Ma et al, Epidemiology 2008; John et al, Int J Cancer 2007; Hill et al, Cancer Causes Control 2002)
- **Radiotherapy:**
 - (Hill et al, Blood 2005; Shore et al, JNCI 1986; Kenney et al, Ann Int Med 2004; Hooning et al, JCO 2008)

Roles of radiotherapy and chemotherapy in the development of contralateral breast cancer

Maartje Hooning, Berthe Aleman, Michael Hauptmann, Margreet Baaijens, Jan Klijn, Ruth Noyon, Marilyn Stovall, Flora van Leeuwen

M. Hooning J Clin Oncol 2008; 26(34):5561-8.

Funded by the Dutch Cancer Society



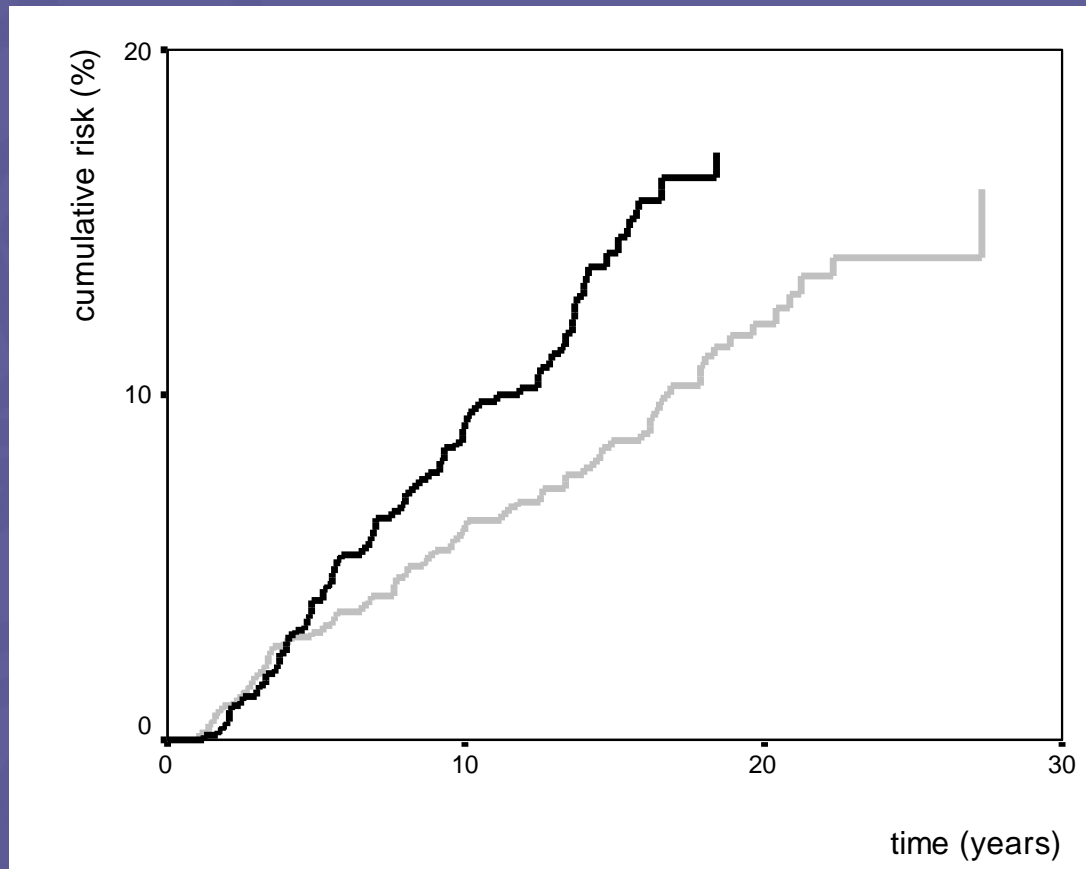
Dutch Late Effects of Breast Cancer Study

- **Retrospective cohort study (n=7425)**
- **Patients with breast cancer stage I-III**
- **Admitted to NKI (Amsterdam) or DDHK (Rotterdam)**
- **Primary treatment between 1970-1986**
- **Age at diagnosis: up to 70 years**
- **94% complete follow-up**
- **Median follow-up 14 years**

M. Hooning J Clin Oncol 2008; 26(34):5561-8.

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Risk of CBC by treatment modality, in patients <45 yrs at BC diagnosis



— Postlumpectomy RT
tangential fields
— Postmastectomy RT

HR vs postmast RT: 1.53 (1.11 – 2.09)

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M. Hooning J Clin Oncol 2008; 26(34):5561-8.

Radiation dosimetry

1044 patients at NKI, treated before age 45

Detailed data collection:

- Quadrant of CBC
- Details on RT (field configuration, RT technique [rad energy], total dose, fractionation)
- Dose to CBC was estimated by M. Stovall for 31 different RT regimens: various RT regimens for tangential breast field, IMC field, chest wall fields etc., and brachy-therapy

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Effect of radiation dose on risk of medially located CBC; Cox analysis in patients < 45 yrs (n=1044)

Radiation dose on
medial part of CB

Risk of medial CBC*

Gy

HR (95% CI)

0

1.0 (ref)

0-3.6

1.23 (0.34-4.48)

3.6-6.6

2.72 (0.75-9.79)

≥ 6.6

5.26 (1.44-19.3)

Linear ERR per Gy**

0.37 (0.04-1.78), p=0.013 (trend)

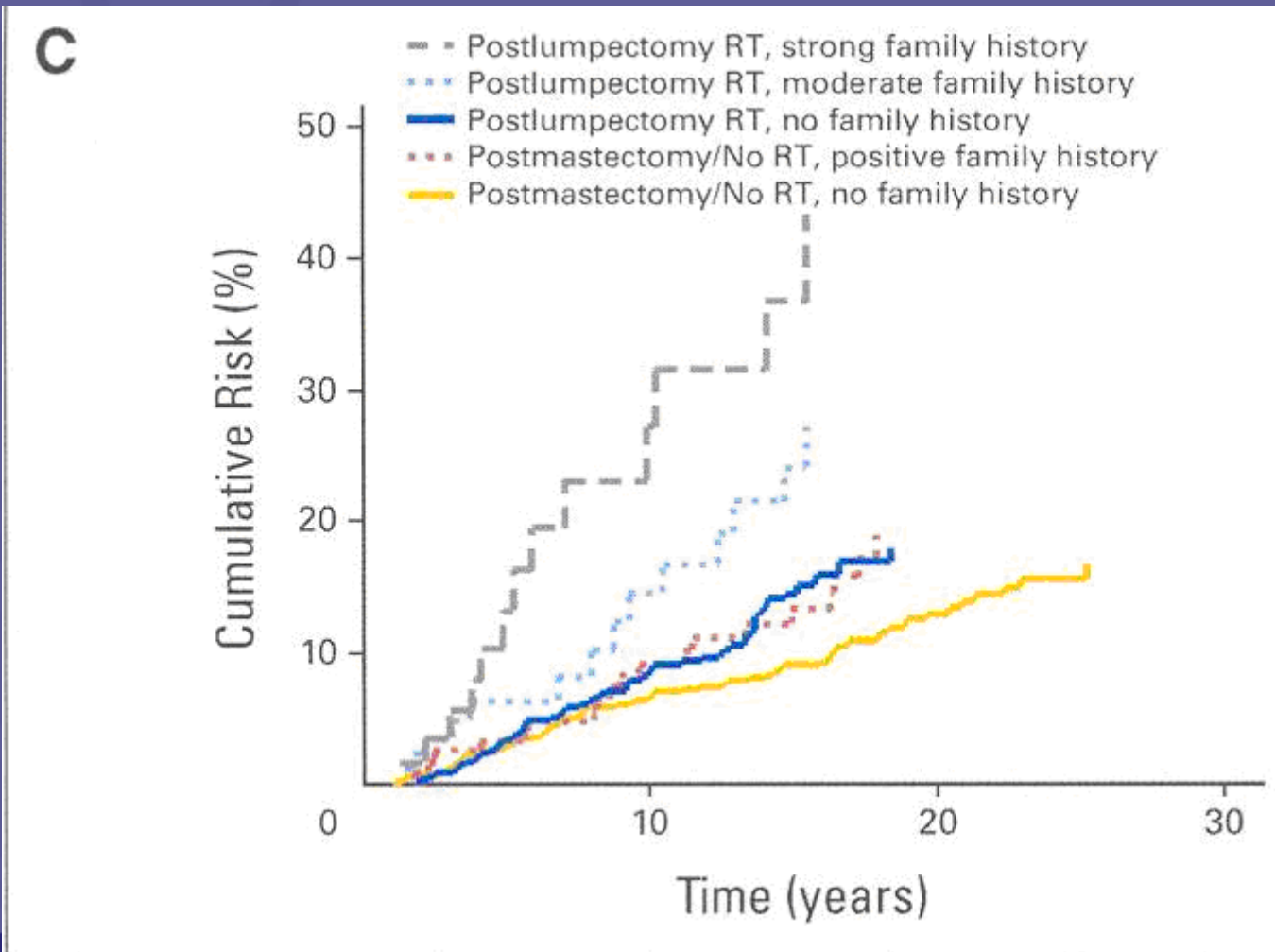
* Adjusted for age (continuous), adjuvant CT

** Based on model $RR=1+\beta \cdot \text{dose}$ where $\beta=ERR$

M. Hoening J Clin Oncol 2008; 26(34):5561-8.

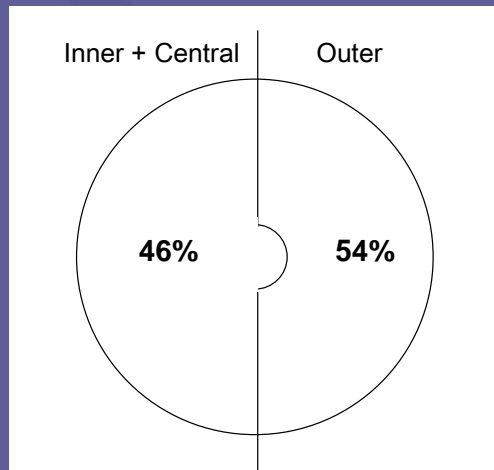
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Independent and joint effect of radiotherapy (RT) regimen and family history of BV on CBC risk (Cox model) in patients <45 yrs at BC diagnosis, CT, chemotherapy, HR, Hazard ratio

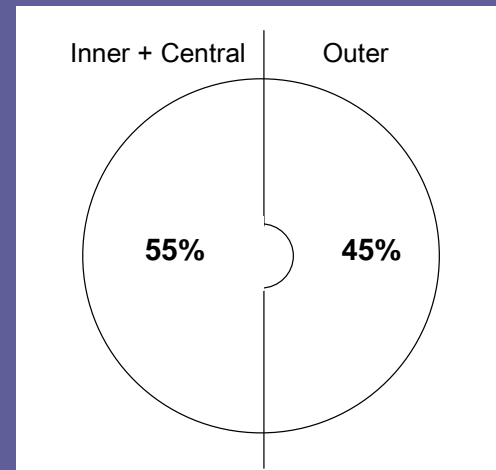


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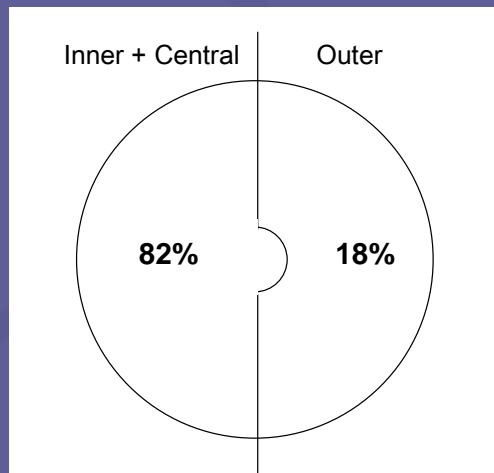
Distribution of localization of CBC by family history of BC, in patients irradiated < age 45 yrs (n=943)



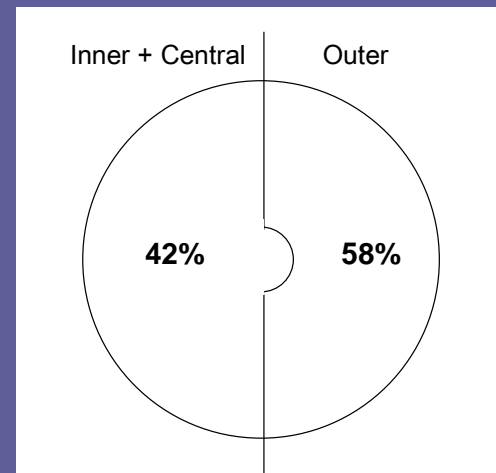
Overall



≥ 1 Relatives with BC



≥ 3 Relatives with BC



No relatives with BC

Preliminary conclusions

Increased risk of radiation-induced breast cancer in BRCA carriers?

- Inconsistent results
- Radiation sensitive subgroup of BRCA 1/2 carriers?
- Or radiation-sensitive subgroup of women with mutations in other BC genes/gene variants?
- Need for large and well-designed studies!

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GENE-RAD-RISK

*Radiation exposures at an early age:
impact of genotype on breast cancer risk*



- **Coordination: IARC**
- **Aims:**
 - To test whether mutations or polymorphisms in specific DNA repair genes increase the risk of radiation induced cancer, with specific focus on breast cancer.
 - To study the possible modifying effects of reproductive factors and cancer therapies other than radiation on the risk of radiation-induced breast cancer.
- **2 study arms:**
 - Cancer survivor cohorts: childhood cancer survivors and Hodgkin's Disease (HD) patients,
 - **BRCA1/2 mutation carrier cohorts**



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GENE-RAD-RISK

BRCA1/2 mutation carrier cohort



- **3 nationwide cohort studies:**
 - UK (EMBRACE), France (GENEPSO), the Netherlands (GEO-HEBON)
- **Estimated sample size: N=2000 (43% affected)**
- **Information on:**
 - Fluoroscopies, chest X-rays, mammograms, CT-scans, high dose radiotherapy, and other sources of ionizing radiation (incl. occupational)
 - Measures: ever/never, age 1st, number <20 / 20-29 / 30-39 (/ 40-49)
- **Analysis**
 - Single and combined measures, and *cumulative breast dose score* based on exposure- and calendar-specific dose estimates