Genetic Radioepidemiology of Contralateral Breast Cancer: A WECARE Study Update

The Intersection of Radiobiology, Radioepidemiology, and Safety: Memorial Symposia for Jean St. Germain

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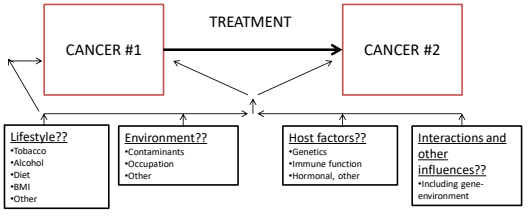
Goal: Demonstrate there are subgroups of women at increased risk of treatment–associated contralateral breast cancer (CBC) by virtue of their genetic make-up

- **Challenges of studying contralateral breast cancer**
- **WECARE Study overview**
- **WECARE Study results: rare candidate genes and common genetic variants (GWAS)**
- **Conclusion**

Studies of contralateral breast cancer



Study cancer survivors and determine risk factors associated with second primary breast cancer. Many influences will contribute, including interactions between exposures. Focus is on known breast cancer risk factors

Adapted from Travis LB. Acta Oncologica 2002

Studies of genetic treatment-associated second cancers require large numbers of patients, long-term follow-up, biospecimens and detailed treatment data

Study	Size	First Cancer Dx	Second Cancer dx	Dosimetry /Agent	Genes Implicated
CCSS Mertens et al, 2004	650 Survivors	Any Childhood cancer	Various	No	*XRCC1* *GSTM1* *GSTT1*
Best et al, 2011	100 cases	Childhood HL	Various	No	*PRDM1*
CCSS + SJ-LIFE Morton et al, 2017	207 Cases 2,774 Controls	Any childhood cancer	Breast	Yes	*PROX1* *TAGLN* *RPS6KC1*

Childhood cancer survivor studies provide best evidence of radiation associated genetic risks.

Genetic risks of second primary cancers and treatment in adults, poorly studied

Study	Size	First Cancer Dx	Second Cancer dx	Dosimetry /Agent	Genes Implicated
CBC in Dutch Women Broeks et al, 2007	247 CBC Cases	Breast	Breast	No	*BRCA1* *BRCA2* *CHEK2* *ATM[Truncating]*
Treatment-related AML Anderson et al, 2008	51 t-AML 89 Controls	Various	AML	No	*NPM1*
HNC treatment study Zhang et al, 2011	1,269 HN Cases (Cohort)	HNC	Various	No	*P53* *P73*
WECARE Study					

WECARE Study one of the few specifically designed to examine joint effects of treatment and genetics in the etiology of breast cancer

- **Cases are women with contralateral breast cancer (CBC)**
- **Controls are women with unilateral breast cancer (UBC)**

Hypothesis

Women who are carriers of certain genetic mutations will be more susceptible to treatment-, and especially radiation-, induced breast cancer than are non-carriers.

Bernstein et al, Br Ca Res 2004

Eligibility of the WECARE Study Cases and Controls

CBC Cases (*n* = 1521)

- Diagnosed since 1/1/1985 with incident breast cancer
- Diagnosed since 1/1/1986 with contralateral breast cancer (CBC)
- One year or longer time between primaries
- < 55 at first primary dx
- No other cancer diagnosis

UBC Controls (*n* = 2212)

- With unilateral breast cancer (UBC)
- Individually matched to cases on:
  - Registry
  - Age
  - Dx date of first breast cancer
  - Race
- No other cancer diagnosis

WECARE Study population was recruited in two phases (WECARE I & WECARE II) using nearly identical data collection methods/protocols

WECARE I Study, 2001- 2004 (CBC=708, UBC=1399)	WECARE II Study, 2010 - 2013 (CBC=813, UBC=813)
Matching: 1:2 counter-matching	Matching: 1:1 matching
Recruitment: SEER (Seattle, LA, Iowa, Irvine) and Danish Cancer Society	Recruitment: SEER (Seattle, Iowa, Northern CA), Danish Cancer Society, and Toronto
Eligibility: • 1 st br ca dx: 1/1/1985 and 1/1/2000 • ≥1 yr interval 1st & 2nd in situ/invasive (cases only)	Eligibility: • 1st br ca dx: 1/1/1990 and 1/1/2008 • ≥2 yr interval 1st & 2nd invasive (cases only)
Biospecimens : blood, cryopreserved lymphocytes, cell lines, tissue	Biospecimens: saliva, buccal cell, tissue
Mutation screening: ATM; CHEK2; PAIB2, BRCA1/2; GWAS 1M SNPs, Whole genome sequencing (WGS) Whole Exome Sequencing (WES)	Genotyping 30k custom select SNPs
	Other: Mammographic Density

Treatment for a first primary effects risk of developing CBC: however, protective effect of chemotherapy and tamoxifen may not persist

Treatment	Time since Dx (yrs)	RR*	95% CI
Chemo	1-4	0.6	0.5 – 0.8
	5-9	0.7	0.6 – 0.9
	≥10	0.9	0.7 – 1.3
Tamoxifen	1-4	0.7	0.5-0.9
	5-9	0.8	0.6-1.0
	≥10	0.9	0.7-1.3

* Adjusted for exact age at first breast cancer diagnosis, family history of breast cancer, histology, stage, and all treatments

Bertelsen et al, JNCI 2008; Langballe Br Ca Res 2016

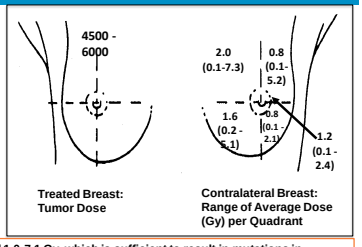
Variability in efficacy of tamoxifen treatment may be due to CYP2D6 phenotype

Phenotype	Tamoxifen	Case	Control	RR*	95% CI
Extensive Metabolizer	No	904	1190	1.0	
	Yes	386	676	0.63	0.5-0.8
Intermediate Metabolizer	No	88	130	1.0	
	Yes	58	77	0.9	0.6-1.6
Poor Metabolizer	No	57	21	1.0	
	Yes	98	32	1.2	0.6-2.4

Adjusted for exact age, are adjusted for age at menarche, number of full term pregnancies, age at menopause, family history, treatment (hormone, RT), histology, ER status, stage. *Brooks et al, BMC 2018*

Scatter doses received to the contralateral breast during radiotherapy (RT) can be substantial and varies across the breast

- Sources of treatment/tumor characteristics from:
  - registry records
  - Hospital charts
  - Pathology/surgery reports
  - Doctor office /mammography records
  - Radiation oncology files
- Missing Data
  - ~ 7% patient records inadequate for dosimetry
  - ~ 2% participants had no info



Scatter dose from RT can be substantial 1.0-7.1 Gy, which is sufficient to result in mutations in oncogenes and tumor suppressor genes. Excess risk range ~5.5-10.7 cases/104 woman-years/Gy

Stovall, INT J RAD BIOL 2010

Overall no evidence of excess risk CBC associated with radiation using different estimates of radiation exposure

RT Measure	Dose CB* (Gy)	Case	Control	RR***	95% CI
Never RT	--	641	522	1.0	
Ever RT	--	880	1689	1.0	0.9-1.2
Average dose to the CB	0	632	510	1.0	
	0 < - 1.0	263	451	1.1	0.9-1.3
	≥ 1.0 (1-8.9)	621	1245	1.0	0.9-1.2
Location-specific dose to the CB	0	542	452	1.0	
	0 < - 1.0	435	807	1.1	0.9-1.3
	≥ 1.0 (1-9.3)	347	659	1.1	0.9-1.3

*Scatter radiation dose to the CB ***Adjusted for age at first diagnosis of breast cancer, age at menarche, family history of breast cancer, total number full-term pregnancies, age at menopause, chemo/hormonal treatment, histology, and stage

Updated from Stovall, INT J RAD BIOL 2010

Risk of radiation-associated CBC is inversely related to age at exposure and proportional to dose (location-specific dose)

Age/Latency	Dose [a] (Gy)	Case	Control	RR[b]	95% CI
	0	85	81	1.0	
< 40	0 < - 1.0	84	159	1.2	0.8-1.8
5+yr latency	≥ 1.0 (1-7.3)	76	111	2.0	1.2-2.9
	0	124	96	1.0	
40-44	0 < - 1.0	105	202	1.1	0.7-1.5
5+yr latency	≥ 1.0 (1-5.1)	74	145	0.9	0.6-1.3
	0	333	275	1.0	
45-54	0 < - 1.0	246	446	1.1	0.9-1.4
5+yr latency	≥ 1.0 (1-9.3)	197	403	1.0	0.8-1.3

Scatter radiation dose to the CB ***Adjusted for age at first diagnosis of breast cancer, age of menarche, family history of breast cancer, total number of full-term pregnancies, age at menopause, chemo/hormonal treatment, histology, and stage. *Updated from Stovall, INT J RAD BIOL 2010*

BRCA1/2 screening of 2107 WECARE Study participants reveals 181 carriers of deleterious mutations

- 113 unique known deleterious mutations
  - 57 on *BRCA1*
  - 56 on *BRCA2*
- 181 carriers of deleterious mutations
  - 73 UBC
  - 108 CBC
- 72 carriers of deleterious *BRCA2*
- 109 carriers of deleterious *BRCA1*

Malone et al, JCO 2009

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Carriers of *BRCA1/2* mutations have an increased risk of CBC

Carrier Status	Case	Control	RR	95% CL
No BRCA	597	1325	1.0	
BRCA1	67	42	4.5	2.8 – 7.1
BRCA2	41	31	3.4	2.0 – 5.8
BRCA1/2	108	73	4.0	2.8 – 5.7
<40	59	30	7.2	3.9 – 13.4
40-54	49	43	2.7	1.7 – 4.5

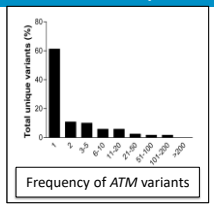
Adjusted for exact age, are adjusted for age at menarche, number of full term pregnancies, age at menopause, family history, treatment (chemo, hormone), histology, and stage. *Begg et al., JAMA 2008*

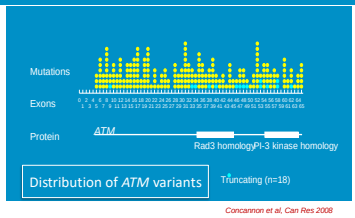
No evidence that risk of CBC among *BRCA1/2* Carriers is modified by radiation exposure

Carrier Status	Dose (Gy)	Case	Control	RR*	95% CI
No BRCA	No	256	223	1.0	
	0<1.0	133	508	1.0	0.8-1.3
	≥1.0	118	406	1.2	0.9-1.6
BRCA1/2	No	40	9	1.0	
	0<1.0	35	27	1.9	0.7-4.6
	≥1.0	21	26	1.1	0.4-2.6

Adjusted for exact age, are adjusted for age at menarche, number of full term pregnancies, age at menopause, family history, treatment (chemo, hormone), histology, stage. *Bernstein et al. Eur J Cancer, 2013*

ATM mutation screening in 2192 WECARE Study participants identified 242 unique variants; most rare





Concannon et al, Can Res 2008

ATM Mutation screening results:

- Distribution strongly skewed towards rare variants:15 variants had minor allele frequency >1%
- > 50% of the variants each occurred in only a single subject: 103 predicted to cause an amino acid change; 18 distinct truncating mutations in 21 patients (A-T causing)

Risk of CBC by *ATM* carrier status shows no significant increase

Mutation Classification	Cases	Controls	RR[b] (95% CI)
Variant Broadly Classified			
Wildtype	223	418	1.0
Silent	78	134	1.1 (0.8-1.6)
Missense	68	113	1.2 (0.8-1.8)
Splicing	4	14	0.7 (0.2-2.4)
Truncation	11	6	2.8 (0.9-8.9)
Common[a]	308	655	0.8 (0.6-1.0)
Clinical Classification[c]			
Wildtype	223	418	1.0
Pathogenic/likely	18	16	1.9 (0.9-3.6)
Rare missense	39	56	1.5 (0.9-2.5)

*Common variants refers to ATM variants carried by ≥1%; [b] Adjusted for exact age at first primary, age at menarche, nulliparity, family history of breast cancer, chemo, RT. Menopausal status, histology, stage, hormonal treatment, BRCA1/2. [c]ClinVar. *Updated Concannon et al, Can Res 2008, Bernstein et al, JNCI 2010*

Risk of CBC is increased among *ATM* missense carriers who received radiation

ATM Status	Dose (Gy)	Case	Control	RR[2] (95% CI)
Variants Broadly Classified				
Wildtype	0	112	72	1.0
	0<1.0	57	177	1.0 (0.7-1.6)
	≥1.0	54	169	1.1 (0.7-1.7)
Pathogenic/likely	0	8	5	1.0
	0<1.0	5	5	1.6 (0.4-7.0)
	≥1.0	5	6	1.7 (.06-4.8)
Rare Missense	0	26	30	1.0
	0<1.0	21	45	2.7 (1.2-6.4)
	≥1.0	21	38	3.3 (1.4-8.0)
SIFT Missense Classification				
Tolerated	0	12	16	1.0
	0<1.0	9	27	1.6 (0.5-5.2)
	≥1.0	10	23	1.8 (0.6-5.8)
Deleterious	0	14	14	1.0
	0<1.0	12	17	5.3 (1.6-17.3)
	≥1.0	11	15	5.8 (1.8-19.0)

[1] Common variants refers to ATM variants carried by ≥1%; [2] Adjusted for exact age at first primary, age at menarche, nulliparity, family history of breast cancer, chemo, RT. Menopausal status, histology, stage, hormonal treatment, BRCA1/2. [3]ClinVar. *Updated Bernstein et al, JNCI 2010*

Risk is further increased among youngest exposed ATM carriers

Age/SIFT Score	RT	Case	Control	RR (95% CI)
<45 years				
Tolerated	No	7	3	1.0
	Yes	9	25	0.4 (0.1-2.4)
Deleterious	No	5	10	1.0
	Yes	10	16	10.4 (2.3-47.2)
≥45 years				
Tolerated	No	10	14	1.0
	Yes	10	30	1.9 (0.6-6.2)
Deleterious	No	9	5	1.0
	Yes	15	25	2.4 (0.6-9.5)

*Adjusted for exact age, age at menarche, number of full pregnancies, age at menopause, family history, treatment (chemo, hormone), histology, and stage. *Bernstein et al, JNCI 2010*

GRS approach examining for (published) SNPS in NHEJ pathway known to be associated with radiation

- Chose top 69 literature based SNPs from the 7 genes in NHEJ pathway
  - (*DCLRE1C, LIG4, NHEJ1, PRKDC, XRCC4, XRCC5, XRCC6)*
- Of these, 24 were excluded due to strong disequilibrium ($r^2 > 0.5$) with others in the pathway.
- For an initial pass at risk, we used directionality from WECARE main effect (vs published)
- Number of alleles across all NHEJ SNPs were summed. Dichotomized score at median based on all women.

Watt et al, submitted

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Published SNPs (n=52) from NHEJ pathway explain increased risk of CBC due to radiation, but in small subset

Level	RT GRS Median	Dose (Gy)	Case	Control	RR	95%CI	P	Ptrend
<40	Below (36-58)	0	65	74	Ref			
		0.01-<1	46	111	0.8	0.4-1.7	0.64	
		1+	37	92	1.1	0.5-2.3	0.86	<0.0001
	Above (59-75)	0	58	38	1.6	0.8-3.0	0.15	
		0.01-<1	32	54	1.9	1.0-3.7	0.06	
		1+	46	42	4.4	2.3-8.6	<0.0001	
<40, 5+ yrs Latency	Below (36-58)	0	39	45	Ref			
		0.01-<1	31	59	1.4	0.6-3.2	0.47	
		1+	26	49	1.6	0.6-4.1	0.31	0.0009
	Above (59-75)	0	33	26	1.3	0.6-2.9	0.45	
		0.01-<1	17	29	1.8	0.8-4.2	0.18	
		1+	28	19	5.5	2.2-13.6	0.0002	

Adjusted for 3 eigenvectors, age at first diagnosis, stage at first diagnosis, histology at first diagnosis, menopausal status one year prior to first diagnosis, age at menarche, number of full-term pregnancies at first diagnosis, non-RT treatment of the first primary, and family history of breast cancer. *Watt submitted*

24% of radiation-associated CBC among young women exposed to ≥ 1Gy of radiation can be attributable to SNPs in the NHEJ pathway.

Age/Latency	Dose * (Gy)	Case	Control	RR***	95% CI
	0	85	81	1.0	
< 40	0 < - 1.0	84	159	1.2	0.8-1.8
5+yr latency	≥ 1.0 (1-7.3)	76	111	2.0	1.2-2.9
	0	124	96	1.0	
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45-54	0 < - 1.0	246	446	1.1	
5+yr latency	≥ 1.0 (1-9.3)	197	403	1.0	0.8-1.3

Population attributable risk due to NHEJ GRS and dose is 24%

Scatter radiation dose to the CB ***Adjusted for age at first diagnosis of breast cancer, age of menarche, family history of breast cancer, total number of full-term pregnancies, age at menopause, chemo/hormonal treatment, histology, and stage.

Summary: There appear to be subgroups of women at increased risk of treatment–associated CBC by virtue of their genetic make-up

- Especially evidence of radiation-sensitive sub-group of young women with breast cancer (eg <40, 5+ latency) who carry genetic factors that may explain excess risk.
- Risks associated with rare genetic factors are relatively high, but only count for <3-4% the total population
- Common genetic factors may account for a substantial amount of risk, among subgroups.

Further studies are needed to identify women who are particularly susceptible to CBC due to genetic host factors, exposures or a combination

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