INTERACTIONS OF FAMILY HISTORY OF BREAST CANCER WITH RADIOTHERAPY IN RELATION TO THE RISK OF BREAST CANCER RECURRENCE IN A POPULATION-BASED BREAST CANCER REGISTRY

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE

UNIVERSITY OF FLORIDA

2016

To Jemma

ACKNOWLEDGMENTS

Foremost, I would like to express my sincere gratitude to my advisor Professor Lusine Yaghjyan for the continuous support of my study and research, for her patience, motivation, enthusiasm, and immense knowledge. Her guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my master study.

Besides my advisor, I would like to thank the rest of my thesis committee: Professor Volker Mai and Professor Travis Gerke, for their encouragement, insightful comments, and hard questions.

I would like to acknowledge The Breast Cancer Registry of Greater Cincinnati (BCRGC), which is supported by funding from NIEHS (P30-ES006096). We thank the many members of the BCRGC for providing the data used in this analysis.

Last but not the least, I would like to thank my family: my husband Peng Shi and my parents Weigang Li and Jinxia Wang, for their love and support throughout my life.

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May 2016

Chair: Lusine Yaghjyan
Major: Epidemiology

Radiation therapy is a common therapeutic approach for breast cancer that reduces the risk of breast cancer recurrence. However, ionizing radiation is a known breast cancer risk factor. Individuals with a family history of breast cancer could represent individuals with impaired DNA repair capacity who are more susceptible to the effects of radiation. Whether a family history of breast cancer differentially affects the risk of breast cancer recurrence in women with and without radiotherapy is poorly understood. We examined the interaction between radiotherapy and a family history of breast cancer in relation to the risk of breast cancer recurrence.

Participants (n=2,440) were selected from women enrolled in the Breast Cancer Registry of Greater Cincinnati (BCRGC), an established population-based breast cancer registry with more than 15 years of follow-up. Information on breast cancer risk factors, including a detailed family history of breast cancer, characteristics of the primary breast cancer diagnosis, treatment history, and recurrence status were collected at baseline and via updates thereafter. Associations of the family history of breast cancer with the risk of breast cancer recurrence were examined separately in women with and without

radiotherapy using survival analysis, while adjusting for age and body mass index at diagnosis and a history of breast surgery. Associations were assessed for the family history of breast cancer in the first-degree relatives and in all relatives combined.

Over an average follow up time of 8.78 years in this study population, no associations were found between the family history of breast cancer and the risk of breast cancer recurrence among women with a history of radiotherapy (Hazard Ratio [HR]=0.96, 95% CI 0.75-1.23). Among women without a history of radiotherapy, the total number of relatives with breast cancer was positively associated with breast cancer recurrence risk (HR=1.21, 95% CI 1.00-1.47). A formal test of the interaction effect in multivariable survival models did not reach significance for any of the family history variables (p-interaction >0.05 for all).

The findings of this study do not support a hypothesis that radiotherapy for a primary breast cancer in women with a family history of breast cancer increases the risk of breast cancer recurrence. However, given a significant association of the family history with the recurrence risk in women without radiotherapy, future studies are warranted to explore possible reasons for these association patterns.

CHAPTER 1
INTRODUCTION

A family history of breast cancer is a well-established, strong risk factor for breast cancer [1-6]. Some previous studies suggested that the family history of breast cancer also increases the risk of breast cancer recurrence and the risk of the second primary breast cancer [7-10]. Previous studies report a 1.62-4.5 times increase in the risk of breast cancer recurrence in women with a family history of breast cancer [11, 12]. Other studies further focused on the relationship between genetic mutations contributing to the familial breast cancer and the risk of breast cancer recurrence [8, 13]. A majority of these studies investigated the associations of mutations in BRCA 1 and BRCA 2 genes with breast cancer risk as well as the risk of breast cancer recurrence [14-18]. However, mutations in BRCA1 and BRCA2 are found only in about 25% of all breast cancer patients with a family history, suggesting that other genetic factors may contribute to the family history of breast cancer [8, 19]. Among these factors, other DNA repair genes have received increasing attention [20]. Impaired DNA repair capacity in individuals with selected genetic variations in DNA repair genes could result in slower rates of DNA damage repair caused by endogenous and exogenous influences, thus increasing cancer risk [21-24].

Among environmental risk factors inducing DNA damage, ionizing radiation has been long recognized as a breast cancer risk factor [25-28]. Findings from studies in atomic bomb survivors indicated a significant linear association between radiation dose and breast cancer risk [25, 26]. Consistent results were reported by other studies [29-31]. Moreover, some studies suggested that the association between ionizing radiation and breast cancer risk is stronger in women with a family history of breast cancer as

compared to women without a family history [32, 33]. On the other hand, because of the sensitivity of malignant breast tissue to the effects of ionizing radiation, radiation has been widely used for treatment of patients with breast cancer [18, 34]. However, some concerns were raised regarding the potential damaging effects of radiation therapy on the surrounding normal tissue and the tissue in unaffected breast. Recognizing this concern, a few studies investigated the association of radiation therapy with the risk of recurrence and the risk of contralateral breast cancer. Some of these studies found significant positive associations of radiotherapy with the risk of contralateral breast cancer [35, 36]. Further, a few reports suggested that radiotherapy could increase the risk of tumor initiation in patients with a family history of breast cancer [17, 37].

The results of the previous studies on the association between radiotherapy and breast cancer risk among individuals with a family history of breast cancer are inconsistent. A retrospective study in 247 breast cancer patients showed that breast cancer patients with BRCA1/2 or CHEK2 mutation were more likely to develop contralateral breast cancer after radiotherapy as compared to non-carriers [16], while another study found no difference in the risk of breast cancer recurrence after receiving radiotherapy in women with and without a family history [38].

The purpose of the current study was to examine the association between a family history of breast cancer and the risk of breast cancer recurrence in women with and without radiation therapy in a large population-based breast cancer registry.

CHAPTER 2
PATIENTS AND METHODS

Study Population and Data Collection

The Breast Cancer Registry of Greater Cincinnati (BCRGC), which was established by the University of Cincinnati, Department of Environmental Health in 2003, aimed to collect information on breast cancer cases in the Greater Cincinnati area and explore the risk factors for breast cancer in this population. Men and women living in the Greater Cincinnati area and diagnosed with breast cancer were recruited through the local oncology practices, media, and community outreach events. Demographic information, clinical characteristics of the tumor, treatment information, reproductive history, and detailed family history of cancer were collected via the baseline self-administered questionnaire. The data on recurrence of the tumor and updated information on breast cancer risk factors were collected in 2006, 2011 and 2013. Out of the 5,725 women in the BCRGC, we excluded women with missing diagnosis data (n=125) and prior history of breast cancer recurrence at enrollment or missing recurrence date at the baseline (n=618). To be eligible for the study, women were required to have at least one update completed during the follow-up and to know the history of their biological family (n=2,503). We further excluded women with missing radiotherapy history information (n=63). The final study sample included 2,440 women (42.62% of all participants in BCRGC), of which 1,486 had a history of radiotherapy and 954 women did not receive radiotherapy (Figure 2-1). This study was approved by the University of Florida and University of Cincinnati IRBs.

Radiotherapy and Family History

Information about radiation therapy for the initial breast cancer diagnosis was collected at baseline. Detailed information on the family history of breast cancer in the first- (mother, sister and daughter) and second-degree relatives (paternal and maternal grandmothers and aunts) was collected at baseline and updated at each follow up cycle. For these analyses, the family history of breast cancer was defined in several ways: (1) having any first-degree relative with breast cancer diagnosis (any or none); (2) total number of first-degree relatives with breast cancer; (3) total number of relatives with breast cancer; and (4) a total family history score which was calculated as the sum of the number of first-degree relative with breast cancer and second-degree relatives with breast cancer multiplied by 0.5.

Covariates

Several patient characteristics were considered as potential confounders including age (years) and BMI(kg/m^2) at the time of diagnosis, menopausal status and postmenopausal hormone use (premenopausal, postmenopausal and never used hormones, postmenopausal with hormone use history, and postmenopausal with unknown hormone use status), receptor status (positive or negative for each of the estrogen, progesterone, and human epidermal growth factor receptor 2), history of benign breast biopsies (yes/no), parity and the age at first birth (nulliparous, any children with age at first birth <25 years, and any children with age at first birth of ≥ 25 years), a history of surgery (yes/no), chemotherapy (yes/no), or adjuvant therapy (yes/no), nodal involvement (positive/negative), a history of alcohol consumption (any/none), and smoking (yes/no). The missing indicator method was used for covariates with missingness in the survival analysis.

Statistical Analysis

Distributions of baseline characteristics in women with and without a history of radiotherapy were compared using t-test (for continuous variables) and Chi-square (for categorical variables). Cox proportional hazards models with time since diagnosis in months as the underlying time variable were used to calculate hazards ratios (HRs) and the corresponding 95% confidence intervals (95% CI). The primary endpoint, breast cancer recurrence, was defined as an episode of recurrence self-reported on any of the update questionnaires. For individuals with breast cancer recurrence, follow-up begins at the time of the breast cancer diagnosis and ends at the date of breast-cancer recurrence. If the exact date of recurrence was not specified, the mid-point between the previous contact and the date of the update when the recurrence was reported was used as the estimated date of recurrence (n=16). For women without breast cancer recurrence, the follow-up begins at the time of diagnosis and ends at the time of the last contact or the end of the study (December 31, 2014), whichever occurred first. The survival analysis was stratified by the history of radiotherapy. We used multivariable models to adjust for potential confounders. As age and BMI have shown significant associations with breast cancer-free survival in the previous studies [7, 39], both of these variables were forced into the survival models. The best fitting model was selected using step-wise model selection approach and only covariates that met statistical significance at 0.05 level were kept in the final models. The survival models were run separately in women with and without radiation therapy.

Proportional hazards assumption was tested for the survival models within each of the radiotherapy strata. In the models for women without radiotherapy, the test was significant for the total number of first-degree relatives with breast cancer (p=0.030), the

total number of relatives with breast cancer (p=0.021), and the total Score (p=0.023) among the non-radiotherapy group. Plots of scaled Schoenfeld residuals were not perfectly flat, but substantial time-trends were not observed and the results were likely influenced by a small number of outliers. We further performed Supremum tests for proportional hazards assumptions and the results were not significant, suggesting no assumption violations. Hence, we proceeded with the Cox proportional hazards models for the survival analysis.

The differences in the associations of each of the family history variables with the risk of breast cancer recurrence in women with and without radiotherapy were tested by including an interaction term in the survival model for the entire study sample. All the tests were two-sided and significance of the effects was assessed at 0.05 level. All analyses were preformed using SAS statistical software (SAS institute Inc., Version 9.4).

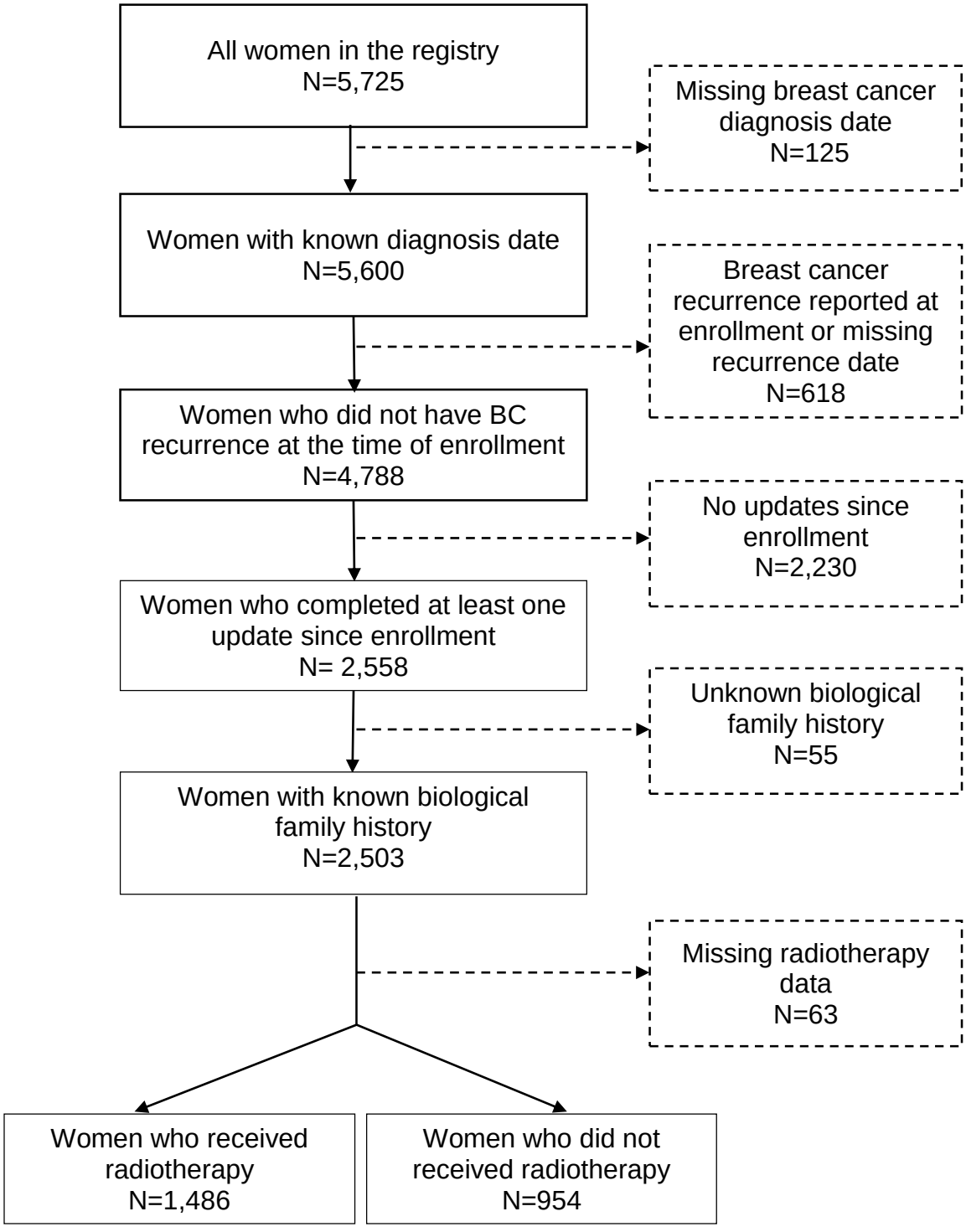

Figure 2-1. Subject selection diagram

CHAPTER 3
RESULTS

This study included 2,440 women with breast cancer. The average follow-up time was 8.78 years with the average of 8.42 years for women with radiotherapy (range 0.33 - 48.86) and 9.51 years for women without radiotherapy (range 0.17 - 46.95). During the follow-up, there were 109 reported recurrences (69 in women with radiotherapy and 40 in women without radiotherapy). The distribution of selected characteristics among study participants by the status of radiotherapy and recurrence are presented in the Table 3-1. Compared to the participants without radiotherapy, cases who received radiotherapy were older (55.94 vs. 54.11 years, $p<0.001$), had shorter follow-up period (83.04 vs. 101.90 months, $p=0.006$), had greater BMI (27.36 vs. 26.30, $p<0.001$) at the time of breast cancer diagnosis, were less likely to have any first-degree relative with breast cancer (24.24% vs. 26.81%, $p=0.025$) or total number of relatives with breast cancer (0.27 vs. 0.32, $p=0.003$), and were less likely to have a history of chemotherapy (51.48% vs.61.74%, $p<0.001$). There was also a significant difference in women's menopausal status and postmenopausal hormone use between the two groups ($p<0.001$); women who received radiotherapy were more likely to be postmenopausal and to have a history of postmenopausal hormone use. Among participants with a history of radiotherapy, women with a recurrence were more likely to have greater BMI (29.8 vs. 27.24, $p=0.002$), less likely to have a history of adjuvant therapy (53.12% vs. 72.12%, $p=0.002$), and less likely to have estrogen receptor-negative or progesterone receptor-negative tumors (65.31% vs. 83.00%, $p=0.002$ and 33.33% vs. 57.77%, $p=0.019$, respectively). The distribution of other demographic characteristics, treatment history, and tumor characteristics were similar in women with and without a recurrence

in this stratum. Among women with no history of radiotherapy, those with recurrence were less likely to have a history of alcohol consumption (52.63% vs.68.05%, p=0.005), and more likely to be nulliparous (25% vs. 13.46%, p=0.018) and smoking (48.72% vs. 42.00%, p=0.041) (Table 3-1).

Table 3-2 summarizes the results of survival analysis in women with and without a history of radiotherapy. Among women with a history of radiotherapy, breast cancer recurrence was not associated with any of the variables for the family history after adjustment for age and BMI at diagnosis and a history of surgery (any first-degree relative with breast cancer: HR=0.98, 95% CI 0.58-1.68; total first-degree relatives with breast cancer: HR=0.89, 95% CI 0.57-1.39; total number of relatives with breast cancer: HR=0.96, 95% CI 0.75-1.23; total family history score: HR=0.92, 95% CI 0.65-1.32.)

Among women without a history of radiotherapy, the total number of relatives with breast cancer was positively associated with breast cancer recurrence with approximately 21% increase in the risk of recurrence per any additional family member with breast cancer (HR= 1.21, 95% CI 1.00-1.47). Corresponding Kaplan-Merier survival curves for breast cancer-specific survival in relation to total number of relatives who had breast cancer history in women with and without radiotherapy are shown in the Figure 3-1. None of the other family history variables were associated with the risk of breast cancer recurrence in women without radiotherapy.

There were no interactions of any of the family history variables with radiotherapy (p-interaction for all>0.05).The results were similar when we incorporated interaction terms for radiotherapy with each of the covariates in the full model.

Table 3-1. Characteristics of study participants by radiotherapy status and breast cancer recurrence

Characteristic	Women with Radiotherapy (n=1,486)			Women without Radiotherapy (n=954)		
	All	Recurrence (n=69)	No recurrence (n=1417)	All	Recurrence (n=40)	No recurrence (n=914)
Mean (Standard Deviation)						
Age at diagnosis, years	55.94(10.94)	53.97(11.05)	56.03(10.93)	54.11(11.49)	52.56(13.74)	54.17(11.39)
Length of follow-up, months	100.98(70.48)	83.04(52.41)	101.85(71.14)	114.07(83.40)	101.40(88.77)	114.37(83.17)
Body Mass Index at diagnosis, kg/m^2	27.36(6.31)	29.80(6.73)	27.24(6.27)	26.30(5.56)	26.82(5.83)	26.28(5.56)
Age at menarche, years	12.57(3.53)	12.35(1.25)	12.58(3.60)	12.57(1.50)	12.55(1.48)	12.57(1.50)
Age at natural menopause, years	47.14(7.29)	48.35(8.62)	47.09(7.22)	46.81(7.20)	46.97(7.79)	46.80(7.19)
Total number of first-degree relatives with breast cancer	0.27 (0.53)	0.29(0.49)	0.27(0.54)	0.32(0.59)	0.40(0.84)	0.32(0.57)
Total number of relatives with breast cancer	0.65(0.93)	0.72(0.87)	0.65(0.94)	0.78(1.11)	1.15(0.66)	0.77(1.08)
Total family history score	0.46(0.67)	0.51(0.61)	0.46(0.68)	0.55(0.77)	0.78(1.12)	0.54(0.76)
Number (%)						
Race/ethnicity						
Caucasian	1322(88.96)	64(92.75)	1258(88.78)	829(86.90)	33(82.50)	796(87.09)
African American	44(2.96)	1(1.45)	43(3.03)	36(3.77)	1(2.50)	35(3.83)
Other race	120(8.08)	4(5.80)	116(8.19)	89(9.33)	6(15.00)	83(9.08)
Benign breast biopsies (yes)	393(27.07)	19(28.36)	374(27.00)	269(29.05)	7(18.42)	262(29.50)
Alcohol use (ever)	1019(69.94)	49(74.24)	970(69.73)	627(67.42)	20(52.63)	607(68.05)
Smoking status (ever)	648(44.32)	33(48.53)	615(44.12)	397(42.28)	19(48.72)	378(42.00)
Any first-degree relative with breast cancer(yes)	342(23.01)	19(27.54)	323(22.79)	256(26.83)	11(27.50)	245(26.81)

Table 3-1. Continued

Characteristic	Women with Radiotherapy (n=1,486)			Women without Radiotherapy (n=954)		
	All	Recurrence (n=69)	No recurrence (n=1417)	All	Recurrence (n=40)	No recurrence (n=914)
Parity and age at first child's birth						
Nulliparous	234(15.75)	12(17.39)	222(15.67)	133(13.94)	10(25.00)	123(13.46)
Any children with age at first birth <25 years	703(47.31)	31(44.93)	672(47.42)	451(47.27)	22(55.00)	429(46.94)
Any children with age at first birth of ≥ 25 years	549(36.94)	26(37.68)	523(36.91)	370(38.78)	8(20.00)	362(39.61)
Menopausal status/PMH history						
Premenopausal	112(7.54)	10(14.49)	102(7.20)	135(14.15)	6(15.00)	129(14.11)
Postmenopausal, never used hormones	696(46.84)	33(47.83)	663(46.79)	459(48.11)	19(47.50)	440(48.14)
Postmenopausal, with hormone use history	639(43.00)	24(34.78)	615(43.70)	338(35.43)	13(32.50)	325(35.56)
Postmenopausal, unknown hormone use status	32(2.15)	2(2.90)	30(2.12)	18(1.89)	2(5.00)	16(1.75)
Breast cancer diagnosis-related						
Breast surgery (yes)	1399(94.34)	63(91.30)	1336(94.48)	886 (93.17)	37(92.50)	849(93.19)
Chemotherapy (yes)	764(51.48)	39(56.52)	725(51.24)	589(61.74)	28(70.00)	561(61.38)
Adjuvant therapy (yes)	1059(71.27)	37(53.62)	1022(72.12)	564(59.12)	23(57.50)	541(59.19)

Table 3-1. Continued

Characteristic	Women with Radiotherapy (n=1,486)			Women without Radiotherapy (n=954)		
	All	Recurrence (n=69)	No recurrence (n=1417)	All	Recurrence (n=40)	No recurrence (n=914)
Nodal involvement (positive)	967(65.07)	49(71.01)	918(64.78)	592(62.05)	19(47.50)	573(62.69)
Estrogen receptor status (positive) *	828(82.14)	32(65.31)	796(83.00)	487(75.50)	17(62.96)	470(76.05)
Progesterone receptor status (positive) *	257(56.48)	8(33.33)	249(57.77)	168(51.38)	10(52.63)	158(51.30)
HER2 receptor status (positive) *	47(29.01)	0(0.00)	47(29.56)	49(35.00)	0(0.00)	49(36.03)

Abbreviations: PMH - postmenopausal hormone use

* Percentages calculated for women with non-missing data on receptor status

Table 3-2. HRs for recurrence according to family history by radiotherapy status *

Family History Variables	Women with radiotherapy	Women without radiotherapy
Any first-degree relative with breast cancer	0.98(0.58, 1.68)	0.86(0.42, 1.73)
Total first-degree relative(s) with breast cancer	0.89(0.57, 1.39)	1.05(0.66, 1.68)
Total number of relative(s) with breast cancer	0.96(0.75, 1.23)	1.21(1.00, 1.47)
Total family history score	0.92(0.65, 1.32)	1.26(0.92, 1.73)

* Adjusted for age and body mass index at diagnosis and a history of surgery

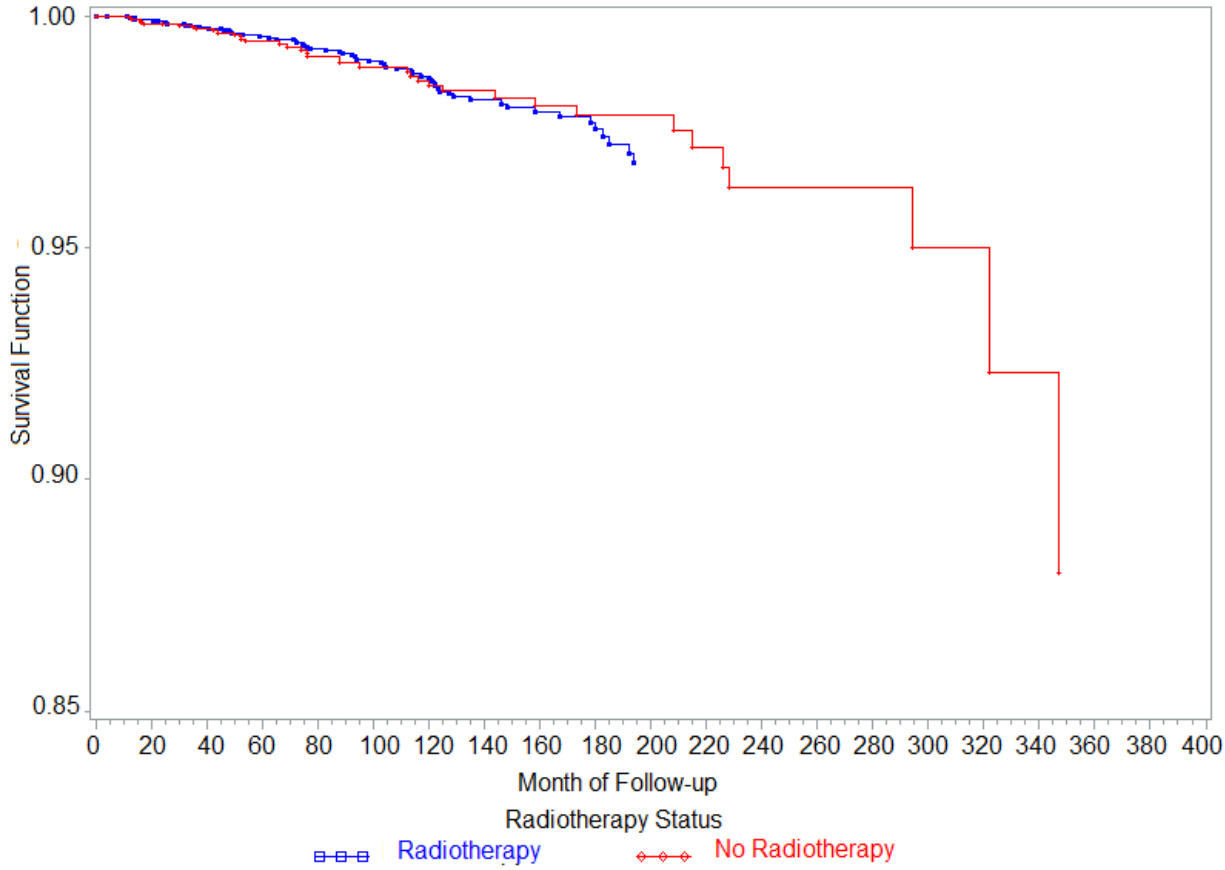

Figure 3-1. Cumulative survival in relation to the total number of relatives with breast cancer, by the status of radiotherapy

CHAPTER 4
DISCUSSION

Using data from a population-based prospective breast cancer registry, we examined the interactions between radiotherapy and a family history of breast cancer in relation to the risk of breast cancer recurrence. Our findings suggest that there is no difference in the associations of the family history of breast cancer with the risk of breast cancer recurrence by the status of radiotherapy.

Consistent with previous reports, we found no association of the family history of breast cancer with the risk of breast cancer recurrence among women receiving radiotherapy. Chabner et al. examined the association of a family history of breast cancer in the first-degree relatives with the risk of the local recurrence in women receiving radiotherapy [38]. In this cohort study of 201 women diagnosed with stage I or II invasive breast cancer, no difference was found between patients with or without positive family history of breast cancer in regard to the risk of recurrence.

We found a significant association of the total number of relatives with breast cancer with the risk of breast cancer recurrence among women who did not receive radiotherapy. The results of the previous studies on the family history of breast cancer and the risk of recurrence are inconsistent. Table 4-1 summarizes the results of the previous studies on the association between a family history of breast cancer and the risk of breast cancer recurrence. Four studies have found significant positive associations. A retrospective study by Turkoz, et al. reported an increased recurrence risk among family history- positive breast cancer cases with young age or triple negative breast cancer (HR=1.62 and 1.82, respectively) [40]. Similarly, Jobsen et al. found a positive association between a family history of breast cancer and the risk of local

recurrence among young breast cancer patients (age≤40 years old) [41]. Some studies included both breast cancer and/or ovarian cancer (BOC) in the definition of family history of breast cancer. A case-control study conducted in China suggested a significantly higher risk of recurrence in breast cancer patients with a family history of BOC (P=0.04) [42]. However, three cohort studies found no association between family history of BOC and the risk of breast cancer recurrence [43-45]. Eccles, et al. only reported a non-significant trend towards higher breast cancer recurrence risk among patients with family history of breast cancer compared to those without a family history [46]. In a previous case-control study by Harold et al. [47], 52 women with local breast cancer recurrence after lumpectomy and radiotherapy were compared to 52 matched controls who remained cancer-free. The study found no associations of the family history of breast cancer with the recurrence risk.

Our study utilized an established population-based cohort with more than 15 years of follow-up. Information on breast cancer risk factors, tumor characteristics, treatment history, and breast cancer recurrence status was self-reported. Previous studies suggest a high accuracy of self-reported cancer history [48-50]. The prospective data collection also minimizes the possibility of misclassification. Our study population appears to be representative of breast cancer cases reported by SEER registries in terms of the distributions of the receptor statuses [51,52]. However, the Registry did not collect the information on breast cancer stage and tumor size. As treatment regimens are based on these tumor features and as we examined the effect of the treatment history in our analysis (surgery, adjuvant therapy and chemotherapy), it is very unlikely that the absence of the information on tumor stage influences our findings. Unlike

previous studies, we defined a family history of breast cancer using various approaches which allowed us to examine separately the effects of the family history in first-degree relatives, a family history in both first and second-degree relatives as well as a total score that accounts for the nature of these familial relationships. It is possible, however, that some of the effects were not detected due to the relatively small number of recurrences in this cohort. Finally, misclassification of recurrence cannot be excluded completely. However, a previous study suggested high accuracy in self-reported recurrence status and recall of the relevant medical data among breast cancer patients [53]. After comparison of the self-reported data (recall time 1.6- 9 years, mean 3.2 years) with the medical records, the agreement between two data sources was 99% for a history of radiotherapy and 97% for the breast cancer recurrence status.

Some previous studies suggested that breast cancer patients with a positive family history of breast cancer tend to undergo cancer screening more frequently and from younger age [15, 16]. Higher dose and early age at exposure to ionizing radiation have been linked to breast cancer risk in previous studies [29, 30, 32]. Mammography represents a source of medical ionizing radiation in women and it is possible that the cumulative exposure to this radiation in women with a family history of breast cancer might contribute to the higher risk of breast cancer recurrence. Information on the number of prior mammograms, however, was not collected by the Registry and could not be controlled for in this analysis. Future studies would benefit from inclusion of this important information in the analysis which would allow to account for the woman's total cumulative exposure to ionizing radiation.

In conclusion, our findings do not support a hypothesis that radiotherapy in breast cancer cases with a family history of breast cancer might increase the risk of breast cancer recurrence. Future studies are warranted to systematically examine these associations in larger population-based studies with complete information on other sources of ionizing radiation.

Table 4-1. Summary of previous studies on the association between a family history of breast cancer and the risk of breast cancer recurrence

Author, year, place	Study design	Sample size	Follow-up time (mean, range)	Definition of positive family history	Type of breast cancer cases	Covariates used in adjustment	Main findings
Turkoz et al. 2012, Turkey	Retrospective cohort study	1,987	27 months (range 1-400)	FDR, SDR and TDF of BOC	Not specifically mentioned	Age, tumor size and nodal status	1+ relative with BC ≤50 years: HR 1.62; 95% CI 1.15-2.27; p=0.006) Among triple negative cases: HR=1.82; 95% CI 1.44-2.29; p<0.0001
Buist et al., 2010, US	Cohort study	17,286	5 years	Any FDR with BC	DCIS or early stage (I/II) invasive breast cancer	Stage, adjuvant therapy, age at diagnosis, and registry	Women with a FH of BC had higher rates of second primaries but not recurrences
Cao et al. 2011, China	Case-control	693 (Case: 348 Control: 345)	55.7 month (range: 6-120)	≥2 FDR with BOC	Females without distant metastasis at initial diagnosis, and with infiltrative carcinoma	Age, stage, HER2 status, chemotherapy, radiotherapy, hormone therapy	FH of BOC had higher risk of recurrence/metasatsis (log rank p=0.04), HR=0.012, 95% CI 0.02–0.57) in the HR(ER or PR)+ population

Table 4-1. Continued

Author, year, place	Study design	Sample size	Follow-up time (mean, range)	Definition of positive family history	Type of breast cancer cases	Covariates used in adjustment	Main findings
Figueriredo JC et al., 2006, Canada	Prospective population-based cohort	967	Not reported	FDR of BOC	All cases	Tumor characteristic and adjuvant treatment	No associations
Eccles D, et al., 2001, UK	Retrospective cohort study	304	7 years (range: 0-47)	Significant FH (1+ FDR < 60 years old or 1+ paternal SDR <60) or BRCA 1 mutation	Not reported	Not reported	No associations
Harris, et al., 2000, US	Prospective cohort study	146	7.8 years (range: <1-20)	FDR or any other relative with BOC	DCIS	Not reported	No associations
Jobson, et al. 2000, Netherland	Prospective cohort study	1,204	70 month (range: 2-175)	First-degree relative	Early BC (T1, T2<=3cm)	Not reported	A significant positive relationship between LR and FH in young BC patients ≤ 40 years
Szelei-Stevens, et al. 2000, US	Prospective cohort study	128	8.7 years (Median; range: 2.0-16.1)	FDR and SDR with BC	*DCIS*	Not reported	FH significantly increased the local recurrence rate (p=0.05)

Abbreviations: BC - breast cancer; DCIS - ductal carcinoma in situ; FH - family history; LR - local recurrence; RR - regional recurrence; OS - overall survival; FDR - first-degree relative; SDR - second-degree relative; TDR - third-degree relative; BOC - breast and/or ovarian cancer; HR - hormone receptor; ER - estrogen receptor; PR - progesterone receptor.

LIST OF REFERENCES

1. Palmer J R, Boggs D A, Adams-Campbell L L, et al. Family history of cancer and risk of breast cancer in the Black Women's Health Study[J]. Cancer Causes & Control, 2009, 20(9): 1733-1737.

2. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease[J]. The Lancet, 2001, 358(9291): 1389-1399.

3. Pharoah P D P, Day N E, Duffy S, et al. Family history and the risk of breast cancer: A systematic review and meta- analysis[J]. International Journal of cancer, 1997, 71(5): 800-809.

4. Phipps A I, Buist D S M, Malone K E, et al. Family history of breast cancer in first-degree relatives and triple-negative breast cancer risk[J]. Breast cancer research and treatment, 2011, 126(3): 671-678.

5. Colditz G A, Kaphingst K A, Hankinson S E, et al. Family history and risk of breast cancer: nurses' health study[J]. Breast cancer research and treatment, 2012, 133(3): 1097-1104.

6. Oldenburg R A, Meijers-Heijboer H, Cornelisse C J, et al. Genetic susceptibility for breast cancer: how many more genes to be found? [J]. Critical reviews in oncology/hematology, 2007, 63(2): 125-149.

7. Fowble B, Hanlon A, Freedman G, et al. Second cancers after conservative surgery and radiation for stages I–II breast cancer: identifying a subset of women at increased risk[J]. International Journal of Radiation Oncology* Biology* Physics, 2001, 51(3): 679-690.

8. Reiner A S, John E M, Brooks J D, et al. Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: a report from the Women's Environmental Cancer and Radiation Epidemiology Study[J]. Journal of Clinical Oncology, 2013, 31(4): 433-439.

9. Bouchardy C, Benhamou S, Fioretta G, et al. Risk of second breast cancer according to estrogen receptor status and family history[J]. Breast cancer research and treatment, 2011, 127(1): 233-241.

10. Baeyens A, Claes K, Willems P, et al. Chromosomal radiosensitivity of breast cancer with a CHEK2 mutation[J]. Cancer genetics and cytogenetics, 2005, 163(2): 106-112.

11. Szelei-Stevens KA, Kuske RR, Yantsos YA, Cederbom GJ, Bolton JS, and Fineberg BB. The influence of young age and positive family history of breast cancer on the prognosis of ductal carcinoma in situ treated by excision with or without radiation therapy or by mastectomy. Int. J. Radiation Oncology Biol. Phys 2000. 48:943–949.

12. Turkoz F P, Solak M, Aksoy S, et al. Association between family history and clinicopathologic characteristics in 1987 breast cancer patients: single institution experience from Turkey[J]. Journal of BU ON.: official journal of the Balkan Union of Oncology, 2012, 17(4): 649.

13. Edvardsen H, Tefre T, Jansen L, et al. Linkage disequilibrium pattern of the ATM gene in breast cancer patients and controls; association of SNPs and haplotypes to radio-sensitivity and post-lumpectomy local recurrence[J]. Radiation oncology, 2007, 2(1): 1.

14. Kirova Y M, Stoppa-Lyonnet D, Savignoni A, et al. Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy[J]. European journal of cancer, 2005, 41(15): 2304-2311.

15. Gronwald J, Pijpe A, Byrski T, et al. Early radiation exposures and BRCA1-associated breast cancer in young women from Poland[J]. Breast cancer research and treatment, 2008, 112(3): 581-584.

16. Broeks A, Braaf L M, Huseinovic A, et al. Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study[J]. Breast Cancer Res, 2007, 9(2): R26.

17. Pijpe A, Andrieu N, Easton D F, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK)[J]. 2012.

18. Drooger J C, Hooning M J, Seynaeve C M, et al. Diagnostic and therapeutic ionizing radiation and the risk of a first and second primary breast cancer, with special attention for BRCA1 and BRCA2 mutation carriers: A critical review of the literature[J]. Cancer treatment reviews, 2015, 41(2): 187-196.

19. Andreassen C N, Alsner J. Genetic variants and normal tissue toxicity after radiotherapy: a systematic review[J]. Radiotherapy and Oncology, 2009, 92(3): 299-309.

20. Euhus D M, Robinson L. Genetic predisposition syndromes and their management[J]. Surgical Clinics of North America, 2013, 93(2): 341-362.

21. Smith T R, Miller M S, Lohman K K, et al. DNA damage and breast cancer risk[J]. Carcinogenesis, 2003, 24(5): 883-889.

22. Jasin M. Homologous repair of DNA damage and tumorigenesis: the BRCA connection[J]. Oncogene, 2002, 21(58).

23. Venkitaraman A R. Cancer susceptibility and the functions of BRCA1 and BRCA2[J]. Cell, 2002, 108(2): 171-182.

24. Powell S N, Kachnic L A. Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation[J]. Oncogene, 2003, 22(37): 5784-5791.

25. Land C E, Tokunaga M, Koyama K, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990[J]. Radiation research, 2003, 160(6): 707-717.

26. Goodman M T, Cologne J B, Moriwaki H, et al. Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors[J]. Preventive medicine, 1997, 26(1): 144-153.

27. Lundell M, Mattsson A, Karlsson P, et al. Breast cancer risk after radiotherapy in infancy: a pooled analysis of two Swedish cohorts of 17,202 infants[J]. Radiation research, 1999, 151(5): 626-632.

28. Carmichael A, Sami A S, Dixon J M. Breast cancer risk among the survivors of atomic bomb and patients exposed to therapeutic ionising radiation[J]. European Journal of Surgical Oncology (EJSO), 2003, 29(5): 475-479.

29. John E M, Phipps A I, Knight J A, et al. Medical radiation exposure and breast cancer risk: findings from the Breast Cancer Family Registry[J]. International journal of cancer, 2007, 121(2): 386-394.

30. Ronckers C M, Doody M M, Lonstein J E, et al. Multiple diagnostic X-rays for spine deformities and risk of breast cancer[J]. Cancer Epidemiology Biomarkers & Prevention, 2008, 17(3): 605-613.

31. Preston D L, Mattsson A, Holmberg E, et al. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts[J]. Radiation research, 2002, 158(2): 220-235.

32. Hill D A, Preston-Martin S, Ross R K, et al. Medical radiation, family history of cancer, and benign breast disease in relation to breast cancer risk in young women, USA[J]. Cancer Causes & Control, 2002, 13(8): 711-718.

33. Hiramatsu H, Bornstein B A, Recht A, et al. Local recurrence after conservative surgery and radiation therapy for ductal carcinoma in situ: Possible importance of family history[J]. The cancer journal from Scientific American, 1994, 1(1): 55-61.

34. Radiotherapy, in: B.W. Stewart, P. Kleihues (Eds.), World Cancer Report, IARC Press, International Agency for Research on Cancer (IARC), World Health Organisation(WHO), Lyon, 2003, pp. 277–280.

35. Viani G A, Stefano E J, Afonso S L, et al. Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomized trials[J]. Radiation Oncology, 2007, 2(1): 1.

36. Gao X, Fisher S G, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study[J]. International Journal of Radiation Oncology* Biology* Physics, 2003, 56(4): 1038-1045.

37. Schnitt S J, Connolly J L, Harris J R, et al. Pathologic predictors of early local recurrence in stage I and II breast cancer treated by primary radiation therapy[J]. Cancer, 1984, 53(5): 1049-1057.

38. Chabner E, Nixon A, Gelman R, et al. Family history and treatment outcome in young women after breast-conserving surgery and radiation therapy for early-stage breast cancer[J]. Journal of clinical oncology, 1998, 16(6): 2045-2051.

39. Kroenke C H, Chen W Y, Rosner B, et al. Weight, weight gain, and survival after breast cancer diagnosis[J]. Journal of clinical oncology, 2005, 23(7): 1370-1378.

40. Turkoz F P, Solak M, Aksoy S, et al. Association between family history and clinicopathologic characteristics in 1987 breast cancer patients: single institution experience from Turkey[J]. Journal of BU ON.: official journal of the Balkan Union of Oncology, 2012, 17(4): 649.

41. Jobsen J J, Meerwaldt J H, van der Palen J. Family history in breast cancer is not a prognostic factor?[J]. The Breast, 2000, 9(2): 83-87.

42. Cao A, He M, Di G H, et al. Influence of a family history of breast and/or ovarian cancer on breast cancer outcomes[J]. Experimental and therapeutic medicine, 2011, 2(5): 917-923.

43. Buist D S M, Abraham L A, Barlow W E, et al. Diagnosis of second breast cancer events after initial diagnosis of early stage breast cancer[J]. Breast cancer research and treatment, 2010, 124(3): 863-873.

44. Figueiredo J C, Ennis M, Knight J A, et al. Influence of young age at diagnosis and family history of breast or ovarian cancer on breast cancer outcomes in a population-based cohort study[J]. Breast cancer research and treatment, 2007, 105(1): 69-80.

45. Harris E E R, Schultz D J, Peters C A, et al. Relationship of family history and outcome after breast conservation therapy in women with ductal carcinoma in situ of the breast[J]. International Journal of Radiation Oncology* Biology* Physics, 2000, 48(4): 933-941.

46. Eccles D, Simmonds P, Goddard J, et al. Familial breast cancer: an investigation into the outcome of treatment for early stage disease[J]. Familial cancer, 2001, 1(2): 65-72.

47. Harrold E V, Turner B C, Matloff E T, et al. Local recurrence in the conservatively treated breast cancer patient: a correlation with age and family history[J]. The cancer journal from Scientific American, 1997, 4(5): 302-307.

48. Kerber RA, Slattery ML. Comparison of Self-reported and Database-linked Family History of Cancer Data in a Case-Control Study. Am. J Epidemiology 1997.148: 244-248.

49. Barisic A, Glendon G, Weerasooriya N, Andrulis IL, Knight JA. Accuracy of Self-Reported Breast Cancer Information amongWomen fromthe Ontario Site of the Breast Cancer Family Registry. Journal of Cancer Epidemiology 2012.

50. Zhu K, McKnight B, Stergachis A, Daling JR, Levine RS. Comparison of self-report data and medical records data: results from a case-control study on prostate cancer. International Journal of Epdidemiology 1999. 28: 409-417.

51. Cook KL, Clarke R. Estrogen receptor-α signaling and localization regulates autophagy and unfolded protein response activation in ER+ breast cancer. Receptors Clin Investig. 2014; 6: e316.

52. Li CI, Malone KE, Daling JR. Differences in Breast Cancer Hormone Receptor Status and Histology by Race and Ethnicity among Women 50 Years of Age and Older. Cancer Epidemiol Biomarkers Prev 2002. 11:601-607.

53. Phillips K A, Milne R L, Buys S, et al. Agreement between self-reported breast cancer treatment and medical records in a population-based Breast Cancer Family Registry[J]. Journal of Clinical Oncology, 2005, 23(21): 4679-4686.

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