

## RELATIONSHIP OF FAMILY HISTORY AND OUTCOME AFTER BREAST CONSERVATION THERAPY IN WOMEN WITH DUCTAL CARCINOMA *IN SITU* OF THE BREAST

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**Purpose:** The purpose of this study was to evaluate the relationship between a family history of breast or ovarian cancer and outcome after breast-conserving surgery and radiation in women presenting with an initial diagnosis of ductal carcinoma *in situ* (DCIS) of the breast.

**Methods and Materials:** A total of 146 consecutive women with a pathologic diagnosis of ductal carcinoma *in situ* as their first diagnosis of any breast cancer were identified; 28 (19%) had a positive family history of breast or ovarian cancer in a first-degree relative, 27 (19%) had a positive family history in a second-degree relative, and 91 (62%) had no family history. Pathologic, clinical, and treatment factors, and clinical outcomes for each family history group were compared. Cosmesis and complications were recorded at each follow-up. Patients were treated between 1978 and 1995, and the median follow-up was 7.1 years.

**Results:** Patients with a positive family history in a first- or second-degree relative each had an 8% incidence of local failure at 10 years, while the negative family history group demonstrated a 16% local failure rate ( $p = 0.33$ ). Overall survival at 10 years for patients with a positive family history in a first- or second-degree relative was 100% and for those with a negative family history was 91% ( $p = 0.08$ ). The negative family history group had a higher median age that may account for the difference in overall survival. Cause-specific survival (CSS) was 97%, 100%, and 99%, respectively, at 10 years ( $p = 0.25$ ). There were no differences in the cosmetic results or complication rates between women with a positive or negative family history.

**Conclusion:** We have shown that a family history of breast and/or ovarian cancer is not associated with an adverse outcome for women treated with breast conservation therapy for DCIS. Local recurrence, cause-specific survival, overall survival, cosmesis, and complication rates were comparable to that of similarly treated women with negative family histories. Therefore, a positive family history is not a contraindication for breast conservation therapy in women with DCIS. © 2000 Elsevier Science Inc.

**Breast cancer, Ductal carcinoma *in situ*, Family history, Local recurrence, Radiation therapy, Breast-conserving therapy.**

### INTRODUCTION

A family history of breast or ovarian cancer increases a woman's lifetime risk of developing breast cancer. The greatest risk is associated with cancer in a first-degree relative (mother, sister, or daughter), with relative risk estimates of 2.1 for any affected first-degree relative (1). An increased relative risk is also associated with a history of breast or ovarian cancer in second-degree relatives. A positive family history of breast cancer is associated with an increased risk of early onset breast cancer (2) and bilateral breast cancer (3). It is known that some breast and ovarian cancers are related to the genetic predisposition acquired through the inheritance of certain genetic defects. These

include inheritance of mutations or loss of the breast-ovarian cancer genes (BrCa1 and BrCa2) (4), the ataxia-telangiectasia (ATM) gene (5), or the p53 gene (Li-Fraumeni syndrome) (6). In the absence of comprehensive genetic testing, the family history serves as a surrogate marker of a patient's risk category. Patients with a positive family history but who are not known carriers of one of the known breast cancer susceptibility genes appear to be at an intermediate increased risk of developing breast cancer.

Concerns over the possible interactions of radiation and chemotherapy with tissues of women with genetic mutations have prompted investigations on the impact a positive family history on outcome for women with breast cancer. It

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Presented in part at the 41st Annual Meeting of the American Society for Therapeutic Radiology and Oncology, San Antonio, TX, October 31–November 4, 1999.

Accepted for publication 1 June 2000.

has long been known that certain genetic defects are associated with increased radiation sensitivity, such as mutations in the ataxia-telangiectasia gene. Increased radiosensitivity could result in more severe acute and late effects after irradiation in normal tissues, but could also result in improved tumor cell kill and thus improved local control. In addition, certain genetic defects predispose patients to second malignancies in irradiated tissues (e.g., the loss of the retinoblastoma gene (7)). The BrCa1 and BrCa2 genes have been implicated in DNA damage repair pathways (8). Therefore, there has been concern that breast cancer gene defects might also be associated with an increased risk of radiation-induced second malignancies. However, to date, there is little evidence that patients with known germline mutations of breast cancer susceptibility genes are at increased risk for treatment-related sequelae or that these patients have a worse outcome, stage for stage.

The relationship of the histology of breast cancer with family history is uncertain. It has been suggested that the histologic characteristics of breast carcinoma might correlate with the genetic predisposition of a patient (9). Some studies have reported clustering of tumor types and others have noted heterogeneity within families. With regards to ductal carcinoma *in situ* (DCIS), few studies have considered the importance of family history. For patients with DCIS, survival is excellent and therefore local control, complications, and cosmetic outcome are of primary concern. The purpose of this study is to evaluate the relationship between a family history of breast or ovarian cancer and outcome after breast-conserving surgery and radiation in women presenting with an initial diagnosis of DCIS.

## METHODS AND MATERIALS

A total of 146 women with a pathologic diagnosis of unilateral DCIS as their first diagnosis of any breast cancer were identified from among all patients treated for breast cancer in the Department of Radiation Oncology at the University of Pennsylvania. Women who had prior contralateral invasive or noninvasive breast cancers were not included in the study population. All patients had American Joint Committee on Cancer (AJCC) stage TisN0 M0 ductal carcinoma *in situ* (10). The cohort includes all consecutive patients with a diagnosis of DCIS. All patients were treated between January 1978 and December 1995 with breast-conservation therapy, consisting of complete surgical excision of all gross tumor and definitive whole breast irradiation with or without a boost to the tumor bed. In the earlier years of the study, axillary lymph node dissection was performed in 33 patients as part of the staging work-up. No patient received adjuvant chemotherapy or hormonal therapy at the time of their initial diagnosis of DCIS. While no histologic subgroup of DCIS was excluded, microinvasive cancers were not included in this analysis.

Three categories of family history of breast and ovarian cancer were defined as follows: (a) history of breast and/or ovarian cancer in a first-degree relative (mother, sister,

and/or daughter); (b) history of breast and/or ovarian cancer in any other relative; (c) no history of any breast or ovarian cancer. Family histories were obtained prospectively for all patients. Family histories of cancer were self-reported by the patients and recorded in their charts at the time of their initial diagnoses of DCIS. Cancer diagnoses in family members subsequent to initial treatment were not considered because to do so would introduce follow-up bias and would not reflect the level of information known at the time of diagnosis, when treatment decisions are made.

Treatment- and patient-related factors that were examined for comparison included age (39 years or less, 40–49 years, and 50 years or greater), final pathologic margin status (negative, close or positive, and unknown), total radiation dose (< 50 Gy, 50–59 Gy, and  $\geq$  60 Gy), and histology (comedo, noncomedo, and not specified). All diagnoses of ductal carcinoma *in situ* were confirmed by pathologists at the University of Pennsylvania. In the earlier years of the study, pathologic specimens were not routinely inked, accounting for the unknown margin status in some patients. In addition, close or positive margins were uncommon; therefore, these margin categories were combined. Final pathologic margin was defined from the primary surgical excision or from the re-excision if done, and was considered to be negative if no residual tumor was seen in a re-excision specimen. Grade was recorded when known, but was not routinely reported along with histology for several of the early study years; therefore there were too many patients with unknown grade to analyze this particular treatment factor separately. Histology of local recurrence or contralateral breast cancers was also recorded. Method of detection was recorded as physical examination only, mammographically detected only, detected by both physical examination and mammography, or other.

All patients were treated with tangent fields to the ipsilateral breast. The majority of patients (88%) also received a boost to the tumor bed, for a total dose of 60 Gy or more. In the early years of the study, there were 15 patients who received whole breast tangents alone, to a total dose of 50 Gy. In addition, 2 patients stopped radiation before the completion of the planned course and received total doses of 42 and 46 Gy, respectively. Cosmesis was routinely noted at each follow-up visit and recorded as excellent, good, fair, or poor. Complications were noted at each follow-up and coded for severity.

The median follow-up for the overall group of patients was 7.1 years, and mean follow-up was 7.8 years (range < 1–20 years). Treatment outcomes for the three groups were compared. Local control, cause-specific survival, and overall survival at 5 and 10 years were determined for each family history group. Local recurrence was defined as histologically-proven invasive or noninvasive cancer in the previously treated breast, regardless of location in the breast. The incidence of subsequent contralateral breast cancer was also examined, defined as any histologically-proven invasive or noninvasive cancer that was diagnosed in the contralateral, previously untreated breast. Failure for

Table 1. Patient, tumor, and treatment characteristics by family history group

Treatment factor	Family history-positive First-degree relative no. patients (%)	Family history-positive Any other relative no. patients (%)	Family history-negative no. patients (%)	<i>p</i> value*
Total no. patients	28 (19)	27 (19)	91 (62)	
Age at diagnosis				
39 years or less	5 (18)	1 (4)	6 (7)	0.02
40–49 years	7 (25)	13 (46)	19 (20)	
50 years or more	16 (57)	13 (46)	66 (73)	
Final pathologic margin				
Negative	18 (64)	18 (67)	43 (47)	0.21
Close or positive	6 (21)	4 (15)	19 (21)	
Unknown	4 (14)	5 (18)	29 (32)	
Total dose				
Less than 69 Gy	2 (7)	2 (7)	13 (14)	0.57
Greater than or equal to 60 Gy	26 (93)	25 (93)	78 (86)	
Histologic subtype				
Noncomedo	9 (32)	11 (41)	33 (36)	0.62
Comedco	10 (36)	12 (44)	32 (35)	
Unknown	9 (32)	4 (15)	26 (29)	

\*Comparison of significance between the three family history groups.

cause-specific survival was defined as death secondary to breast cancer, potentially including deaths from contralateral breast cancers, but not death from any other cause. For overall survival, failure was defined as death from any cause; patients alive at the time of last follow-up were not scored as failures.

Actuarial survival and failure time distributions were estimated by the Kaplan-Meier method (11). Statistical comparisons of the distributions were performed using the Mantel-Cox log-rank test (12). Tests for equality of proportions of clinical characteristics across family history groups were performed using a Chi-square test or Fisher's exact test where appropriate (13).

## RESULTS

Of the 146 consecutive patients treated with breast conservation therapy for ductal carcinoma *in situ*, 28 (19%) had a positive family history of breast or ovarian cancer in a first-degree relative, 27 (19%) had a positive family history in any second-degree relative, and 91 (62%) had no family history of breast or ovarian cancer. The data for patient, tumor, and treatment characteristics are presented in Table 1. The family history groups were balanced with regard to status of the final

pathologic margin, defined as negative, close, or positive, and unknown. The groups were also well balanced in total dose administered. Histologic subtype was recorded if reported and the family history groups were also well balanced for comedo and noncomedo subtypes. The only statistically significant difference seen between the three family history groups was the number of women in each age group. There were proportionally more women of age 39 or less and 40–49 years in the family history-positive groups than in the family history-negative group ( $p = 0.02$ ). These findings are not unexpected, given that it is known that women with a positive family history of breast or ovarian cancer are at risk for developing breast cancer at a younger age.

The method of detection of breast cancer was compared according to the family history group. Method of detection was recorded as physical examination only, mammographically detected only, detection by both physical examination and mammography, or other, such as nipple discharge. Table 2 presents the numbers of patients in each family history group and their method of detection. The majority of patients within each family history group were detected by mammogram alone and the overall percentage of patients diagnosed by mammogram alone was 70%. Within the family history groups, tumors detected by mammogram

Table 2. Method of detection by family history group

Method of detection	Family history-positive First-degree relative no. patients (%)	Family history-positive Any other relative no. patients (%)	Family history-negative no. patients (%)	Entire group no. patients (%)	<i>p</i> value*
Physical exam only	3 (11)	3 (11)	12 (13)	18 (12)	0.69
Mammogram only	20 (71)	21 (78)	60 (66)	101 (70)	
Both PE & Mammo	5 (18)	2 (7)	18 (20)	25 (17)	
Other	0	1 (4)	1 (1)	2 (1)	

\*Comparison of differences in method of detection by family history group.

Table 3. Actuarial outcomes by family history group

Outcome	Family history-positive First-degree relative	Family history-positive Any other relative	Family history-negative	Entire group	<i>p</i> -value*
Overall survival (%)					
5 years	100	100	98	98	0.08
10 years	100	100	91	94	
Cause-specific survival (%)					
5 years	100	100	99	99	0.25
10 years	100	100	95	97	
Local failure (%)					
5 years	8	0	2	3	0.33
10 years	8	8	16	12	
Contralateral breast cancer (%)					
5 years	7	0	1	2	0.23
10 years	18	8	8	10	

\*Comparison of significance between the three family history groups.

alone included 71% of women with a positive first-degree family history, 78% of women with a second-degree family history, and 66% of women with no family history. The differences in method of detection between family history groups was not statistically significant ( $p = 0.69$ ). When the method of detection was analyzed by age group, 42% (5/12) of women age 39 or less had tumors detected by mammogram only, compared to 72% of women age 40–49 and 72% of women age 50 or more ( $p = 0.08$ ). An additional 17% of patients overall had tumors detected on both mammogram and on physical examination, for a positive mammogram rate of 86%. Detection by both methods was recorded in 16% of women age 39 or less, 15% of women age 40–49, and 18% of women age 50 or more.

Outcomes for local recurrence rate, overall survival, cause-specific survival, and the risk of contralateral breast cancer for each of the three family history groups were examined at 5 and 10 years (Table 3). There were a total of 14 local failures, and 9 (64%) of these were invasive histologies. Local recurrences were diagnosed at a median of 7.8 years (range 1–16) after initial treatment. Ten local failures (71%) were noted in the same quadrant as the initial tumor at a median of 7.3 years (range 1–16). The other 4 ipsilateral breast recurrences occurred in another quadrant of the breast than the original tumor at a median of 9 years (range 2–12). Five patients who experienced a local recurrence had breast tangent irradiation without a boost, and 4 of these had recurrences in the same quadrant as the original tumor. Four women with local failure had a positive family history and all had recurrences in the same quadrant as the original tumor. Overall local failure rates were 3% at 5 years and 12% at 10 years. There were no statistically significant differences in local failure among the family history groups (Fig. 1). When invasive local failures only were compared, there was also no significant difference between family history groups ( $p = 0.22$ ). The patients with breast or ovarian cancer in first-degree relatives had an 8% local failure rate at 5 and 10 years. Women with a positive family history in other relatives had no local failures at 5 years and a rate of 8% at 10 years. The women with no family history

of breast or ovarian cancer demonstrated 2% local failure at 5 years and 16% at 10 years ( $p = 0.33$ ).

The overall cause-specific survivals at 5 and 10 years were 99% and 97%, respectively. Cause-specific survivals were 100% at 5 and 10 years for both positive family history groups. In the negative family history group, cause-specific survival was 99% and 97% at 5 and 10 years, respectively ( $p = 0.25$ ). No significant difference was seen in overall survival among the family history groups. The overall survival for the entire cohort was 98% at 5 years and 94% at 10 years. Overall survival for both positive family history groups was 100% at 5 and 10 years. For the negative family history group, the overall survival was 98% at 5 years and 91% at 10 years ( $p = 0.08$ ). There were more patients in the older age group in the negative family history cohort, which may account for the decrease in overall survival in this cohort. Fourteen patients developed contralateral breast

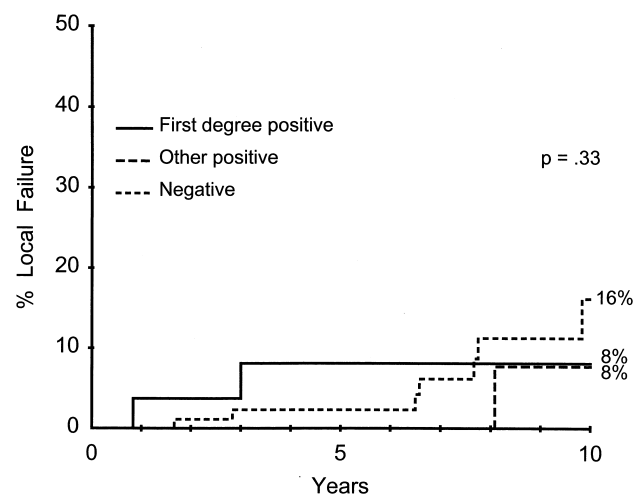


Fig. 1. Actuarial local failure percentage by family history group. The 10-year local failure rate for women with a positive first-degree family history was 8% (95% confidence interval [CI] of 2, 27), for women with a positive second-degree family history was 8% (95% CI of 1, 39), and for women with no family history was 16% (95% CI of 7, 33)

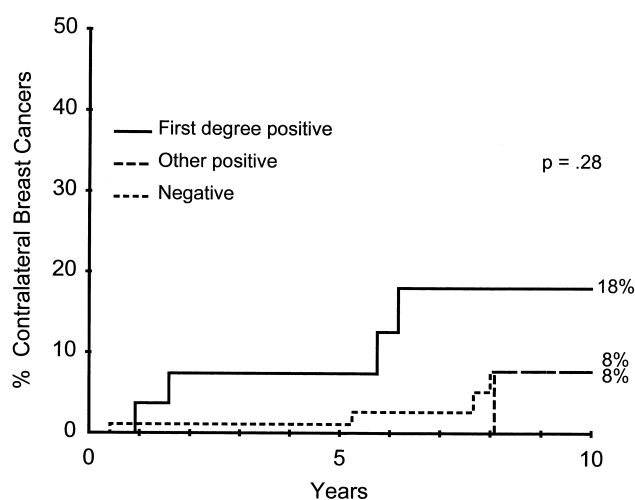


Fig. 2. Actuarial risk of developing a contralateral breast cancer by family history group. The 10-year percentage of contralateral breast cancers for women with a positive first-degree family history was 18%, with a positive second-degree family history was 8%, and with a negative family history was 8% ( $p = 0.28$ ).

cancers, and there were no statistical differences in contralateral breast cancer occurrence between the family history-positive and family history-negative groups. In this study, 5 of 28 women (18%) with a positive first-degree family history, and 1 of 27 women (4%) with a second-degree family history were diagnosed with a contralateral breast cancer. Eight of 91 (9%) women with negative family history developed a contralateral breast cancer. As shown in Fig. 2, the actuarial rate of contralateral breast cancer occurrence at 10 years was 18% for a positive first-degree family history, 8% for a positive second-degree family history and 8% for family history negative patients ( $p = 0.28$ ).

The relationship of age and family history group was examined. Table 4 shows the percentage of local failures by age of diagnosis. None of the differences was statistically significant. There were very few patients in the 39 or less age group ( $n = 12$ ), and only one local failure was noted in this group. For age 39 or less, the overall local control rate was 92%, compared to 87% for age 40–49 and 91% for age 50 or more ( $p = 0.76$ ). Because patients of younger age and a positive family history appear to be at highest risk for genetic breast cancer, the interaction between these two variables and outcome was evaluated. Due to small patient numbers, we combined all of the family history-positive

patients age 49 or less and age 50 or more and compared these to all the family history-negative patients in these same age groups. Table 5 demonstrates that when these age and family history groups are compared, no significant differences in local failure were detected. For patients age 49 or less with any positive family history, the local failure rate at 5 years was 0% compared to 9% for the family history negative patients ( $p = 0.23$ ). For patients age 50 or greater, the local failure rate at 5 years for any positive family history was 9% compared to 3% for patients with no family history ( $p = 0.73$ ). Overall, we were not able to detect any combined age group and family history group that predicted for a higher risk of local failure after breast conservation therapy. However, there were insufficient numbers of patients in the youngest age group (39 years old or less) to assess local control differences.

Cosmesis was examined at each follow-up and recorded as excellent, good, or fair. There were no instances of poor cosmesis. Only patients with a minimum of 5 years of follow-up were included in the analysis of cosmesis with respect to family history group. A total of 90 patients had at least 5 years of follow-up for the cosmesis comparison, representing 60% (33/55) of all patients with a positive family history and 63% (57/91) of all patients with a negative family history. Overall cosmetic scores were excellent in 52%, good in 40%, and fair in 8%. For patients with a positive first-degree family history, cosmesis was excellent in 9 (50%), good in 8 (44%), and fair in 1 (6%). For patients with a positive family history in second-degree relatives, cosmesis was excellent in 11 (73%), good in 3 (20%), and fair in 1 (7%). For the negative family history group, cosmesis was excellent in 27 (47%), good in 24 (42%), and fair in 6 (11%). There were no significant differences in cosmesis among the three family history groups ( $p = 0.45$ ).

Treatment complications were also recorded and scored for grade at each follow-up. Arm edema, cellulitis of the arm or breast, breast fibrosis, and axillary vein thrombosis were complications that were noted among the entire group of patients. One patient undergoing axillary dissection had 2 complications, mild cellulitis and lymphedema of the arm. One or more significant (moderate or severe) complications occurred in 7 (5%) patients. Among the patients experiencing significant complications, 4 of 7 (57%) had undergone axillary lymph node dissection. Therefore, of patients who had axillary surgery, 12% (4/33) experienced significant complications, compared with a complication rate of 3% (3/113) among patients who did not have any axillary sur-

Table 4. Relationship of age to risk of local failure

Age group	Local failure no. patients (%)	No local failure no. patients (%)	Total no. patients	$p$ value
Age 39 or less	1 (8)	11 (92)	12	0.76
Age 40–49	5 (13)	34 (87)	39	
Age 50 or greater	8 (9)	84 (91)	92	

\*Comparison of significance between age groups.

Table 5. Local failure by age groups and family history groups

Age group (years)	Family History				Family History				<i>p</i> value*
	Positive		Negative		Positive		Negative		
	% at 5 years	no. at risk	% at 5 years	no. at risk	% at 10 years	no. at risk	% at 10 years	no. at risk	
49 or less	0	19	0	15	7	11	Insufficient data		0.23
50 or more	9	16	3	49	9	8	12	15	0.73

\*Comparison of positive and negative family history for each age group

gery. The complications in women who had axillary dissection included lymphedema in 3 women and axillary vein thrombosis in 1 patient. The complications in women who had not undergone axillary dissection included lymphedema in 1 patient, significant breast fibrosis in 1 patient, and a breast wound infection in 1 patient.

Because of the small numbers of complications overall, to assess the relationship of the family history group to complication rates, we combined the two positive family history groups for comparison to the negative family history group. There was no significant difference in complication rates between these two family history groups ( $p = 0.39$ ). We also examined the impact of having undergone axillary dissection on complication rates. Whether or not a patient had axillary dissection, a positive or negative family history had no additional significant relationship to the risk of developing complications ( $p = 0.68$  and  $0.67$ , respectively). However, having axillary dissection was a highly significant factor in the risk of developing any complication for the entire study group ( $p = 0.003$ ). The data regarding cosmesis and complications among the family history groups is summarized in Table 6.

## DISCUSSION

In this study, we examined the impact of a positive family history of breast or ovarian cancer on local control, survival, cosmesis, and complications in 146 consecutive women treated with breast-conserving surgery and radiation for ductal carcinoma *in situ* of the breast. Our results show no significant differences in local control, cause-specific sur-

vival, or overall survival between women with a positive family history and those with no known family history at the time of diagnosis. Furthermore, there was no increased risk of developing a second contralateral breast cancer or of experiencing a worse rate of complications or cosmetic outcome in women with a positive family history. When the family history groups were further subdivided by age, we did not find any evidence of worse outcome for younger women with a positive family history, although there were few women in the youngest age group of 39 years or less.

Although mastectomy was the traditional treatment of choice for ductal carcinoma *in situ* for many years, a number of series have demonstrated good outcomes for breast conservation therapy for overall survival, despite somewhat higher rates of local recurrence when compared to mastectomy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 randomized trial compared the results of lumpectomy plus breast irradiation to lumpectomy alone (14). In women treated with radiation, local control at 8 years was 93%. Results from the EORTC 10853 randomized trial of similar design also showed improved local control in the radiation arm (15). A long-term follow-up report of a large collaborative group study of women with DCIS treated with breast conservation therapy demonstrated a 10-year cause-specific survival of 96% and a 14% overall local failure rate at 10 years (16). From these randomized trials and institutional series, it is evident that breast conservation therapy is a reasonable and effective alternative to mastectomy for women with DCIS.

The relationship of the histologic subtype of breast cancer to family history is not well characterized. It is not clear

Table 6. Relationship of cosmesis and complications to family history

	Family history-positive	Family history-negative	<i>p</i> -value*
Cosmesis	<i>n</i> = 33 (%)	<i>n</i> = 57 (%)	
Excellent	20 (61)	27 (47)	0.49
Good	11 (33)	24 (42)	
Fair	2 (6)	6 (11)	
Complications <i>n</i> = 7			
Axillary dissection	4	0	
No axillary dissection	1	2	

\*Comparison of relationship of family history group to cosmetic outcome.

whether DCIS in particular is significantly associated with a family history of breast cancer. Rosen *et al.* reported that no particular histology of breast cancer was consistently linked to either a high- or low-risk category of breast cancer development (17). For patients diagnosed with DCIS, 11% had a positive family history in a first-degree relative only, and 23% had a positive family history in a second-degree relative only. While it is not known whether DCIS is part of the genetic breast cancer spectrum, it has been noted that fewer than expected intraductal cancers occur in women with known BrCa1 mutations (19). Other series have found a smaller percentage of intraductal component in documented BrCa-associated tumors than in sporadic tumors (20, 21). Such data imply that the biologic behavior of genetic breast cancers includes early invasion with no *in situ* transition or precancerous stage. Israeli *et al.*, however, found significantly more DCIS in women with a positive family history (first- or second-degree relative) compared women with no family history ( $p < 0.01$ ) (18). Such data suggesting that DCIS may be somewhat more common among women with a positive family history could be the result of a number of factors. The development of DCIS may be associated with as yet unidentified genetic changes that result in an intermediately increased risk of breast cancer. Alternately, perhaps women with a family history more commonly undergo breast cancer screening beginning at an earlier age. The increased use of screening mammography in the population has resulted in a dramatic increase in the incidence of DCIS, often detected in asymptomatic women (22). In the present study, however, younger women were not more commonly diagnosed by mammography alone than older women. Although 70% of women in this series overall were diagnosed by mammography alone, among the women age 39 or less, only 42% (5/12) were mammographically detected. Half of this group (6/12) had a positive family history. The difference in method of detection was not significant and the number of younger women in this series is likely too small to describe their screening behavior.

A report from the Joint Center for Radiation Therapy by Hiramatsu *et al.* found that family history was associated with an increased rate of local recurrence (23). In a group of 76 women with DCIS treated with breast-conserving surgery and radiation, 22% had any positive family history of breast cancer. The actuarial local recurrence rates at 10 years were 37% for patients with a positive family history compared to 9% for patients with a negative family history ( $p = 0.008$ ). The authors examined a number of other pathologic and treatment-related features, including final margin status, volume of resection, interval between surgery and irradiation, and mode of detection. None of these factors was significantly associated with an increased local recurrence risk. However, smaller total excision volumes (< 60 cc) were associated with a 25% local recurrence rate compared to 0% for larger excision volumes ( $p = 0.04$ ). In addition, lack of re-excision was also associated with a somewhat higher rate of local recurrence. Age was not a

significant factor with respect to local recurrence, and the family history groups were not further subdivided by age group. Therefore, while there was no significant association between markers of volume of resection and local recurrence, there may have been too few patients in this study to detect such a difference. The relationship of resection volume within family history groups was not examined; therefore, the impact of family history alone on local recurrence risk cannot definitively be established in this series. In the present series of 146 patients, no significant association between family history and local recurrence was found.

In this study, we noted that a significantly increased percentage of women with a diagnosis of DCIS in the two younger age groups (39 years or less and 40–49 years) had a positive family history. Therefore, we wanted to ascertain whether younger women with a positive family history in particular were at increased risk for local recurrence after breast-conservation therapy, especially because these patients are at highest risk of BrCa1 or BrCa2 mutations. Age as a prognostic factor for breast cancer in women with ductal carcinoma *in situ* has been shown to be associated with an increased risk of local recurrence. McCormick *et al.* noted that 60% of local recurrences after breast-conservation therapy occurred in premenopausal women (24). Fowble *et al.* found only a trend toward increased local recurrence in similarly treated young women with DCIS (25). However, Sananes *et al.* found no difference in the incidence of local recurrence risk in women under age 35 with DCIS when compared to the general population of women in their study (26). In a report by Solin *et al.*, local failure as a function of age was examined (16). Local recurrence developed in 25% (14/56) women age 50 or younger, and in 2% (1/54) of women age 51 or older, and a shorter interval to recurrence was noted in the younger age group. However, this study showed no difference between the age groups in final pathologic margin status, grade, or histologic subtype. Kestin *et al.* examined the impact of age in 146 women treated with breast-conservation therapy for DCIS (27). These authors found that age less than 45 (or age as a continuous variable) was independently associated with an increased risk of local recurrence. Other factors associated with local recurrence risk were size (reported as number of slides with DCIS), final margin status, and volume of resection. Younger patients were noted to more often have larger tumors and smaller volumes of initial resection. In fact, the increase in local recurrence risk was seen only in young patients with small (< 40 cc) re-excision volumes. In patients undergoing re-excision, age was no longer a prognostic factor, and volume of re-excision was the only significant predictor of recurrence. In the present study, we did not find any difference in local recurrence or survival in women age 39 or less or age 40–49, compared to women 50 or more. It should be noted, however, that we had a small number of women and very few events in the youngest age group.

Between 2–11% of women diagnosed with invasive breast cancer will develop a second contralateral breast

cancer (28). A number of series have reported that women with a family history of breast cancer are at even higher risk for developing a second, contralateral breast cancer. In a series by Gogas, a 4.2% rate of metachronous contralateral breast cancers was noted and women with bilateral tumors were more likely to have a positive family history (29). An analysis of the Connecticut Tumor Registry showed that a family history of breast cancer in a first- or second-degree relative was associated with an odds ratio of 2.8 for developing a contralateral breast cancer (30). Data from the Utah Population Database revealed that women who developed a contralateral breast cancer within 3 years of their initial breast cancer diagnosis were 10 times as likely to have a first-degree relative with breast cancer (31). Chabner *et al.* found a relative risk of 5.7 associated with development of an opposite breast cancer compared with being without evidence of disease in young women treated with breast-conservation therapy who had a positive family history (32). The crude risk of developing an opposite breast cancer as the only site of failure was 14% (4/20) for women with a positive first-degree family history compared to 6% (6/100) for women with a negative family history. However, Kunkler *et al.* found no increased risk of contralateral breast cancer in a group of over 3,900 women treated with mastectomy and chest wall irradiation with very long-term follow-up (median 35 years) (33). For women with an initial diagnosis of DCIS, the risk of developing a subsequent contralateral breast cancer and the influence of family history is not known. Hiramatsu *et al.* noted one contralateral invasive breast cancer among 17 (6%) women with a positive first- or second-degree family history treated with breast conservation therapy for DCIS compared with one contralateral invasive breast among 58 (2%) women with a negative family history (23). In the present study, the actuarial risk of developing a contralateral breast cancer at 10 years was 18% in women with a positive first-degree family history compared to 8% for those with a negative family history ( $p = 0.23$ ). While not statistically significant, there were small numbers at risk in the positive family history group, and the data suggest that further investigation into the relationship of family history to the development of contralateral breast cancers in women with DCIS is warranted.

The impact on outcome for women with a positive family history of breast cancer treated with radiotherapy has been questioned, partly because of concerns over the interaction of radiation with tissues of women with possible genetic mutations. Certain genetic defects are known to be associated with increased radiosensitivity and a predisposition to radiation-induced second malignancies. Therefore, concerns about normal tissue effects have prompted investigators to examine the use of breast conservation therapy in high-risk patients. Pierce *et al.* reported no differences in acute or chronic morbidity after breast irradiation for invasive carcinomas in women with known BrCa1 and BrCa2 mutations

compared to historical controls with sporadic breast cancers (34).

There are few studies that have examined the impact of a positive family history on cosmesis and complications in women with DCIS treated with breast-conservation therapy. Mills *et al.* previously reported our experience with complications and cosmetic outcome in women with DCIS treated with conservative surgery and radiation (35). At 5 years, cosmetic outcome was excellent or good in 97% of patients. Complications were noted in 10% of patients, and the complication rate was significantly higher in women who had undergone axillary dissection. In the present study, we documented complications in 12% of women who had an axillary dissection compared to 3% of women who had no axillary surgery, while there was no significant correlation between complications and family history. We noted excellent or good cosmesis in 94% of women with a positive family history and in 89% of women with a negative family history. We examined the incidence of complications and the cosmetic results with relation to family history in women with DCIS and found that a positive family history did not result in a higher rate of complications or in poorer cosmetic outcome after breast irradiation.

This study and others have examined outcomes in women who have undergone breast-conservation treatment for DCIS, including breast irradiation. A treatment approach advocated by some institutions for selected patients omits radiation to the breast, using wide excision alone. The impact of family history and age in this group of patients is not well documented. Hetelekidis *et al.* reported outcomes in 59 women with DCIS treated with excision alone (36). These authors documented a number of prognostic factors, including age and family history. There was no difference in local recurrence in women younger than 54 years compared to older women. Positive family history was not associated with increased local recurrence. In fact, although not statistically significant, there were no local recurrences at 5 years in women with a positive family history, compared to 13% in women whose family history was negative. However, the definition of family history used for this analysis was not stated, and was unknown in 22% of patients.

In conclusion, the present study demonstrates that there is no difference in outcome with respect to local recurrence, survival, or contralateral breast cancer occurrence in women with ductal carcinoma *in situ* treated with breast conservation therapy regardless of family history status. We noted an increased percentage of younger women with a positive first- or second-degree family history, as expected. Younger women with a positive family history did not appear to be at increased risk for local recurrence, although there were few women in the youngest age group (39 years or less). We have also shown that a positive family history does not result in higher complication rates or in poorer cosmetic outcome after breast conservation treatment including breast irra-

diation. Our data show that a family history of breast or ovarian cancer in women diagnosed with ductal carci-

noma *in situ* should not be an exclusion criterion when evaluating women for breast-conservation treatment.

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