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No Evidence of Familial Correlation in Breast Cancer Metastasis

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Abstract

Purpose—Animal experiments support the hypothesis that the metastatic potential of breast cancer is a heritable trait of the host. Our objective was to evaluate correlations in metastasis occurrence in large families with multiple cases of breast cancer.

Methods—We evaluated correlation among pairs of relatives in the occurrence and timing of distant metastasis using retrospective cohort data from 743 female breast cancer patients in 242 families. We adjusted for correlation in their age at diagnosis, year of diagnosis, educational level, lymph node involvement, and estrogen receptor status.

Results—Distant metastasis occurred in 255 patients (34.3%) mean followup of 11.7 years. None of the correlation coefficients for metastasis in blood relatives differed significantly from zero. The estimated correlation coefficient in first-degree relatives was -0.03 (95% confidence interval -0.11 to 0.06).

Conclusions—These findings suggest that a family history of metastatic breast cancer does not contribute substantially to risk of metastasis for breast cancer patients.

Keywords

breast cancer; metastatic potential; familial correlation

The occurrence of cancer metastasis is thought to depend on somatic mutations generated during cancer development. Recently, however, germline genetic modifiers of metastatic propensity have been identified in mice [1–3]. These discoveries provide experimental support for the hypothesis that metastatic potential is a heritable trait. If this hypothesis was verified

in humans, it would have major implications for the early detection, diagnosis and treatment of breast cancer.

Cancer metastasis to distant sites is the primary factor contributing to cancer-related deaths. Some 60–70% of cancers are thought to have initiated the metastatic process prior to diagnosis [4]; thus better understanding of the factors determining metastasis is important. This is particularly true for breast cancer, a common cancer with relatively high incidence in young women. The percentage of all lymph-node-negative breast cancer patients who subsequently develop metastases ranges from 21% to 33% [5–10]. Even node-negative patients with small primary cancers have a significant (15%–25%) chance of developing distant metastases [11]. Because of the poor prognosis of metastatic cancer, a patient's potential metastasis is of considerable importance for clinical diagnosis and therapy. However, we have poor understanding of the mechanisms by which metastases arise from primary cancers and the factors that regulate cancer progression. Here we use retrospective cohort data from 743 female breast cancer patients in 242 US families to test the hypothesis that the metastatic risks of blood relatives are correlated. Such correlation may arise because relatives' cancers are similar in severity or aggressiveness. We addressed this issue by evaluating correlations in lymph node involvement at diagnosis, and in estrogen receptor (ER) status. Alternatively, correlations may arise because, for any given level of cancer severity at diagnosis, the likelihood of subsequent metastasis is similar in relatives. We addressed this issue by evaluating correlations in metastatic status and times to metastasis within families, with and without adjustment for lymph node involvement and ER status.

Methods

Study Population

Families with multiple cases of breast cancer were identified through Fox Chase Cancer Center (FCCC) in Philadelphia, Pennsylvania, and Huntsman Cancer Institute (HCI) at the University of Utah. These clinical research centers participate in the Breast Cancer Family Registry (Breast CFR), an international consortium of investigators in the US (Northern California, Utah, New York, Philadelphia), Canada and Australia whose infrastructure has been funded by the US National Cancer Institute since 1995. The participating sites have developed resources to facilitate a broad spectrum of multidisciplinary research. All living registry participants are contacted periodically for new information concerning cancer occurrence and recurrence in themselves and in their relatives. Further details about the Breast CFR resource can be found in [12] and at: http://epi.grants.cancer.gov/CFR/about_breast.html.

We ascertained all families registered at the FCCC & HCI study sites containing at least two female blood relatives with medically confirmed invasive breast cancer. Patients from these families were included in the analysis if their ages at diagnosis and calendar years of diagnosis were known, and if we were able to determine the presence or absence of subsequent breast cancer metastasis using the procedures described below. At FCCC, we ascertained 72 families containing 264 female breast cancer patients with known age and year of diagnosis. We were able to determine the metastatic status of 210 (80%) of the patients in these families. At HCI, we ascertained 184 families containing 683 female breast cancer patients with known age and year of diagnosis, and we were able to determine the metastasis status of 533 (78%) patients in 170 of the families. In total, the analysis included 242 families containing 743 breast cancer patients who contributed an average of 11.7 years of followup between diagnosis of first invasive breast cancer and subsequent metastasis or censoring. We determined patients' education levels (years of schooling) from questionnaire information provided by family members; patients with unknown educational level were assigned that of their closest relative. The study protocol was approved by the Institutional Review Boards (IRB) of all three participating institutions.

Determination of metastatic status and time to metastasis

The primary sources of information used to determine patients' metastatic statuses and times to metastasis were pathology reports, personal interviews with family members conducted with structured questionnaires by trained nurse-interviewers or genetic counselors, and cause of death from death certificates. Metastatic breast cancer patients were those listed on pathology reports, questionnaires or death certificates as having experienced one of the following outcomes: a) breast cancer spread to a distant site at diagnosis (N=14), b) cancer occurrence at a common breast cancer metastatic site (brain, bone, lung, liver) (N=68); or c) death due to breast cancer (N = 173). Metastasis-free survival time for these patients was defined as time from date of first invasive breast cancer diagnosis until date of the metastatic outcome for patients with outcomes of types (a) and (b), and until two years before death for patients with outcomes of type (c). Survival times for patients last observed to be metastasis-free were right-censored at the date of last observation. Of the 242 families included in the study, 141 were enrolled in the Breast CFR by family members without breast cancer, and 101 were enrolled by members with the disease. Survival times for these 101 patients were left-censored at the date of enrollment, since these patients had to have survived long enough to register their families.

Statistical analysis

We estimated correlation coefficients for prognostic features (lymph node involvement at diagnosis, ER status) and metastatic outcomes (metastasis occurrence, and metastasis-free survival time in months since diagnosis) in pairs of relatives. We obtained these estimates using estimating equations for multivariate binary outcomes [13] and for multivariate metastasis-free survival data [14]. For a given outcome, these methods provide estimates of familial correlation coefficients that are adjusted for correlation in covariates associated with the outcome (such as age at diagnosis, treatment efficacy, and socioeconomic status (SES)). We used calendar year of diagnosis as a surrogate for treatment efficacy, and educational level as a surrogate for SES. The estimating equations for binary outcomes are based on a logistic regression model for the marginal distribution of each patient's outcome, and on a quadratic exponential model for the covariance of outcomes in pairs of related patients. The estimating equations for metastasis-free survival times are based on a proportional hazards model for each patient's marginal hazard rate, and the semiparametric model of Clayton [15] for the pairwise covariance of relatives' survival data. Both methods allow inference on pairwise correlations in families containing varying numbers of breast cancer patients, and regression of the correlation coefficients against the kinship coefficients and types of relationship for the various pairs of relatives. Significance levels are based on the Wald test, and all p-values are two tailed.

Results

Table 1 shows the distribution of the 242 families included in the analysis, according to their numbers of breast cancer patients with and without metastasis. These families contained 743 members and 1419 pairs of members with breast cancer. The cancers of 255 members (34.3%) were classified as having metastasized to a distant site, with the remaining 488 members last observed to be free of such metastasis.

The demographic characteristics of the 743 breast cancer patients are shown in Table 2. Forty-nine percent of the patients were between the ages of 40–60 years at diagnosis and most (98.7%) were white. As expected, these patients were more highly educated than the general US population born in the same years (because they were in families ascertained by clinical research centers). Compared to the 2000 US census population for Whites, they were less likely to have had at most grammar school education (0.5% versus 14%) and more likely to have had at least some college education (65% vs 55%).

Prognostic features

Table 2 also shows data on the cancers' lymph node involvement and ER status at diagnosis, for the subset of patients with available data. Data were less likely to be available for patients with subsequent metastasis than for patients without it. Among those with data, 33% of patients presented with positive lymph nodes, and 65% presented with ER-positive cancer.

We examined associations between each of the two prognostic features (lymph node involvement, ER status) and demographic characteristics (age at diagnosis, year of diagnosis, educational level). These analyses indicated that younger patients were more likely to be diagnosed with node-positive cancer (p-value for decreasing trend with age given by p_{trend} = 0.03) and with ER-negative cancer (p_{trend} <0.001). Patients with no college education were more likely than those with at least some college to present with positive lymph nodes (odds-ratio = 1.6, p = .01). Calendar year of diagnosis was not associated with either nodal status or ER status.

We also estimated correlation coefficients for nodal involvement and ER positivity in pairs of relatives, by type of relationship (e.g., mother-daughter, sister-sister, other blood relation). All estimates were adjusted for correlation in the patients' demographic characteristics. Lymph node involvement was not significantly correlated in pairs of blood relatives: correlation coefficients for mother-daughter and sister-sister pairs were close to zero, and no overall trends were seen with increasing kinship coefficient of the pairs of relatives. However statistically significant positive correlation was seen in the ER statuses of the cancers of first-degree relatives (correlation coefficient (CC) = 0.37, 95% confidence interval (CI) = 0.10–0.64), but not in pairs of more distant blood relatives (CC = 0.10, CI = −0.29–0.48). The correlation was higher for sister-sister pairs (CC = 0.41, CI =0.00–0.83) than for mother-daughter pairs (CC = 0.28, CI =−0.14–0.42).

Metastatic occurrence and time to metastasis

Table 3 gives the distribution of the 1419 pairs of family members according to their degrees of relationship and metastatic statuses. Among all types of relationship combined, both members developed metastatic disease in 203 pairs (14%), neither member developed metastasis in 561 pairs (40%), and the remaining 655 pairs (46%) were metastasis-discordant. The combined concordance rate (positive or negative for metastasis) was 56% for first-degree relatives, 53% for second-degree relatives, 53% for more distant blood relatives, and 53% for family members related only by marriage. These concordance rates are slightly higher than the 50% rate expected under the null hypothesis of no familial correlation among family members, but there is little evidence of an increasing trend with increasing genetic kinship of the pairs.

Table 4 shows results of combined logistic regression and correlation analysis of metastasis occurrence as a binary outcome. The upper part of the table shows odds-ratios relating metastasis risk to patients' demographic characteristics and lymph node status at diagnosis. Risk of metastasis was inversely associated with calendar year of diagnosis, and strongly positively associated with lymph node involvement. In the subset of patients with known ER status, risk also was positively associated with ER-negative status (data not shown). The lower part of the table gives estimated correlation coefficients for metastatic occurrence, by type of relationship. These estimates are adjusted for possible familial correlation in year of diagnosis and lymph node status. As seen in the table, none of the correlation coefficients for pairs of blood relatives differed significantly from zero; in particular, correlation coefficients for mother-daughter and sister-sister pairs are close to zero. In addition, no overall trend was seen with increasing kinship coefficient of the pair (data not shown). The estimated correlation coefficients remained close to zero when we analyzed the data without adjusting for lymph node status, and when we included other demographic covariates in the analysis.

The mean time from diagnosis to metastasis or censoring for the 730 patients with known temporal data was 11.7 years, with a total of 8,518 person-years of followup. Proportional hazards regression and correlation analysis of time to metastasis, adjusted for lymph node involvement and year of diagnosis, produced familial correlations similar to those shown in Table 4 for metastasis occurrence, and none of them differed significantly from zero.

Finally, we performed proportional hazards regression of patients' metastasis risks in relation to presence or absence of metastatic outcome in their mothers, and in their first-born sisters. The hazard rate for patients whose mothers had metastatic disease was 1.22 (CI: 0.70–2.13) times that of patients whose mothers had nonmetastatic disease. The hazard rate for patients whose first-born sisters had metastatic disease was 0.64 (CI: 0.39–1.22) times that of patients whose first-born sisters had nonmetastatic disease. Thus, we found no statistically significant evidence that daughters or younger sisters of patients with metastatic breast cancer were themselves at elevated risk of metastasis.

Discussion

These data from 1419 pairs of breast cancer patients in 242 largely Caucasian families provided no evidence to support the hypothesis that the breast cancers of blood relatives have similar propensities to metastasize. None of the estimated correlation coefficients for metastatic risk in pairs of relatives differed significantly from zero, regardless of the outcome (occurrence of metastasis or metastasis-free survival time), the kinship coefficient of the relatives, and the covariates included in the correlation analysis. Similarly, the presence of lymph node involvement at diagnosis was uncorrelated in family members. However the ER statuses of cancers in first-degree relatives were positively correlated.

The absence of correlation in metastatic risk contrasts with observations from Swedish national data for some 2000 pairs of mother–daughter breast cancer patients [16–18]. These data showed significantly elevated breast cancer death rate ratios of 1.6 to 1.8 among patients whose mothers had poor breast cancer outcome, compared to patients whose mothers had good outcome. Reasons for the differences in the US and Swedish data include different distributions of potential confounding factors between the two populations, and chance. In particular, the positive findings in the Swedish data could reflect confounding by familial correlation in SES, a strong determinant of breast cancer prognosis [19,20]. Alternatively, the negative results reported here could reflect lack of statistical power in the present data.

According to the first of these two explanations, there is no strong correlation in metastatic risk among relatives, and the positive correlations in the Swedish data reflect residual confounding by SES that did not affect the educated, homogeneous clinic-based population studied here. The population of Sweden is heterogeneous with respect to SES, and although the death rate ratios were adjusted for occupational status (recorded as the highest job category held in a household as obtained from census data), this measure is crude and residual confounding by SES cannot be excluded.

The second explanation for the discrepant findings is lack of statistical power in the present study. According to this explanation, metastatic potential is correlated in close relatives independently of SES, and the current negative findings are due to insufficient sample size. To investigate this possibility, we used simulations to assess the power of this study to detect correlations of various magnitudes in the metastatic statuses of the 420 available pairs of first-degree relatives. The simulations suggest that this sample size would have 84% power to detect correlation coefficients of magnitude 0.13 and higher, and 92% power to detect those of magnitude 0.15 and higher. In a population of breast cancer patients with 33% risk of metastasis, correlation coefficients of these magnitudes would correspond at most to risks of

about 43% among the daughters, sisters and mothers of metastatic patients. Thus the present negative findings indicate that, if patients with a family history of metastatic breast cancer themselves have increased metastatic risk, the increase is unlikely to be large.

The absence of detectable correlation within families noted here, if replicated, would imply that germline variants with strong effects on breast cancer metastatic potential are unlikely in humans. However common variants of moderate effect cannot be excluded, since such variants would not produce easily detectable familial correlations in metastasis occurrence. Evidence of such variants from animal experiments is provided by the development of inbred mouse strains that harbor unidentified genetic modifiers of metastatic progression in mammary tumors [21], and by findings linking such progression to variants in the genes Sipa1 [3] and Brd4 [22]. Epidemiological studies suggest that variants in several candidate genes, including TP53, may be associated either with prognostic characteristics at diagnosis [22–25] or subsequent recurrence or breast cancer death [26–28]. However apart from associations concerning variants in the TP53 gene, none of the findings have been replicated.

Some limitations of the current study warrant consideration. First, we did not have high power to detect positive correlations of magnitude less than 10–15%. Thus we cannot rule out the small correlations that would be expected to arise from modest similarities in metastatic propensity due to genetic variants of small to moderate effect. Second, we did not have data on cancer treatment, particularly adjuvant chemotherapy, and differences in treatment efficacy within families might have obscured underlying correlations in metastatic propensity. Still, in this educated population, treatment efficacy may have been captured adequately by year of diagnosis, which was negatively associated with metastatic risk. Third, our findings concerning educated Caucasian women in families who present to high-risk cancer clinics may not apply to other racial, ethnic or socio-economic groups. However, although the homogeneity of this study population limits the generalizability of the findings, it has the advantage of minimizing possible confounding by familial correlation in SES.

In conclusion, the present data do not support the existence of strong correlation among relatives in the metastatic characteristics of their cancers. These negative findings need replication in other populations. If confirmed, they indicate that a family history of metastatic breast cancer does not influence a patient's risk that her own breast cancer will metastasize, a conclusion with clinical relevance for both the prevention and treatment of breast cancer. For example, a woman's choice between risk-reducing surgery and surveillance may be influenced by her perceptions not only of her risk of developing breast cancer (which is often overestimated), but of her risk of dying from breast cancer. These data suggest that the metastatic outcomes of her relatives' breast cancers should not influence her decisions. Similarly, had the data suggested a strong inherited component to the risk of metastasis, more aggressive treatment for early stage breast cancer would be warranted for patients with a family history of fatal breast cancer than for those with a family history of nonfatal disease. The absence of such evidence mitigates against tailoring the aggressiveness of therapy to patients' family histories of metastatic breast cancer.

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REFERENCES

1. Crawford NP, Alsarraj J, Lukes L, et al. Bromodomain 4 activation predicts breast cancer survival. Proc Natl Acad Sci USA 2008;105:6380–6385. [PubMed: 18427120]
2. Hunter KW, Broman KW, Voyer TL, et al. Predisposition to efficient mammary tumor metastatic progression is linked to the breast cancer metastasis suppressor gene Brms1. Cancer Res 2001;61:8866–8872. [PubMed: 11751410]
3. Park YG, Zhao X, Lesueur F, et al. Sipa1 is a candidate for underlying the metastasis efficiency modifier locus Mtes1. Nat Genet 2005;37:1055–1062. [PubMed: 16142231]
4. Eccles SA, Box G, Court W, et al. Preclinical models for the evaluation of targeted therapies of metastatic disease. Cell Biophys 1994;24–25:279–291.
5. Heimann R, Lan F, McBride R, et al. Separating favorable from unfavorable prognostic markers in breast cancer: the role of E-cadherin. Cancer Res 2000;60:298–304. [PubMed: 10667580]
6. Quiet CA, Ferguson DJ, Weichselbaum RR, et al. Natural history of node-negative breast cancer: a study of 826 patients with long-term follow-up. J Clin Oncol 1995;13:1144–1151. [PubMed: 7738620]
7. Rosen PP, Groshen S, Saigo PE, et al. A long-term follow-up study of survival in stage I ($T_1N_0M_0$) and stage II ($T_1N_1M_0$) breast carcinoma. J Clin Oncol 1989;7:355–366. [PubMed: 2918331]
8. Tan LK, Giri D, Hummer AJ, et al. Occult axillary node metastasis in breast cancer are prognostically significant: results in 368 node-negative patients with 20-year follow-up. J Clin Oncol 2008;26:1803–1809. [PubMed: 18332473]
9. Wang Y, Klijn JGM, Zhang Y, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365:671–679. [PubMed: 15721472]
10. Clare SE, Sener SF, Wilkens W, et al. Prognostic significance of occult lymph node metastases in node-negative breast cancer. Ann Surg Oncol 1997;4:447–451. [PubMed: 9309332]
11. Heimann R, Hellman S. Clinical progression of breast cancer malignant behavior: what to expect and when to expect it. J Clin Oncol 2000;18:591–599. [PubMed: 10653874]
12. John EM, Hopper JL, Beck JC, et al. The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast Cancer Res 2004;6:R375–R389. [PubMed: 15217505]
13. Zhao LP, Prentice RL. Correlated binary regression using a quadratic exponential model. Biometrika 1990;77:642–648.
14. Prentice RL, Hsu L. Regression on hazard ratios in multivariate failure analysis. Biometrika 1997;84:349–363.
15. Clayton DG. A Model for Association in Bivariate Life Tables and Its Application in Epidemiological Studies of Familial Tendency in Chronic Disease Incidence. Biometrika 1978;65:141–151.
16. Hartman M, Lindström L, Dickman PW, et al. Is breast cancer prognosis inherited? Breast Cancer Res 2007;9:R39. [PubMed: 17598882]
17. Hemminki K, Ji J, Försti A, et al. Survival in breast cancer is familial. Breast Cancer Res Treat 2007;110:177–182. [PubMed: 17674192]
18. Lindstrom LS, Hall P, Hartman M, et al. Familial concordance in cancer survival: a Swedish population-based study. Lancet Oncol 2007;8:1001–1006. [PubMed: 17921068]
19. Bradley CJ, Given CW, Roberts C. Race, Socioeconomic Status, and Breast Cancer Treatment and Survival. J Nat Cancer Inst 2002;94:490–496. [PubMed: 11929949]
20. Dalton SO, Ross L, Düring M, et al. Influence of socioeconomic factors on survival after breast cancer--a nationwide cohort study of women diagnosed with breast cancer in Denmark 1983–1999. Int J Cancer 2007;121:2524–2531. [PubMed: 17680561]
21. Lifsted T, Le Voyer T, Williams M, et al. Identification of inbred mouse strains harboring genetic modifiers of mammary tumor age of onset and metastatic progression. Int J Cancer 1998;77:640–644. [PubMed: 9679770]
22. Crawford NP, Ziogas A, Peel DJ, et al. Germline polymorphisms in SIPA1 are associated with metastasis and other indicators of poor prognosis in breast cancer. Breast Cancer Res 2006;8

23. Costa S, Pinto D, Pereira D, et al. Importance of TP53 codon 72 and intron 3 duplication 16bp polymorphisms in prediction of susceptibility on breast cancer. BMC Cancer 2008;8:32. [PubMed: 18230179]

24. Hoyal CR, Kammerer S, Roth RB, et al. Genetic polymorphisms in DPF3 associated with risk of breast cancer and lymph node metastases. J of Carcinogenesis 2005;4:13–21.

25. Nordgard SH, Ritchie MD, Jensrud SD, et al. ABCB1 and GST polymorphisms associated with TP53 status in breast cancer. Pharmacogenetics and Genomics 2007;17:127–136. [PubMed: 17301692]

26. Goode EL, Dunning AM, Kuschel B, et al. Healey CS, Day NE, Ponder BAJ, Easton DF, Pharoah PPD. Effect of Germ-Line Genetic Variation on Breast Cancer Survival in a Population-based Study. Cancer Res 2002;62:3052–3057. [PubMed: 12036913]

27. Schmidt MK, Tollenaar RAEM, de Kemp SR, et al. Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2*1100delC germline mutation. J Clin Oncol 2007;25:64–69. [PubMed: 17132695]

28. Udler M, Maia AT, Cebrian A, et al. Common germline genetic variation in antioxidant defense genes and survival after diagnosis of breast cancer. J Clin Oncol 2007;25:3015–3023. [PubMed: 17634480]

Table 1

Distribution of 242 Families[a] according to Number of Breast Cancer Patients in Family with and without Distant Metastasis

	Family Members with Metastasis					
Family Members without Metastasis	0	1	2	3–4	5+	Total
0	0	10	7	2	0	19
1	23	36	12	10	0	81
2	42	14	12	3	0	71
3–4	22	19	8	7	0	56
5+	2	3	2	3	5	15
Total	89	82	41	25	5	242

[a]Table shows numbers of families containing the designated numbers of members with and without metastasis. Eligible families must have two or more members with medically verified breast cancer, at least one of whom has complete data for age and year of diagnosis and metastatic status.

Table 2

Distribution of 743 Breast Cancer Patients with Known Metastatic Status according to Demographic Characteristics and Cancer Prognostic Features

	Metastatic Status					
	Positive		Negative		Total	
	N	(%)	N	(%)	N	(%)
All Patients	255	(100)	488	(100)	743	(100)
Study site						
FCCC [a]	62	(24)	148	(30)	210	(28)
HCI [a]	193	(76)	340	(70)	533	(72)
Year of dx						
< 1960	38	(15)	37	(7)	75	(10)
1960–1989	148	(58)	213	(44)	361	(49)
1990+	69	(27)	238	(49)	307	(41)
Age (yrs) at dx						
<40	62	(24)	116	(24)	178	(24)
40–59	126	(49)	240	(49)	366	(49)
60+	67	(26)	132	(27)	199	(27)
Race						
White	253	(99)	480	(98)	733	(99)
Nonwhite	2	(1)	8	(2)	10	(1)
Years of education						
No high school	1	(0.4)	3	(0.6)	4	(0.5)
High school	95	(37)	160	(33)	255	(34)
Some college	159	(62)	325	(67)	484	(65)
Lymph node status						
Positive	29	(11)	67	(14)	96	(13)
Negative	27	(11)	167	(34)	194	(26)
Unknown	199	(78)	254	(52)	453	(61)
ER status [b]						
Positive	15	(6)	109	(22)	124	(17)
Negative	18	(7)	48	(10)	66	(9)
Unknown	222	(87)	331	(68)	553	(74)

[a] FCCC = Fox Chase Cancer Center, HCI = Huntsman Cancer Institute

[b] ER = estrogen receptor

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Table 3

Distribution of 1419 Pairs of Family Members with Invasive Breast Cancer according to Familial Relationship and Metastatic Status

	Metastatic Status						
	Concordant Positive		Concordant Negative		Discordant		Total
	N	(%)	N	(%)	N	(%)	
Degree of Relationship							
First-degree	58	(14)	175	(42)	187	(44)	420
Mother-Daughter	28	(14)	90	(45)	80	(40)	198
Sister-Sister	30	(13)	85	(38)	107	(48)	222
Second-degree	30	(11)	114	(42)	126	(47)	270
Third-degree or higher	54	(12)	182	(41)	207	(47)	443
Related by marriage	61	(21)	90	(32)	135	(47)	286
Total	203	(14)	561	(40)	655	(46)	1419

Table 4

Odds-ratios (ORs) and Familial Correlation Coefficients (CCs) for Occurrence of Breast Cancer Metastasis

	Number of Patients		OR [a]	CI [b]
	No Metastasis	Metastasis		
Age at dx (yrs)				
<40	116	62	1.0	-
40–50	240	126	1.0	0.7, 1.5
60+	132	67	1.1	0.6, 1.7
Year of dx				
<1990	123	112	1.0	-
1990+	365	143	0.6	0.5, 0.9
Education				
No college	163	96	1.0	-
Some college	325	159	0.78	0.6, 1.2
Lymph Nodes				
Negative	167	27	1.0	-
Positive	67	29	2.7	1.5, 4.9
Unknown	254	199	4.0	2.5, 6.4
	Number of Pairs			
	Concordant	**Discordant**	**CC [c]**	**CI**
Type of Relationship				
Mother-daughter	118	80	0.03	−0.11, 0.16
Sister-sister	115	107	−0.07	−0.14, 0.06
Other blood	380	333	−0.00	−0.07, 0.07

[a] all odds-ratios are adjusted for other variables

[b] CI = 95% confidence interval

[c] All correlation coefficients are adjusted for age at diagnosis, year of diagnosis, and lymph node status (positive, negative, unknown)