Original Article

Breast Cancer Histologic Subtypes Show Excess Familial Clustering

N. Lynn Henry, MD, PhD [1,2]; and Lisa A. Cannon-Albright, PhD [2,3,4]

BACKGROUND: The inherited predisposition to developing specific histologic subtypes of invasive breast carcinoma has been incompletely investigated. By using a large, population-based database, the authors sought to investigate familial clustering of breast cancer by histologic subtype. **METHODS:** By using the Utah Population Database, which links genealogy records to the National Cancer Institute's statewide Surveillance, Epidemiology, and End Results cancer registry, the authors identified patients with breast cancer by histology and tested for evidence of shared genetic predisposition to histologic specific subtypes by examining pairwise relatedness and estimating the relative risk (RR) among first-degree, second-degree, and third-degree relatives. **RESULTS:** The authors identified 23,629 individuals in the Utah Population Database who had at least 3 generations of genealogy and at least 1 primary breast cancer, 2883 (12.2%) of which were specific histologic subtypes other than invasive ductal carcinoma (including inflammatory [n = 178], lobular [n = 1688], and mucinous [n = 542]). Statistically significant excess distant relatedness was identified for the mucinous subtype ($P = .011$) as well as for inflammatory breast cancers ($P = .024$). The RR for breast cancer of any histology in second-degree relatives was significantly increased for patients with inflammatory (RR, 1.32; 95% CI, 1.02-1.68; $P = .03$), lobular (RR, 1.36; 95% CI, 1.25-1.47; $P < .001$), and mucinous (RR, 1.27; 95% CI, 1.12-1.44; $P = .00021$) subtypes. **CONCLUSIONS:** These findings provide evidence for significant familial clustering within histological subtypes for lobular, mucinous, and inflammatory breast carcinomas. Further research is required to identify the underlying genetic variants responsible for the increased risk. Studies of high-risk pedigrees segregating a specific histologic subtype could be a powerful design for predisposition gene identification. ***Cancer*** **2019;125:3131-3138**. © *2019 American Cancer Society.*

KEYWORDS: breast cancer, familiality, inflammatory, lobular, mucinous, Utah Population Database (UPDB).

INTRODUCTION

Breast cancer is a heterogeneous disease. According to the World Health Organization, breast cancer can be classified based on histopathologic characteristics, including cell morphology, architecture, and growth patterns, into 21 distinct subtypes.[1,2] Although the majority of invasive breast cancers are ductal carcinomas, there are several more uncommon histologic subtypes that are associated with either a more aggressive or a more indolent disease course.

Pure mucinous and tubular breast cancers are examples of more indolent tumor subtypes. Mucinous tumors comprise 1% to 2% of breast cancers and are typically hormone receptor-positive and HER2-negative.[3] They are frequently diagnosed at an older age and are associated with a better than average breast cancer-specific survival. In addition to being histologically distinct, mucinous cancers also differ genomically from more common breast cancer subtypes, including lower genomic instability and a lower frequency of mutations in genes in the PI3K pathway.[3,4]

Inflammatory breast cancer, in contrast, is an aggressive type of breast cancer. It is not a specific histology per se but, rather, is diagnosed based on characteristic clinical changes, including rapid development of diffuse erythema and edema of the breast.[5-8] About 2.5% of patients diagnosed with breast cancer have inflammatory breast cancer, and it is often at an advanced stage at the time of diagnosis.[6] Dermal lymphatic invasion can be noted on pathology, although this finding is not required for the diagnosis. Prior reports have shown an increased risk of inflammatory breast cancer in younger patients and those with a higher body mass index.[9]

Approximately 5% to 10% of breast cancers are inherited. Patients with mutations in specific genes, including *BRCA1*, *BRCA2*, *TP53*, and *PTEN*, have a high risk of developing breast cancer.[10] More recently, it has become apparent that mutations in numerous additional genes, including *CHEK2* and *PALB2*, are associated with a more moderate risk of breast cancer.[11] However, the only histologic subtypes that have been associated with mutations

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in specific genes are lobular carcinoma with *CDH1*, which encodes e-cadherin,[12] and medullary carcinoma with *BRCA1*.[13] Other histologies, including mucinous carcinoma, have not previously been associated clearly with a family history of breast cancer. Recently, inflammatory breast cancer reportedly has been associated with a first-degree family history of breast cancer in some but not all studies; mutations in specific genes have not yet been identified.[9,14,15]

The possibility of additional genetic contributions to breast cancer exists. Identification of excess familial clustering using the genealogical index of familiality (GIF) is a method that can be used to provide evidence that the risk of a disease is mediated by inherited genetic factors. The GIF has previously been described in studies evaluating the familiality of cancer.[16-19] Determining whether a disease exhibits familial clustering can be used to calculate disease risk in relatives, to increase understanding of the disease pathogenesis, and ultimately can permit the identification of underlying causative mutations. In the context of the excess familial clustering that is generally recognized for breast cancers of any histology, we used this established methodology to investigate hypotheses of additional genetic contributions to predisposition to specific breast cancer histologic subtypes and inflammatory breast cancer using a large, population-based database.

MATERIALS AND METHODS

Utah Population Database

A unique Utah resource consisting of the genealogy of the Utah Northern European founders from the mid-1800s and their descendants to modern day linked to a statewide National Cancer Institute Surveillance, Epidemiology, and End Results cancer registry from 1973 was used to describe the familial clustering of breast cancer cases by histologic subtypes and of inflammatory breast cancer. This resource, the Utah Population Database (UPDB),[20,21] includes data on greater than 11 million individuals. The approximately 3 million of these individuals who have at least 3, and up to 16, generations of genealogy data connecting to Utah founders were analyzed here. The Utah Cancer Registry was established statewide in 1966 and became one of the original Surveillance, Epidemiology, and End Results registries in 1973. All independent primary cancers diagnosed or treated in Utah are recorded. Study approval was obtained from the University of Utah Institutional Review Board and the Utah Resource for Genetic and Epidemiology Research Review Board. Statistical analyses were performed using tools created specifically for the UPDB.

Breast Cancer Cases

Approximately 150,000 of the 3 million individuals with genealogy in the UPDB have a linked Utah Cancer Registry record; 23,629 of these linked cancer records are for individuals diagnosed with breast cancer, and 155 of these breast cancers occurred in males. Breast cancer cases were identified using the International Classification of Diseases for Oncology Revision 3 definition of the primary site coded from 500 to 509 and including histology codes 8000 through 9589 (leukemias and lymphomas excluded). In particular, this classification was used to assign specific histologic subtypes as follows: angiosarcoma (code 9120), apocrine (code 8401), inflammatory (code 8530), lobular (code 8520), medullary (codes 8510, 8512, and 8513), metaplastic (codes 8570-8572 and 8575), mucinous (code 8480), phyllodes (code 9020), and tubular (code 8211).

The Genealogical Index of Familiality Method

The GIF method was developed for use with the UPDB and allows a test of the hypothesis of excess relatedness among individuals with a phenotype of interest. The GIF compares the average pairwise relatedness of a set of individuals (eg, all breast cancer cases) with the expected pairwise relatedness for a similar set of individuals in the UPDB. The coefficient of kinship is used to measure relatedness,[22] and pairs can be defined based on their genetic distance. The expected pairwise relatedness for a group of individuals is estimated in a set of randomly selected, matched controls. Randomly selected controls from the UPDB were matched to cases by sex, 5-year birth year cohort, and birth place (Utah or not Utah). For each GIF test of a set of cases, the expected pairwise relatedness was estimated as the average pairwise relatedness computed for 1000 sets of matched controls. The significance of the case GIF was assessed empirically by its position within the 1000 control GIF statistic values. Breast cancer histologic subsets with sample sizes less than 100 were not analyzed with the GIF method.

The GIF method tests for excess relatedness or familiality but does not distinguish between relatedness because of genetics versus common environment. Therefore, the distant GIF (dGIF) test was created as an extension of the GIF statistic; it is performed while ignoring all relationships closer than third-degree to test for an

excess of distant relationships, which is unlikely in the absence of a heritable contribution.

Estimation of Relative Risk in Relatives

Evidence for a familial or genetic contribution to disease is commonly considered using estimates of relative risk in relatives. Published risks for cancer in relatives are typically limited to close relationships (first-degree). Relative risks (RRs) for breast cancer were estimated in both close and distant relatives in the UPDB using birth-specific and sex-specific cohort rates of breast cancer estimated internally from the UPDB as follows.

All individuals in the UPDB genealogy who had at least 3 generations of genealogy were assigned membership to a birth year-specific (5-year groups), sex-specific, and birthplace-specific (Utah or not Utah) cohort. Internal cohort-specific rates of breast cancer (and histologic subtypes) were calculated for all cohorts separately by summing the number of individuals with the selected breast cancer histology in each cohort and dividing by the total number of individuals in the cohort. Expected numbers of cancer cases for a set of individuals (eg, first-degree relatives [FDRs] of mucinous breast cancer cases) were estimated by counting all FDRs of the set of mucinous breast cancer cases by cohort, multiplying the number of relatives per cohort by the cohort-specific cancer rate, and then summing over all cohorts. The observed numbers of cancer cases were counted, without duplication, in the set of relatives being considered. RR = (observed number of cases)/(expected number of cases) is an unbiased estimator of RR. Exact 2-sided Poisson probabilities were calculated under the null hypothesis that the RR was 1.0, and 95% CIs were calculated based on the assumption that the number of observed cases follows a Poisson distribution, with mean equal to the expected number of cancers.

High-Risk Pedigrees

Given a set of individuals selected from the UPDB, all related clusters of these individuals who descend from a common ancestor can be identified. All such clusters, or pedigrees, were identified for each subset of breast cancer cases with a specific histology; pedigrees were never completely overlapping, but cases could appear in more than 1 pedigree. To determine whether a pedigree is high-risk, the observed number of cases among the descendants is compared with the expected number of cases. The expected number of, for example, breast cancer cases with mucinous histology among the descendants of a set of pedigree founders is calculated by counting all descendants by cohort, multiplying the number of descendants in each cohort by the cohort-specific rate of mucinous type breast cancer (estimated as described above), and summing over all cohorts. An excess of observed to expected affected descendants of $P < .05$ was used to classify a descending pedigree as high-risk for a specific subtype.

RESULTS

We identified 23,629 individuals with at least 3 generations of genealogy connecting to Utah founders who had at least 1 primary breast cancer recorded in the Utah Cancer Registry. The majority of these cases were ductal histology or mammary carcinoma not otherwise specified; 53 apocrine carcinomas, 178 inflammatory breast cancers, 1688 lobular carcinomas, 542 mucinous carcinomas, 134 tubular carcinomas, 38 metaplastic carcinomas, 32 phyllodes tumors, 341 medullary carcinomas, and 12 angiosarcomas were also identified.

Because inflammatory breast cancer does not represent a specific histology but, rather, is a clinical diagnosis, the clinical and pathologic characteristics can be heterogeneous. In this analysis, the cohort of 178 patients with inflammatory breast cancers had median age of 58 years and a median survival of 31 months (see Supporting Table 1). Just over one-half of cancers were poorly differentiated. Almost 15% had metastatic disease at the time of diagnosis. In contrast, the invasive lobular and mucinous cancers were diagnosed in women at an older age, at an earlier stage, with a lower grade, and had a longer overall survival.

Genealogical Index of Familiality

Table 1 shows the results of the GIF test for excess relatedness for all breast cancers and for the 5 histologic subtypes with at least 100 cases observed. Shown for each subtype is the number of cases, the average pairwise relatedness (case GIF), the mean GIF statistic for the 1000 sets of matched controls (mean control GIF), the empirical significance for the overall GIF test (GIF *P* value), the average pairwise relatedness ignoring first-degree and second-degree relationships (case dGIF), the mean dGIF statistic for the 1000 sets of matched controls (mean control dGIF), and the empirical significance for the distant GIF test (dGIF *P* value).

Statistically significant excess relatedness was observed for all breast cancer cases ($P < .001$) and for the lobular ($P = .007$) and mucinous ($P = .003$) subtypes (Table 1). When close relationships were ignored,

TABLE 1. Genealogical Index of Familiality (GIF) Relatedness Analysis[a]

Subtype	No.	GIF			dGIF		
		Case	Mean Control	*P*	Case	Mean Control	*P*
All breast cancers	23,629	2.93	2.72	<.001	2.37	2.38	.676
Inflammatory	178	3.54	2.68	.147	3.54	2.36	.024
Lobular	1688	3.07	2.72	.007	2.36	2.40	.619
Mucinous	542	3.65	2.71	.003	2.88	2.34	.011
Tubular	134	2.52	2.86	.529	2.52	2.47	.426
Medullary	341	2.12	2.69	.897	2.12	2.33	.723

Abbreviation: dGIF, distant genealogical index of familiality.
[a]The number of all breast cancer cases and of each breast cancer subtype included in the analysis, the GIF for cases and controls with *P* values for the comparison, and the dGIF for cases and controls with *P* values for the comparison are provided.

TABLE 2. Estimated Relative Risks (RRs) for Breast Cancer of the Same Histologic Subgroup and for Breast Cancer of Any Histology in First-Degree Relatives (FDRs) of Proband Breast Cancer Cases by Histologic Subgroup

Subgroup	No. of FDRs	Same Histology Subgroup				Any Breast Cancer Histology			
		No. Obs	No. Exp	*P*	RR (95% CI)	No. Obs	No. Exp	*P*	RR (95% CI)
All breast cancers	190,576	—	—	—	—	5846	3308.2	<.001[a]	1.77 (1.72-1.81)
Angiosarcoma	96	0	0.0			6	2.3	.03[a]	2.59 (1.13-5.63)
Apocrine	436	0	0.02			20	7.84	.0002[a]	2.55 (1.56, 3.94)
Inflammatory	1493	0	0.2			42	26.4	.0046[a]	1.59 (1.14-2.15)
Lobular	14,097	48	18.2	<.001[a]	2.64 (1.95-3.50)	551	248.4	<.001[a]	2.22 (2.04-2.41)
Mucinous	5056	6	2.2	.025[a]	2.73 (1.19-5.95)	168	90.4	<.001[a]	1.86 (1.59-2.16)
Phyllodes	251	0	0.01			5	3.97	.61	1.26 (0.41-2.94)
Tubular	1264	0	0.15			47	23.6	1.8e-5[a]	2.00 (1.47-2.65)
Medullary	3058	0	0.79			102	54.1	<.001[a]	1.88 (1.54-2.29)
Metaplastic	313	0	0.01			9	5.43	.099	1.66 (0.76-3.15)

Abbreviations: Exp, expected; Obs, observed.
[a]These *P* values indicate significance.

the dGIF test identified significant excess distant relatedness for the mucinous subtype ($P = .011$) as well as for inflammatory breast cancers ($P = .024$), but not for all breast cancers considered together or for the other tumor subtypes.

Relative Risks

RRs were estimated for (FDRs) (Table 2), second-degree relatives (SDRs) (Table 3), and third-degree relatives (TDRs) (Table 4) for all breast cancers and for each of the histologic subgroups. Each table shows the subgroup, the number of relatives (FDRs, SDRs, and TDRs, respectively), the observed number of breast cancer cases of the same histologic subgroup (Obs), the expected number of breast cancer cases of the same histologic subgroup (Exp), the significance of the test of RR = 1.0 (*P* value), and the estimated RR and 95% CI; the observed and expected numbers of cases and the significance and the RR with CI for breast cancer of any histologic type also are shown for each histologic subgroup.

FDRs with the same histologic type as the proband were observed only for the 2 largest sets of probands—lobular and mucinous histologies—and a significantly increased RR was observed for each (Table 2). The RR for breast cancer of any histology in FDRs was significantly increased for patients with all examined histologic subtypes and was increased, but not significantly, for 2 of the smallest subgroups—phyllodes and metaplastic tumors.

Similarly, for SDRs, affected relatives were only observed for the 2 largest subgroups—lobular and mucinous; significantly increased risk in SDRs was only observed for the lobular subgroup (RR, 1.56; $P = .003$) (Table 3). The RR for breast cancer of any histology in SDRs was significantly increased for patients with inflammatory (RR, 1.32; 95% CI, 1.02-1.68; $P = .03$), lobular (RR, 1.36; 95% CI, 1.25-1.47; $P < .001$), and mucinous (RR, 1.27; 95% CI, 1.12-1.44; $P = .00021$) subtypes.

For TDRs, a significantly elevated risk for breast cancer of the same tumor subtype was observed for

TABLE 3. Estimated Relative Risks (RRs) for Breast Cancer of the Same Histologic Subgroup and for Breast Cancer of Any Histology in Second-Degree Relatives (SDRs) of Proband Breast Cancer Cases by Histologic Subgroup

		Same Subgroup Type				Any Breast Cancer			
Subgroup	No. of SDRs	No. Obs	No. Exp	*P*	RR (95% CI)	No. Obs	No. Exp	*P*	RR (95% CI)
All breast cancers	559,835					7395	5916	<.001[a]	1.25 (1.22-1.28)
Angiosarcoma	294	0	0.0			—[b]	—[b]	.56	1.29 (0.35-3.32)
Apocrine	1518	0	0.03			15	17.4	.72	0.87 (0.48-1.43)
Inflammatory	4983	0	0.33			66	49.9	.03[a]	1.32 (1.02-1.68)
Lobular	46,875	49	31.3	.003[a]	1.56 (1.16-2.07)	642	473.3	<.001[a]	1.36 (1.25-1.47)
Mucinous	17,889	6	4.6	.47	1.32 (0.48-2.86)	251	197.2	2.1e-4[a]	1.27 (1.12-1.44)
Phyllodes	913	0	0.01			8	10.3	.64	0.77 (0.33-1.53)
Tubular	4252	0	0.21			52	42.9	.17	1.21 (0.91-1.59)
Medullary	10,316	0	1.49			115	106.3	.21	1.08 (0.89-1.30)
Metaplastic	981	0	0.01			13	10.4	.25	1.24 (0.66-2.13)

Abbreviations: Exp, expected; Obs, observed.
[a]These *P* values indicate significance.
[b]Observed counts <5 are censored.

TABLE 4. Estimated Relative Risks (RRs) for Breast Cancer of the Same Histologic Subgroup and for Breast Cancer of Any Histology in Third-Degree Relatives (TDRs) of Proband Breast Cancer Cases by Histologic Subgroup

		Same Subgroup Type				Any Breast Cancer			
Subgroup	No. of TDRs	No. Obs	No. Exp	*P*	RR (95% CI)	No. Obs	No. Exp	*P*	RR (95% CI)
All breast cancers	1,140,944					12,138	11,260	<.001[a]	1.08 (1.06-1.10)
Angiosarcoma	872	0	0.0			6	9.3	.41	0.65 (0.24-1.41)
Apocrine	4188	0	0.10			64	46.9	.02[a]	1.36 (1.05-1.74)
Inflammatory	13,624	—[b]	—[b]	.27	2.00 (0.24-7.21)	139	143.3	.77	0.97 (0.82-1.15)
Lobular	123,396	118	87.3	.001[a]	1.35 (1.12-1.62)	1527	1267	<.001[a]	1.21 (1.15-1.27)
Mucinous	51,280	23	12.5	.007[a]	1.84 (1.16-2.76)	560	512.9	.04[a]	1.09 (1.02-1.19)
Phyllodes	2696	0	0.03			24	27.9	.57	0.86 (0.55-1.28)
Tubular	11,228	—[b]	—[b]	.17	2.73 (0.33-9.85)	129	114.2	.17	1.13 (0.94-1.34)
Medullary	28,053	—[b]	—[b]	.23	0.49 (0.06-1.77)	319	278.4	.02[a]	1.15 (1.02-1.28)
Metaplastic	2527	0	0.05			26	25.6	.49	1.02 (0.66-1.49)

Abbreviations: Exp, expected; Obs, observed.
[a]These *P* values indicate significance.
[b]Observed counts <5 are censored.

lobular (RR, 1.35; 95% CI, 1.12-1.62; $P = .001$) and mucinous (RR, 1.84; 95% CI, 1.16-2.76; $P = .007$) cancers (Table 4). The RR for breast cancer of any histology in TDRs was significantly elevated for patients with lobular (RR, 1.21; 95% CI, 1.15-1.27; $P < .001$), mucinous (RR, 1.09; 95% CI, 1.02-1.19; $P = .04$), medullary (RR, 1.15; 95% CI, 1.02-1.28; $P = .02$), and apocrine (RR, 1.36; 95% CI, 1.05-1.74; $P = .02$) subtypes.

High-Risk Pedigrees

An analysis of all relationships among breast cancer cases for the inflammatory and mucinous subtypes (the 2 subtypes with significant excess relatedness observed) identified 48 high-risk inflammatory breast cancer pedigrees, including between 2 and 4 inflammatory breast cancer cases, and 110 high-risk mucinous breast cancer pedigrees, including between 2 and 13 mucinous breast cancer cases. Figure 1 shows an example high-risk mucinous breast cancer pedigree. The top generation shows a male with 2 spouses. Of the total of over 10,630 descendants of this male founder in the UPDB, 5 have been diagnosed with mucinous breast cancer (0.8 expected; $P = .0018$). Overall, there are 65 breast cancer cases among the descendants, with 43.9 expected ($P = .0017$); the other breast cancers observed include 2 inflammatory breast cancers, 2 lobular breast cancers, and 1 medullary breast cancer. An analysis of all relationships among lobular breast cancer cases (the subtype with significant excess risks for FDRs, SDRs, and TDRs) identified 273 high-risk lobular breast cancer pedigrees, including between 2 and 14 related lobular breast cancer cases.

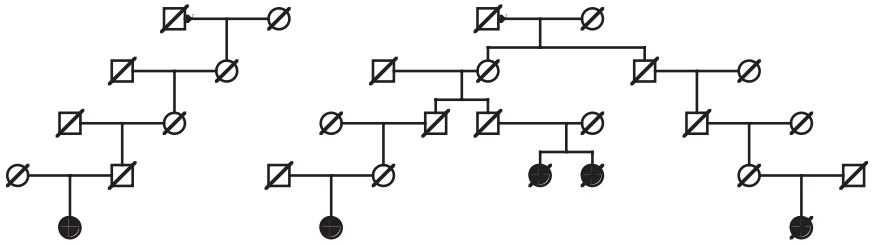

Figure 1. This is an example of a high-risk mucinous breast cancer pedigree from the Utah Population Database. Females are designated by circles, and males are designated by squares. Individuals with mucinous breast cancer are designated by solid symbols. Deceased individuals are shown with a hash mark through the symbol.

DISCUSSION

By using a unique population-based resource linking decades of statewide cancer data to over 150 years of genealogy data, the hypothesis of histology-specific clustering of breast cancer cases has been investigated. Previously published findings from this resource provided evidence for clustering of lobular breast cancers, and these results have been confirmed here.[16] In addition, evidence was observed of significant familial clustering for mucinous and inflammatory breast carcinomas. No significant evidence for increased relatedness or risk for the same histologic subtype of breast cancer was observed for the other breast cancer histologies considered; however, small sample sizes for many of these uncommon subgroups limited power to identify clustering. Most histological subtypes were associated with an increased RR for breast cancer of any histologic type in FDRs, SDRs, and TDRs, which is unsurprising because it is well recognized that a diagnosis of breast cancer is associated with an increased risk to relatives.

The GIF analysis for excess familiality was limited to the larger histologic subgroups and identified significant excess relatedness for distant relationships for both inflammatory and mucinous subgroups, providing strong evidence for a heritable, rather than just a shared-environment, contribution for these specific types of breast cancer. The RR analysis considered even the smaller histologic subgroups, but limited numbers of affected relatives with breast cancer of the same histology were observed. Nevertheless, a significantly increased risk for lobular breast cancers in the FDRs, SDRs, and TDRs of lobular cancer cases was observed, again providing strong evidence for a heritable contribution to predisposition. Elevated risk for mucinous breast cancer was also observed in FDRs, SDRs, and TDRs, and the elevation was statistically significant in the FDRs and TDRs. These findings suggest a genetic contribution to risk, although an additional environmental contribution to risk cannot be excluded.

In a nested case-control study from the Breast Cancer Surveillance Consortium that included 617 inflammatory breast cancer cases, a first-degree family history of breast cancer was associated with an increased risk of inflammatory breast cancer.[9] The multivariable rate ratio was 1.52 (95% CI, 1.15-2.01). In a second study, patients with inflammatory breast cancer had a higher likelihood of a family history of breast cancer compared with unaffected controls but a lower likelihood compared with patients who had noninflammatory breast cancer.[14] Interestingly, in the latter cohort, they identified several patients who had inflammatory breast cancer with multiple first-degree and second-degree family members who had noninflammatory breast cancer. Our findings both confirm and extend this finding, as we were able to examine relationships out to the third-degree (first cousins) and identified a significant excess of distant relatedness. The RR for TDRs of inflammatory breast cancer was elevated, but not significantly (RR, 2.00; 95% CI, 0.24-7.21); sample sizes are small, but this indicates that the evidence for the significant excess relatedness observed in the dGIF test came from an excess of even more distant relationships.

It was somewhat surprising that we did not identify increased relatedness among patients with medullary carcinoma given its known association with tumors with pathogenic variants in *BRCA1*. However, according to the literature, only 10% to 15% of *BRCA1*-mutated tumors have pure medullary histology.[13] In addition, only about 11% of medullary tumors, regardless of family history, had identified pathogenic variants in *BRCA1*.[23] Therefore, our results support prior findings that only a minority of medullary breast cancer cases are likely because of an inherited predisposition.

Strengths of this analysis are the large number of primary cancers in the database, histopathological

confirmation of all cases in the Utah Cancer Registry, and comprehensive genealogy information, including large numbers of FDRs, SDRs, and TDRs with known cancer status. The UPDB includes genealogy from the mid-1800s and statewide cancer data from 1966; nevertheless, some breast cancer histologic subgroups were rarely observed, and significant conclusions for some hypotheses will require larger data sets. The total sample size for primary inflammatory breast cancers was limited, and no FDRs or SDRs diagnosed with inflammatory breast cancer were observed. However, it is possible that inflammatory breast cancer cases may be incompletely represented in the database because it is a clinical, rather than histologic, diagnosis, and cases without evidence of dermal lymphatic invasion in a pathology specimen may not have been identified.

Even among the histologic subgroups with small sample sizes, some pedigrees, including related breast cancer cases with the same histology, were identified to have a significant excess of breast cancer. These rare pedigrees may provide a powerful resource to identify new breast cancer predisposition genes or to enhance our understanding of known predisposition genes.

The analysis has some limitations. Data for some individuals could have been censored because of a diagnosis of cancer outside Utah or before 1966. Pathology reports and slides were not reviewed, and some records date back decades. In addition, changes in histologic classification have occurred over time, and these updates or subclassifications may not be reflected in the available patient-level data. Although it would have been interesting to examine associations between familiality and both clinicopathologic characteristics and disease outcomes, especially for the inflammatory breast cancer cohort, unfortunately, neither receptor status nor treatment information is available at this time.

Censoring also occurred for individuals who did not have genealogy data in the UPDB or who did not appropriately link to their genealogy data. Approximately 60% of Utah Cancer Registry records link to an individual with Utah genealogy data; females have lower record-linking rates than males because of name changes. In addition, genealogy does not always represent biological relationships. These censorship issues can be assumed to occur uniformly across both cases and controls in the UPDB and should not bias analyses, although they can lower power.

The Utah population represented in the UPDB largely consists of individuals of Northern European ancestry. The population has been shown to be genetically identical to other Northern European populations. The original Utah pioneers, who began arriving in Utah in 1847, were largely unrelated; the Utah population continues to have low or normal inbreeding compared with the United States.[24] In addition, the Utah population has a high proportion of women with higher average numbers of pregnancies, younger age at first childbirth, lower alcohol and tobacco use, and lower rates of postmenopausal obesity, all of which could impact the rates of breast cancer incidence. Therefore, the results of this study are likely applicable to populations of females similar to the Utah population but should not be extrapolated to other populations without validation.

In summary, using genealogy data from a large population-based database, this study provides additional evidence supporting a genetic predisposition to inflammatory breast cancer as well as lobular and mucinous breast cancer histologies. Although estimated RRs are modest, the important point is that breast cancer cases with specific histologies appear to cluster more in pedigrees than expected, and these homogeneous pedigrees may be informative for identification of the predisposition genes responsible. Subsequent identification of inherited genetic variants should be performed to identify potential etiologies of specific breast cancer subtypes.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

N. Lynn Henry: Conceptualization, writing–original draft, and writing–review and editing. **Lisa Cannon-Albright:** Conceptualization, formal analysis, visualization, writing–original draft, and writing–review and editing.

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