Population-based Relative Risks for Specific Family History Constellations of Breast Cancer – Towards Individualized Risk Estimation

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Abstract

Background: Estimated Relative Risks (RR) for breast cancer in relatives of breast cancer cases are typically not based on precise family history. Using a large resource linking deep genealogy with decades of cancer data, RRs were estimated for breast cancer based on specific and extended family history.

Methods: RRs for breast cancer were estimated in females with breast cancer family histories that included number of first- (FDR), second-(SDR), and third-degree relatives (TDR), and age at earliest diagnosis in a relative. Relative risks were based on breast cancer rates estimated from 265,677 females in the resource with no FDR, SDR or TDR family history of breast cancer.

Results: RRs for first-degree relatives of BC cases ranged from 2.22 (=1 FDR affected, CI: 2.14, 2.29) to 7.91 (=4 FDRs affected, CI: 5.26, 11.43). RRs for second degree relatives of probands with 0 affected FDRs ranged from 1.49 (≥1 SDR affected, CI: 1.44, 1.54) to 2.60 (≥4 SDRs affected, CI: 1.91, 3.46). RRs for third-degree relatives with 0 affected FDRs and 0 affected SDRs ranged from 1.22 (≥1 TDR affected, CI: 1.18, 1.26) to 1.93 (≥5 TDRs affected, CI: 1.62, 2.28). Increased RRs were observed for decreasing earliest age at diagnosis in a relative.

Conclusions: The majority of women have a positive family history for breast cancer; any number of affected relatives significantly increases risk for breast cancer. Risk prediction derived from specific and extended family history allows identification of women at highest risk and could be a powerful, efficient tool to individualize cancer prevention and screening.

Introduction

Next to sex and age, the strongest risk factor for breast cancer is family history. Risk conferred by family history generally exceeds that associated with reproductive factors, use of post-menopausal hormone replacement therapy, and obesity, but is highly variable and therefore difficult to quantify for any given woman. The most commonly used risk estimation models consider only first degree relative (FDR) family history. Current National Comprehensive Cancer Network guidelines recommend including first, second and third-degree relatives in determining which women are candidates for genetic risk evaluation, but to date, the contribution of affected second and third-degree relatives to risk has not been well defined. We report here estimated risks for breast cancer based on the complete constellation of a woman's family history for breast cancer from first to third-degree relatives. These risk estimates will contribute to better informed and individually tailored decisions about both screening (including age to initiate screening and additional screening modalities such as MRI) and chemoprevention for breast cancer.

Materials and Methods

Utah Population Database (UPDB) and Utah Cancer Registry (UCR)

This study utilized a large and comprehensive genealogical and cancer phenotype resource, the UPDB. The UPDB is a unique resource that has been used to understand familial clustering and genetic predisposition to cancer in Utah for over 45 years.[1] Genealogies of original Utah settlers, created from complete genealogy data computerized in the 1970s, and updated since using Utah Vital Statistics data (e.g. mother, father, and child from a birth certificate) have been linked to the Utah Cancer Registry (UCR), which established statewide required reporting of primary cancers diagnosed or treated in Utah in 1966, and became one of the original NCI Surveillance, Epidemiology, and End Results (SEER) cancer registries in 1973. Today there are over 7 million unique individuals in the UPDB; 2.8 million have at least 3 generations of genealogy, and 1.3 million individuals have at least 12 of their 14 immediate ancestors (both parents, all 4 grandparents, and at least 6 of their 8 great grandparents). This subset of 1.3 individuals with deep ancestral genealogical data was used for this analysis. Among these 1.3 million individuals there are 640,366 women, of whom 45,979 have linked UCR records.

Breast Cancer Family History Constellations

Family history constellation is defined as the complete family history for breast cancer, including first- to third-degree relatives, for both paternal and maternal relatives. The relative risk (RR) for breast cancer for women with various constellations was estimated for the 640,366 women in the UPDB with appropriate genealogy data. To estimate RR for a specific constellation, all women in the UPDB with the specific family history constellation (e.g. 3 FDRs with breast cancer) were identified. These women were termed “probands”, and their breast cancer status was ignored for proband selection. The RR for breast cancer in these probands was estimated as the ratio of the number of observed, to the number of expected, breast cancer cases among the probands. A variety of combinations of first-, second-, and third-degree relatives were considered; age at earliest diagnosis was integrated, and both maternal and paternal family history was considered. Constellations where some relationships were ignored or with a lower bound to the number of affected relatives (e.g. $\geq$3 FDRs) were included to extend utility to women with less precise family history knowledge.

Estimation of rates of breast cancer

To estimate the rate of breast cancer in the UPDB population, women were assigned to cohorts based on 5-year birth year groups and birth state (Utah or other). Cohort-specific rates of breast cancer were calculated from the 265,677 women without a family history of breast cancer (no first-, second-, or third-degree relatives affected); rates were estimated as the number of breast cancer cases observed in each cohort divided by the total number of women in the cohort.

Estimation of Relative Risk (RR)

RRs were estimated for multiple different family history constellations of breast cancer. For each constellation pattern, all women with the specific family history constellation (probands) were identified, and the observed number of probands with breast cancer was compared to the expected number. For each constellation, the observed number of probands with breast cancer was counted by cohort. To determine the expected number of cases (E) in the set of probands for a specific constellation, cohort-specific breast cancer rates (as described above) were applied to the set of probands. The expected number of breast cancer cases was estimated by applying the cohort-specific breast cancer rates to the number of probands in each cohort, and then summing over all cohorts. The constellation relative risk is calculated as the ratio of the observed to the expected number of probands with breast cancer for the specified constellation pattern. The distribution of the number of observed breast cancer cases is assumed to be Poisson with a mean equal to E; 95% confidence intervals for RR are calculated as presented in Agresti.[2]

Results

Breast Cancer Family History in the UPDB

A summary of personal and family history of breast cancer for females in the UPDB is presented in Table 1. The table presents women in three groups: all females, females with a family history of breast cancer (FH+), and females without a family history of breast cancer (FH-);. Family history of breast cancer was defined as having at least one first-, second-, or third-degree female relative with breast cancer. The number of women with a personal history of breast cancer is shown for each group. These data demonstrate that 59% of women in the Utah population have a family history of breast cancer, and that overall, with no consideration of specific family history, a woman with any family history of breast cancer has more than double the risk of having breast cancer than a woman with no family history of breast cancer (3.1% compared to 1.4%). Further categorizations based on family history constellation allow further discrimination of those at highest risk and are examined in more detail below.

Estimated RRs based on first-degree family history

Table 2a shows the estimated RRs based on first degree family history. First-degree relatives include parents, offspring, and siblings. The estimated RRs are based only on number of first-degree relatives (FDR) affected, with second-degree (SDR) and third-degree relatives (TDR) ignored. Significantly elevated risk was observed for women with 0 FDRs (RR = 1.19), indicating the effect from affected SDRs and TDRs even in the absence of any FDR family history. The RR increases from RR = 2.22 for exactly 1 affected FDR to RR = 7.91 for exactly 4 affected FDRs.

Estimated RRs based on second-degree family history

Estimated RR based on affected SDRs are presented in Table 2b. Second-degree relatives include half-siblings, grandmothers, granddaughters, aunts, and nieces. For this set of constellations the probands have 0 affected FDRs and TDRs were ignored.

Risks for up to at least 5 SDRs affected, with no FDRs affected, are significantly increased. The RR for at least 3 affected SDRs but 0 FDRs affected (RR = 2.23) is similar to the RR for exactly 1 FDR affected (RR=2.22, Table 2a), indicating the importance of consideration of SDR family history even in the absence of an affected FDR.

Estimated RRs based on combined first- and second-degree family history

The contributions to RR based on SDR family history in the context of 1 affected FDR are summarized in Table 2c. All estimated RRs were significantly elevated. These results show that SDR family history significantly affects risk, even in the presence of FDR family history. The RR for exactly 1 FDR and at least 2 SDRs (RR = 3.39) is equivalent to the RR for exactly 2 FDRs when other relationships are ignored (RR = 3.39; Table 2a).

Estimated RRs based on third-degree family history

Table 2d presents RR estimates based on TDR family history with no affected FDRs or SDRs. Third-degree relatives include cousins, great aunts, great grandmothers, great granddaughters and grandnieces. Since the breast cancer rates were estimated from the 265,677 women with 0 FDRs, 0 SDRs, and 0 TDRs, the RR for that specific constellation = 1.00, as shown. Even in the absence of affected FDRs and SDRs, a positive TDR family history significantly increases risk (RR = 1.22 for $\geq$1 TDR).

Estimated RRs Considering Earliest Age at Diagnosis of Affected Relative

Table 3 summarizes the RR estimates for constellations that consider the earliest age at diagnosis of breast cancer in the presence of at least 1 affected FDR and ignoring SDRs and TDRs. The estimated RR for at least 1 affected FDR diagnosed at any age is 2.39

(Table 2a). In Table 3 the RRs range from 2.01 for those whose earliest affected FDR was after age 80 years, to 3.10 for those whose earliest affected FDR was before age 50 years. Even when diagnosed at a late age, a family history of even one FDR with breast cancer still doubles risk for breast cancer (RR=2.01).

Estimated RRs for other Family History Constellations

Table 4a presents the estimated RRs for a variety of specific FDR relationships and combinations of specific FDRs and SDRs. The estimated RR for at least one affected daughter (RR = 3.50) is significantly higher than the RR for either an affected mother (RR=2.30) or sister (RR=2.34). Because risk was estimated for probands of all ages for each constellation, the average proband age is likely higher for constellations including affected descendants, resulting in higher estimated risk.

Table 4b shows the estimated RRs for combined maternal and paternal family history. The examples shown are all the equivalent of at least 2 affected SDRs, ignoring FDRs and TDRs (data not shown; n = 30,674 probands, RR = 2.16; 95% CI (2.04, 2.28). All of the confidence intervals for the 4 constellations considered include 2.16, suggesting there is no synergistic effect for combined paternal and maternal contribution to risk.

Table 4c shows the estimated RRs for equivalent paternal and maternal constellations. The 3 constellations considered show overlapping CIs for RRs for maternal compared to paternal family history, suggesting no difference in maternal, versus paternal, family history contribution to breast cancer risk. This result supports the importance of considering family history in both lineages of equal significance when estimating risk for an individual.

Discussion

Much of the recent research in familial breast cancer has focused on high and moderate-risk genes. Mutations in these genes confer a high RR but are infrequent or rare in the population. There is also intense interest in both the scientific and lay communities in modifiable risk factors such as obesity, postmenopausal hormone replacement therapy, breast-feeding, and alcohol ingestion. Although important on a population level, these factors (along with ages at menarche, menopause, and childbearing) generally play a modest role on an individual level, with RRs estimated in the range of 1.2 to 1.5. In this population-based survey representing over 600,000 women, 59% of women had a family history of breast cancer (at least one affected FDR, SDR, or TDR). Even a very limited breast cancer family history was shown to significantly affect risk at a level equivalent to hormonal and reproductive factors, for example, RR = 1.22 (CI: 1.18, 1.26) for even a single affected TDR. Four and a half percent of the studied female population of Utah was estimated to have a RR > 2.0 based only on their family history. Many of these women would be candidates for enhanced screening and/or chemoprevention based on current recommendations. Individualized risk prediction from specific family history, as presented, allows identification of women at highest risk for breast cancer, and would be powerful and efficient for cancer prevention and control if implemented at a population level.

There are a number of commonly used breast cancer risk assessment tools.[3] All incorporate some element of family history, though none incorporate TDRs, and only one considers SDRs. The family history-based RR estimates presented here show that including breast cancer diagnoses for more distant relatives can be essential for precise individualized risk prediction, and suggest that an adequate family history should be

obtained in all women as they near the recommended screening age for breast cancer (40 years or 10 years prior to age at diagnosis of their youngest affected FDR).
The data presented here additionally demonstrate the importance of developing better population-based strategies to collect family history. Future research should also address ways of communicating risk to large populations of women outside of specialized genetics settings. Clinical decision support tools that can generate individualized recommendations about screening and chemoprevention and are tailored to a patient's specific level of risk may assist in various clinical settings[4] and might prove useful in design and recruitment of more powerful clinical/prevention trials.

Because this study was based on data from a homogeneous population representing a single geographic region, it is important to consider how generalizable the findings are. The Utah population has been shown to be genetically identical to other populations of Northern European descent, [5] but does differ from the US population in some ways. First, breast cancer incidence and mortality are lower in Utah than nationally.[6] Factors contributing to the lower incidence may be younger age at first childbirth, higher average number of pregnancies, lower alcohol ingestion and lower rates of post-menopausal obesity.

There have been few other analyses of complete constellations of family history for breast cancer and there are few available databases that would allow these analyses; however, the RRs estimated for the Utah population are in good general agreement with those reported by others. The Collaborative Group on Hormonal Factors in Breast Cancer[7] published a survey of over 58,000 breast cancer cases in 52 studies and characterized risk by particular familial patterns. Although limited to FDRs, some comparisons to Utah constellation RRs are possible. The Collaborative Group study reported RRs of 1.80, 2.93 and 3.90, respectively for FDR = 1, FDR = 2, and FDR$\geq$ 3; these RR estimates from the Utah study (when SDR and TDR family history was ignored) were 2.22, 3.39, and 5.11, respectively. The Collaborative Group study's comparison group was women with FDR = 0, while the Utah comparison group was women with FDR = 0, SDR = 0 and TDR = 0; the Collaborative Group results are therefore conservative with respect to consideration of complete family history. Similar to the Collaborative Group results, the Utah analysis showed that the RR for an affected mother (RR = 2.30) did not differ from the RR for an affected sister (RR = 2.34). Both studies observed similar, moderate, effect of age at youngest FDR diagnosis. Hemminiki and Vaittinen[8] used the Family-Cancer Database from Sweden to estimate familial RRs defined through the mother or daughter, as well as modification of risk by age, and estimated RR = 1.9 for breast cancer in the daughter of an affected mother, and RR = 1.85 – 1.97 for the mother of one, or 2 affected daughter(s), respectively.

The constellation RR approach has limitations. Some data in the UPDB is censored: genealogy data may be missing or incomplete; some individual or cancer data may not have correctly linked to genealogy data; non-biological familial relationships may be included; and cancers diagnosed before 1966 or outside the state of Utah are not included. Decades of studies estimating RRs for cancer using the UPDB have confirmed that Utah risk estimates based on family history are validated in other populations. Some family history constellation RR estimates may have been affected by small sample sizes and this is demonstrated in wider confidence intervals. Finally, these RRs were based only on family history; many factors were not included in risk estimation, most notably proband's age and other known risk factors. Nevertheless, this is the largest population-based data set to be analyzed for breast cancer RRs and comparisons to other similar resources show equivalent results for constellations considered. These results greatly expand published risk predictions for family history.

This study provides strong evidence for significantly elevated risk for breast cancer even in the case of the least significant family history considered (RR = 1.22 for ≥1 affected TDR - e.g. ≥1 first cousin – Table 2d).

This study presents individualized risk predictions that incorporate family history for both close and distant maternal and paternal relatives. In order to provide clinicians and patients with a quick guide to identify women at highest risk for breast cancer, Table 5 summarizes family history constellations with risks > 2.0, > 3.0, and > 4.0, which were observed for 4.5%, 0.4% and 0.04% of females in this population, respectively. Individual physicians and their patients might consider these risk classification groups to help determine the best course of screening and prevention for patients.

Because of the extent of genealogy data available through the UPDB, rates for breast cancer in the absence of family history could be estimated in a set of over 265,000 women with no first, second or third-degree relatives with breast cancer. As a result, the estimated RRs represent the increased risk to a proband that is due to family history. The results are likely applicable to populations of women similar to the Utah population, that is, women largely from Northern European populations, but should not be extrapolated to other populations without validation.

Future extensions to this simple consideration of various family history constellations are underway and will include additional risk factors for breast cancer in the proband and her relatives, as well as genotypes for markers recognized to be associated with increased risk for breast cancer.

This study contributes to the growing field of risk prediction and individualized risk management for cancer. Constellation risks based on the UPDB and using the methods presented here have been presented for colorectal cancer[9], prostate cancer[10] and lethal prostate cancer[11].

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Table 1. Characterization of personal history and family history of breast cancer (BC) in UPDB females.

Population Description	**# in UPDB (%)**	**# with BC (%)**
All females	640,366 (100)	15,316 (2.4)
FHx+	374,689 (59)	11,463 (3.1)
FHx-	265,677 (41)	3,853 (1.4)

Table 2. Estimated RRs for breast cancer based on a proband's first-, second, and third-degree family history.

2a. Number of affected FDRs, ignoring SDRs and TDRs.

Nr. FDRs Aff	**n**	**Obs**	**Exp**	**RR**	**2T p-value**	**2T CI (L)**	**2T CI (U)**
=0	585,393	11,454	9602.8	1.19	≤ 0.0001	1.17	1.21
=1	50,718	3,134	1414.8	2.22	≤ 0.0001	2.14	2.29
≥1	56,813	3,862	1614.6	2.39	≤ 0.0001	2.32	2.47
=2	5,371	592	174.8	3.39	≤ 0.0001	3.12	3.67
≥2	6,095	728	199.9	3.64	≤ 0.0001	3.38	3.92
=3	609	107	21.0	5.11	≤ 0.0001	4.18	6.17
≥3	724	136	25.1	5.43	≤ 0.0001	4.55	6.42
=4	100	28	3.5	7.91	≤ 0.0001	5.26	11.43
≥4	115	29	4.1	7.07	≤ 0.0001	4.74	10.16

Nr. FDRs Aff: number of FDRs affected with breast cancer
n: number of probands with each family history constellation
Obs: observed number of breast cancer cases among the probands
Exp: expected number of breast cancer cases among the probands based on UPDB age-specific rates for women with no family history of breast cancer
RR: estimated relative risk
2T p-value: 2-tailed significance for RR
2T CI L, U: lower (L) and upper (U) bounds of the 95% CI for RR

2b. Number of affected SDRs in the absence of affected FDRs and ignoring TDRs.

Nr. SDRs Aff	**n**	**Obs**	**Exp**	**RR**	**2T p-value**	**2T CI (L)**	**2T CI (U)**
0	461,029	8,180	7400.7	1.11	≤ 0.0001	1.08	1.13
>=1	122,524	3,274	2202.1	1.49	≤ 0.0001	1.44	1.54
>=2	24,480	778	448.1	1.74	≤ 0.0001	1.62	1.86
>=3	5,374	190	85.3	2.23	≤ 0.0001	1.92	2.57
>=4	1,421	47	18.1	2.60	≤ 0.0001	1.91	3.46
>=5	368	10	4.1	2.44	0.01	1.17	4.49

2c. Number of affected SDRs in the presence of at least 1 affected FDR and ignoring TDRs.

Nr. SDRs Aff	n	Obs	Exp	RR	2T p-value	2T CI (L)	2T CI (U)
>=1	17,866	1,153	469.9	2.45	≤ 0.0001	2.31	2.60
>=2	6,194	520	153.2	3.39	≤ 0.0001	3.11	3.70
>=3	1,465	112	32.0	3.51	≤ 0.0001	2.89	4.22
>=4	406	38	7.5	5.07	≤ 0.0001	3.59	6.96
>=5	121	12	1.6	7.32	≤ 0.0001	3.78	12.78

2d. Number of affected TDRs with 0 FDRs and 0 SDRs.

Nr. TDRs Aff	n	Obs	Exp	RR	2T p-value	2T CI (L)	2T CI (U)
0	265,677	3,853	3853.0	1.00	1.00	0.97	1.03
>=1	195,352	4,327	3,547.7	1.22	≤ 0.0001	1.18	1.26
>=2	69,057	1,900	1472.5	1.29	≤0.0001	1.23	1.35
>=3	24,365	804	577.3	1.39	≤ 0.0001	1.30	1.49
>=4	8,800	338	219.0	1.54	≤ 0.0001	1.38	1.72
>=5	3,092	135	70.1	1.93	≤ 0.0001	1.62	2.28

Table 3. Estimated RRs based on at least one FDR, ignoring SDRs and TDRs, considering the earliest age at diagnosis for breast cancer in an FDR.

Dx Age	n	Obs	Exp	RR	2T p-value	2T CI (L)	2T CI (U)
age < 50 years	10,952	848	273.7	3.10	≤ 0.0001	2.89	3.31
50 ≤ age < 60	12,207	823	342.5	2.40	≤ 0.0001	2.24	2.57
60 ≤ age < 70	14,701	1014	435.3	2.33	≤ 0.0001	2.19	2.48
70 ≤ age < 80	12,099	773	361.9	2.14	≤ 0.0001	1.99	2.29
age ≥ 80	6,854	404	201.2	2.01	≤ 0.0001	1.82	2.21

Table 4. Estimated RRs for specific relationships including FDRs, combined maternal and paternal relationships, and paternal compared to maternal relationships.

4a. Named relationships

Constellation Description	n	Obs	Exp	RR	2T p-value	2T CI (L)	2T CI (U)
Mother	18,631	955	416.0	2.30	≤ 0.0001	2.15	2.45
>=1 sister	31,613	2,454	1,050.4	2.34	≤ 0.0001	2.24	2.43
≥ 1 daughter	9,480	853	243.7	3.50	≤ 0.0001	3.27	3.74
Mother and ≥ 1 maternal aunt	3,268	214	80.0	2.68	≤ 0.0001	2.33	3.06
Mother and maternal grandmother	1,113	31	12.7	2.44	≤ 0.0001	1.66	3.46
=1 sister	28,769	2,124	947.0	2.24	≤ 0.0001	2.15	2.34
=2 sisters	2,563	273	92.5	2.95	≤ 0.0001	2.61	3.32
=3 sisters	246	52	9.3	5.58	≤ 0.0001	4.17	7.31
=4 sisters	32	5	1.4	3.49	0.02	1.13	8.14

4b. Combined Maternal and Paternal Relationships

Constellation Description	n	Obs	Exp	RR	2T p-value	2T CI (L)	2T CI (U)
≥ 1 paternal aunt and ≥ 1 maternal aunt	2,842	154	75.4	2.04	≤ 0.0001	1.73	2.39
paternal grandmother and ≥ 1 maternal aunt	1,223	31	11.5	2.70	≤ 0.0001	1.83	3.83
Maternal grandmother and ≥ 1 paternal aunt	1,026	22	11.9	1.86	0.01	1.16	2.81
Paternal grandmother and maternal grandmother	802	9	3.2	2.78	0.01	1.27	5.28

4c. Paternal Compared with Maternal Relationships

Constellation Description	n	Obs	Exp	RR	2T p-value	2T CI (L)	2T CI (U)
Daughter of brother	26,017	1,154	579.5	1.99	<0.0001	1.88	2.11
Daughter of sister	27,054	1,250	631.4	1.98	<0.0001	1.87	2.09
Paternal aunt	33,041	1,239	760.2	1.63	≤ 0.0001	1.54	1.72
Maternal aunt	32,991	1,346	807.5	1.67	≤ 0.0001	1.58	1.76
Paternal grandmother	16,572	129	84.4	1.53	≤ 0.0001	1.28	1.82
Maternal grandmother	16,973	153	106.1	1.44	≤0.0001	1.22	1.69

Table 5. Minimal Family History Constellations associated with RR > 2.0, > 3.0, and > 4.0 for breast cancer.

RR > 2.0 (4.5%*)	RR > 3.0 (0 .4%*)	RR > 4.0 (0.04%*)
≥ 1 FDR	≥ 2 FDR	≥ 3 FDR
≥ 3 SDR	≥ 1 FDR and ≥ 2 SDR	≥ 1 FDR and ≥ 4 SDR
both grandmothers	≥ 1 FDR dx < 50 years ≥ daughter	

* percent of all 640,366 females in UPDB in this risk class