Fifty-year Follow-Up of Cancer Incidence in a Historical Cohort of Minnesota Breast Cancer Families[1]

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Abstract

A family history of breast cancer is well established as a risk factor for the disease. Because family history is a dynamic rather than a static characteristic, longitudinal studies of entire families can be very instructive in quantifying the significance of risk classification. The Minnesota Breast Cancer Family Study is a historical cohort study of relatives of a consecutive series of 426 breast cancer cases (probands) identified between 1944 and 1952. The incidence of cancer and the measurement of risk factors in sisters, daughters, granddaughters, nieces, and marry-ins was determined through telephone interviews and mailed questionnaires. Ninety-eight percent of eligible families were recruited, and 93% of members participated. A total of 9073 at-risk women were studied: 56% were biological relatives of the case probands, whereas the others were related through marriage. Through 1996, 564 breast cancers were identified in nonprobands. Compared to the rate of breast cancer among marry-ins (188 cases), sisters and daughters of the probands were at a 1.9-fold greater age-adjusted risk (128 cases; 95% confidence interval, 1.4–2.4); granddaughters and nieces were at a 1.5-fold greater risk (248 cases, 95% confidence interval, 1.2–1.8). The breast cancer risk since 1952 was not distributed equally across families: although all biological relatives had a family history of breast cancer, 166 families (39%) experienced no additional cases. Most of the cases occurred among a subset of families: 21 families had 5 breast or ovarian cancers, 8 had 6, 2 had 7, and 4 had ≥8. There was no evidence of significantly increased risk for cancer at other sites, including the ovaries, cervix, uterus, colon, pancreas, stomach, or lymphatic tissue, although there was some evidence that stomach cancer in previous generations may help define the susceptible subset. These families contain four to five generations of validated occurrences of cancer, thus minimizing the uncertainty of genetic risk inherent in a disease with a late and variable age at onset. The patterns of breast cancer in these multigeneration families is consistent with the influence of autosomal dominant susceptibility in a subset, low penetrance genes in another, and purely environmental influences in the remainder.

Introduction

A family history of breast cancer is one of the strongest predictors of risk for the disease (1, 2). In some of the families with significant clustering of breast cancer, the underlying cause is inherited alterations in major susceptibility genes like BRCA1, BRCA2, p53, or PTEN (3–7). Genetic counseling and genetic testing are now available for high-risk women (8). Medical indication for such genetic testing is based, in part, on the strength of the family history of cancer. Moreover, even among families with hereditary patterns of cancer, not all appear to be due to the two most well-defined sources of risk, BRCA1 or BRCA2 (9). Finally, because of the unresolved risks associated with genetic testing (10, 11), many women will not want to undergo mutation testing. Therefore, there remains a significant role for a well-collected, validated family history as a part of risk assessment.

Most of the data in support of the association of family history with breast cancer risk come from case-control studies (12). Far fewer data are derived from cohort studies; fewer still are based on families. The distinction is important. Although case-control and cohort studies yield useful estimates of RR,[3] they are not able to take into consideration the fact that family history is a dynamic characteristic rather than one that does not change. Finally, cohort studies are rarely able to produce reliable estimates of cumulative (lifetime) risk, which is the measure of risk most useful in a counseling situation. Family studies can provide estimation of lifetime risk, especially if they include multiple generations and have a prospective component. For a disease with a late and variable age at onset, like breast cancer, the availability of cancer history from birth to death, through multiple generations, can more precisely quantify risk classification.

Most published estimates of cumulative risk associated with family history or genetic predisposition are based on two types of studies: segregation analysis of the patterns of breast cancer in population-based samples of families ascertained through breast cancer cases (*e.g.*, Refs. 13 and 14) or linkage

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[3] The abbreviations used are: RR, relative risk; CI, confidence interval.

analysis of multiple-case families selected on the basis of early age at onset of cancer in several generations (*e.g.*, Ref. 9). The studies by Newman (13) and Claus and colleagues (14) ascertained cases with onset of breast cancer before age 55 years and included only two generations, whereas roughly 80% of all breast cancers occur among women >50 years of age according to the Surveillance, Epidemiology, and End Results data (15). Families used for linkage analysis of complex diseases such as breast cancer are generally biased toward extreme levels of risk, and risk estimates in these types of families may not be generalizable to the entire population, particularly for later onset breast cancer.

In this report, we describe results of a historical cohort study of breast and other cancers in 426 families that were ascertained through a consecutive series of breast cancer patients (probands) at the University of Minnesota Hospital and Clinic between 1944 and 1952. At the time of the original study, occurrences of cancer were validated for parents, maternal and paternal grandparents, aunts, uncles, sisters, brothers, sons, and daughters. Between 1991 and 1996, these original families were recontacted, and their pedigrees were extended to include nieces and granddaughters. Thus, with known cancer history for five generations, we have a rare opportunity to provide a complete and less biased estimation of risks associated with a family history of cancers, including RRs and risks for cancers other than the breast.

Materials and Methods

Details of the study have been previously published (16). Briefly, in 1944, a case-control family study of breast cancer was initiated at the Dight Institute for Human Genetics at the University of Minnesota to examine the influence of hereditary susceptibility on the occurrence of breast cancer. Probands were a consecutive series of all breast cancer patients ascertained at the Tumor Clinic of the University of Minnesota Hospital between 1944 and 1952, although the original diagnosis may have occurred as early as 1931 with ascertainment during a follow-up visit. A total of 544 families were studied, representing data on 4418 family members (17). This total does not include a control group of families ascertained through the probands' husbands. The probands were selected without regard to age at onset or family history and are geographically representative of the distribution of breast cancers in the state at that time. Results of that early study provided some of the first published evidence that breast cancer clusters in families (17).

Our follow-up of this cohort of families, which focused on updating the pedigrees and collecting risk factor information, was restricted to the case families. We excluded those in which the proband was diagnosed before 1940 ($n = 40$) and families where most or all of the relatives, other than the proband, were deceased at baseline ($n = 42$). Families were considered lost to follow-up if we were unable to locate a contact willing and able to help update the family pedigree by providing addresses, phone numbers, and the vital status of other family members ($n = 30$). Families in which the contacts declined participation were considered refusals ($n = 6$). We have previously shown that there are no statistically significant differences in the cancer histories of families that were excluded, those that were lost to follow-up, and the 426 that participated (18).

The pedigree update process focused on ascertaining the vital status of relatives studied during the 1944–1952 investigation and identifying new family members as a result of birth or marriage. Relatives eligible for the pedigree extension and update were sisters, daughters, granddaughters, and nieces of the probands, as well as women who married brothers, sons, grandsons, and nephews.

After the pedigrees were updated, we attempted to interview by telephone all female relatives and marry-ins ≥18 years of age to collect cancer history and assess established risk factors for cancer. Male family members were not included. Those who agreed to the interview (94.6% of the women eligible) were subsequently mailed a body measurements questionnaire to assess present height and weight as well as approximate weight at ages 12, 18, 30, 40, and 50 years. A paper tape measure was included to measure the circumference of waist and hips. A validation study of the body measurement protocol indicates good reliability compared to measures made by trained nurses (19). Data on cancer history and a limited set of risk factors were obtained on deceased and incompetent subjects through surrogates. With rare exceptions, these were first-degree relatives or spouses.

A validation study was conducted to assess the self-reported history of breast cancer. Through pathology reports and medical records, we confirmed 136 of 138 breast cancers for which medical records could be obtained; this represents 98.6% agreement for those cancers for which records were available.

All subjects provided written informed consent, and the protocol was reviewed and approved by the University of Minnesota Institutional Review Board.

Statistical Analysis. The cohort at risk excluded all probands, their relatives with prevalent cancer at baseline in 1952 ($n = 90$), those with unknown age at interview ($n = 7$) or age at death ($n = 4$), and subjects who refused participation, were unavailable (whereabouts unknown to rest of family), or had no available surrogate. Some women were excluded for more than one reason. Thus, a total of 9073 women remained available for analysis; 56% were biological relatives of the proband and 44% had married into the families.

For descriptive analyses, we used standard contingency tables for categorical variables, and we compared means for continuous variables. We determined the association of family history of breast cancer with each type of cancer using Cox proportional hazards regression (20). For all such analyses, survival was modeled as a function of age instead of time-on-study (21). This allowed age to be rolled into the baseline hazard function, adjusting for its effects without having to specify its functional form. We also controlled for possible cohort effects by stratifying each model on birth cohort, categorized by quartiles (<1913, 1913–1925, 1926–1941, ≥1942). Because the study included related individuals, the observations were not independent. To account for this correlated structure of the data within families, we used a robust, jack-knife estimate of variance (22). For each type of cancer, we compiled a list of variables that may have confounded the relationship between cancer and family history and tested for confounding by fitting models both with and without each covariate of interest. If the inclusion of the covariate changed the hazard ratio for any of the family relationship variables by >10%, it was considered a confounder, and it was included in subsequent analyses (23). For each model, we evaluated possible departures from the proportionality assumption using the methods of Grambsch and Therneau (24). All analyses were carried out using S-Plus (Mathsoft, Inc., Seattle, WA) and Statistical Analysis Software (SAS Institute, Inc., Cary, NC).

Results

Table 1 shows the distribution of study subjects by period of enrollment. As one might expect, given the pyramidal structure

Table 1 Description of a cohort of 426 families ascertained through a breast cancer proband between 1944 and 1952

Variable	Relationship to the proband					Total
	Sister	Daughter	Granddaughter	Niece	Marry-in	
Number in 1952	1207	697	50	2605	1395	5954
Number newly identified through 1996	4	4	1582	514	3790	5894
Living relatives (by birth cohort)						
<1913	61	55	5	200	227	548
1913–1925	39	138	70	632	691	1570
1926–1941	5	142	343	602	980	2072
≥1942	0	22	1031	264	1030	2347
Mean age (years)[a]	82.2	69.2	45.5	66.2	58.6	58.6
Deceased relatives (by birth cohort)						
<1913	449	128	7	414	721	1719
1913–1925	22	48	18	242	246	576
1926–1941	0	24	34	60	95	213
≥1942	0	1	13	4	10	28
Mean age (years)[b]	80.5	70.7	50.7	68.9	72.3	72.1

[a] Age at interview.
[b] Age at death.

Table 2 Number of cancers at baseline and during follow-up in a historical cohort study (1952–1996) of 426 Minnesota breast cancer families

Relationship	Period	Cancer Site				
		Breast	Ovary	Colon	Stomach	Other
Proband	Baseline	426				
Sister	Baseline	37	6	5	8	49
	Follow-up	68	5	19	5	17
Daughter	Baseline	4	3	1	0	9
	Follow-up	60	15	15	3	16
Granddaughter	Baseline	0	0	0	0	0
	Follow-up	36	19	11	0	31
Niece	Baseline	13	4	1	0	18
	Follow-up	212	47	57	16	82
Marry-in	Baseline	9	3	2	3	14
	Follow-up	188	59	82	19	132
Total[a]	Baseline	63	16	9	11	90
	Follow-up	564	145	184	43	278
	Total	627[a]	161	193	54	368

[a] Excluding probands.

of families and the number of decades since ascertainment of the families, most of the new members of the cohort were granddaughters, nieces, and marry-ins. In addition, the proportion of family members deceased is greater for the earlier as opposed to the later generations. In total, there are nearly 12,000 female members at the generation of the proband and below. For many of the families, complete information on cancer history was also known for grandparents, aunts, and uncles of the probands. The numbers of these relatives are not depicted in the table.

The number of cancers, by site and degree of relationship to the proband, is shown in Table 2. Since the baseline period ending in 1952, 564 breast cancers were identified in the at-risk cohort. The total number of breast cancers in these families, including the probands and marry-ins, is >1000. Most of the cancers other than breast cancer have occurred since the baseline period of 1952: 89.4% of the ovarian cancers, 96.1% of the colon cancers, and 90.7% of the stomach cancers.

A detailed description of the occurrence of breast or ovarian cancer in these families is presented in Table 3. Shown are the frequency distributions of breast or ovarian cancers per family by degree of relationship and the earliest age at breast or ovarian cancer diagnosis among all relatives.

RRs of cancer were estimated by degree of relationship to the proband after accounting for age and birth cohort (Table 4). The CIs were adjusted to account for the nonindependence of the observations. Adjustment for other breast cancer risk factors did not lead to changes in the point estimates of RR by 10%. Therefore, only age-adjusted results are presented. The mean age at onset of breast cancer among nonprobands was 60 years of age, with a range of 25–92 years. Compared to the rate observed among the marry-ins, sisters and daughters (first-degree relatives) were at a 1.9-fold greater risk (95% CI: 1.4–2.4). When analyzed separately, the RR for sisters (RR = 2.0; CI, 1.4–2.7) and daughters (RR = 1.8; CI, 1.3–2.4) were virtually identical. The RRs were slightly attenuated for granddaughters and nieces (RR = 1.5; CI, 1.2–1.8). These analyses were repeated after stratifying the families on the median age at onset of breast cancer among the probands (55 years). Com-

Table 3 Distribution of breast or ovarian cancer cases per family: Minnesota Breast Cancer Family Study

Total number of cancers in family	Total number of families in category	No. of families												
		No. with affected first-degree relatives[a]					No. with affected second-degree relatives[a]					Earliest age at diagnosis of cancer[a]		
		0	1	2	3	4+	0	1	2	3	4+	<45	45–60	60+
1	166	166	0	0	0	0	166	0	0	0	0			
2	128	81	47	0	0	0	47	81	0	0	0	46	54	28
3	72	24	33	15	0	0	15	33	24	0	0	35	30	7
4	25	3	11	7	4	0	4	7	11	3	0	12	10	3
5	21	2	11	6	1	1	1	1	6	11	2	12	8	1
6	8	0	3	4	1	0	0	0	1	4	3	6	2	0
7	2	1	0	1	0	0	0	0	0	0	2	2	0	0
8	1	0	1	0	0	0	0	0	0	0	1	1	0	0
11	3	1	0	1	0	1	0	0	0	0	3	2	1	0

[a] Numbers reflect the number of families in the category.

Table 4 Risk of breast and other cancer in the Minnesota Breast Cancer Family Study: 1952–1996

Cancer	Relationship	No. of cases	Person years	Risk ratio[a]	95% CI
Breast	Marry-in	188	145,435	1.0	
	Sisters, daughters	128	41,119	1.9	1.4–2.4
	Granddaughters, nieces	248	138,266	1.5	1.2–1.8
Ovarian	Marry-in	59	146,327	1.0	
	Sisters, daughters	20	42,244	1.0	0.5–1.8
	Granddaughters, nieces	66	140,158	1.2	0.9–1.7
Uterine	Marry-in	119	144,853	1.0	
	Sisters, daughters	25	41,870	0.6	0.4–1.0
	Granddaughters, nieces	103	138,894	0.9	0.7–1.2
Colon	Marry-in	82	146,557	1.0	
	Sisters, daughters	34	42,249	0.8	0.5–1.2
	Granddaughters, nieces	68	140,253	1.0	0.7–1.4
Pancreatic	Marry-in	16	147,091	1.0	
	Sisters, daughters	9	42,454	1.0	0.4–2.4
	Granddaughters, nieces	10	140,787	0.8	0.3–1.9
Stomach	Marry-in	19	147,007	1.0	
	Sisters, daughters	8	42,453	0.7	0.3–1.8
	Granddaughters, nieces	16	140,759	1.1	0.5–2.2
Lymphatic	Marry-in	14	146,959	1.0	
	Sisters, daughters	6	42,420	1.1	0.4–3.4
	Granddaughters, nieces	13	140,749	1.0	0.5–2.2

[a] Cox proportional hazards analysis, accounting for age, birth cohort, and possible clustering within families.

pared to the rate observed among the marry-ins, sisters and daughters of probands with onset <55 years were at a 2.4-fold greater risk (95% CI, 1.8–3.2). The corresponding risk to relatives of probands with onset ≥55 years was 1.2 (95% CI, 0.9–1.6). Similar patterns of higher risk among relatives of probands with earlier age at onset were observed for granddaughters and nieces (RR = 1.8; 95% CI, 1.3–2.4 *versus* RR = 1.3; 95% CI, 1.1–1.7), respectively.

Fig. 1 provides the cumulative risks of breast cancer by degree of relationship to the closest affected relative. The lifetime risk to age 80 years was roughly 15% among women with a first-degree relative affected (about 1 in 6–7). For the marry-in group, who are expected to represent the general population, the comparable risk estimate is about 7.5% (1 in 13). RRs for other cancers were not significantly elevated. Uterine cancer was the only other site that showed any association with degree of relationship ($P = .06$), with first-degree relatives reporting significantly fewer uterine cancers than the marry-ins (RR = 0.6; 95% CI, 0.4–1.0). This lower risk was not observed among second-degree relatives (RR = 0.9).

The risks of breast cancer were not distributed evenly across these families. Although all biological members of these families had, by definition, a family history of the disease, 166 of the families (39%) experienced no additional cases of breast (or ovarian) cancer through the 50-year follow-up period. We therefore performed additional analyses that considered the occurrence of breast or ovarian cancer at baseline among nonproband relatives as a stratification variable. For this analysis, we considered the occurrence of breast or ovarian cancer among the probands' mother, grandparents, and maternal and paternal aunts. There were 32 probands who had a known family history of breast or ovarian cancer at baseline in 1952. The mean age at onset of breast cancer among these 32 probands was 52.7 years, which was not statistically significantly earlier than the mean age at onset (56.0 years) in the remaining families ($P = 0.16$; data not shown). These 32 families demonstrated higher risks of breast cancer than the families without such cancer family histories (Table 5). Sisters and daughters were at a 2.3-fold greater risk, and granddaughters and nieces were at a 2.8-fold greater risk.

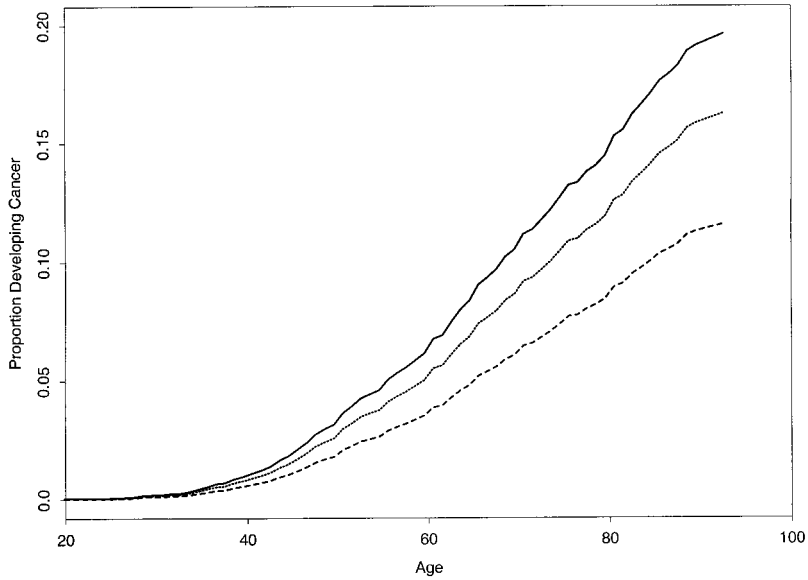

Fig. 1. Cumulative risk of breast cancer by family relationship. *Solid line*, first-degree relative of affected family member. *Dotted line*, second-degree relative of affected family member. *Dashed line*, marry-in.

Table 5 Risk of breast cancer: 1952–1996, by occurrence of nonproband cancers at baseline

Cancers at baseline[a]	Relationship to proband	Family history	No. of cases	Risk ratio[b]	95% CI
Breast, ovarian	Marry-in		188	1.0	
	Sisters, daughters	No	116	1.8	1.4–2.3
		Yes	12	2.3[c]	1.1–4.4
	Granddaughters, nieces	No	216	1.4	1.1–1.7
		Yes	32	2.8[d]	1.8–4.4
Breast, ovarian, gastric	Marry-in		188	1.0	
	Sisters, daughters	No	98	1.8	1.4–2.3
		Yes	30	2.2	1.4–3.4
	Granddaughters, nieces	No	183	1.4	1.1–1.7
		Yes	65	2.1[e]	1.5–3.0

[a] In parents, grandparents, and maternal and paternal aunts and uncles of the probands.
[b] Accounting for age, birth cohort, and correlated data.
[c] Evidence of nonproportionality for this variable ($P < 0.001$).
[d] Evidence of nonproportionality for this variable ($P = 0.02$).
[e] Evidence of nonproportionality for this variable ($P = 0.02$).

The vast majority of founders of the study families were born in the 1800s. For the generations preceding the probands, stomach cancer was the most common cancer of that era. Incidence has gradually decreased since the 1930s. Conversely, incidence of breast cancer has increased an average of 1–2% per year. We hypothesized that if the hereditary predisposition was a reflection of DNA-repair deficiency, then the manifestation of the inherited liability would be dependent upon the predominant source of environmental insult (either endogenous or exogenous). Thus, in previous generations, the inherited susceptibility may have been manifest as increased risk of stomach cancer. To test this hypothesis, we classified the families according to the occurrence of breast, ovarian, or stomach cancer among generations preceding the proband. As shown in Table 5, the risk of breast cancer associated with this broader definition of family history was similar to the risk associated with breast or ovarian cancers alone. The primary difference is that the number of families classified as positive increased from 32 to 80. This represents an increase from 7.5% to 18.8% of the total number of families.

Discussion

Results of the present study confirm the significance of family history as a risk factor for breast cancer. Compared to women who have married into this collection of families, sisters and daughters (first-degree relatives) were at a 2-fold greater risk; nieces and granddaughters were at a 1.5-fold increased risk. Adjustment for other known risk factors for breast cancer did not attenuate these findings. A subset of the 426 probands had a family history of breast cancer at baseline in 1952. These 32 families were found to be at the greatest risk for breast cancer during the follow-up period.

The ability to conduct a retrospective cohort study of this nature is predicated upon the ability to locate family members despite an extended period of noncontact. In fact, the original data records that were collected as part of the 1944–1952 study had not been touched for nearly 40 years before the present study was initiated. To begin the process of ascertaining cancer end points and risk factor data, it was necessary to update and extend the pedigrees. This task was complicated by the lack of social security numbers for study participants. Nonetheless,

because of the relatively low migration from Minnesota, the size of the families, and the persistence of study personnel, 98% of the eligible families were located. More importantly, loss to follow-up within the study families was low, typically no more than one to two individuals per family.

The present collection of 426 families is unique in several respects. First, these are the families of a consecutive series of breast cancer patients initially seen at one of the largest diagnostic and treatment facilities in the state of Minnesota. The probands were selected without regard to age at onset or family history, and they are geographically representative of the distribution of breast cancers in the state at that time. Each family includes at least four generations: parents of the proband; proband plus siblings; offspring plus nieces; and granddaughters. For many families, cancer history among grandparents, aunts, and uncles of the probands is also known. Although it may be possible to recreate four- to five-generation pedigrees without a resource such as this through recall and genealogical research, it would be nearly impossible to replicate the validation of cancer occurrence for the early generations. Investigators have linked the unique genealogic records in Utah to statewide tumor registry data to perform similar studies (25). Although they demonstrate aggregation of breast and other cancers, a longitudinal component was not included. Similarly, Iceland represents another unique resource for genetic epidemiological research because of the stable population, existing genealogies, and a cancer registry (26). Their findings of risk to relatives of breast cancer patients are similar to those presented here. Our study extends their approach by incorporating other breast cancer risk factors in the analysis. Finally, it is worth emphasizing the high degree of compliance of family members with the present investigation: telephone interview rates were >93%.

It is interesting that despite the fact that all relatives of the probands had, by definition, a family history of breast cancer, the subsequent risks for breast cancer were highly variable. For a significant proportion of the families (39%), no additional cases of breast or ovarian cancer developed over four to five decades. With the benefit of a four-generation pedigree, it is easy to classify the probands in these families as being truly "sporadic." This absence of increased risk speaks to the high rate of misclassification when risk is defined based on occurrence of disease in first-degree relatives only.

A relatively small subset of the study families accounted for the vast majority of cancers identified during the follow-up interval. In fact, 60 families (14% of the total) accounted for 173 of the 376 breast cancers (46%) in the blood relatives. Eleven of these 60 families had a family history of breast or ovarian cancer at the baseline period of 1952. It is this subset of 60 families that are likely to reflect those with the greatest inherited susceptibility. It would be important to screen for BRCA1/2 mutations in these families and begin to explore environmental factors as the basis for the variability in risk. Few studies have been conducted in this area, but some evidence exists to suggest that reproductive history (27), smoking history (28), and oral contraceptive use (29) may modify penetrance of inherited mutations.

Data from the Breast Cancer Linkage Consortium suggest that gastric cancer is somewhat elevated in families linked to BRCA1 or BRCA2. In the present study, we included history of gastric cancer in generations prior to the proband to help define the families at greatest risk. Inclusion of gastric cancer as part of the family history phenotype did not materially alter the point estimate of risk associated with a family history of breast or ovarian cancer. However, the number of families classified as high risk increased from 32 to 80. In the course of an ongoing study of cancer among male members of our high-risk families, we have identified a BRCA2 mutation carrier (family 219) who recently developed gastric cancer. This observation lends support to the hypothesis that the manifestation of inherited defects in DNA repair is a function of competing risks, with the phenotype influenced by the type and route of carcinogenic exposure. Evidence to this effect has been recently presented using mouse models for hereditary nonpolyposis colorectal cancer (30).

Roughly 50% of the breast cancers identified among biological relatives of the proband during the follow-up period occurred among the 200 families in which only 1 or 2 relatives besides the proband were affected. It is tempting to hypothesize that these nonmendelian clusters reflect the existence of low penetrance genes or nontruncating mutations in BRCA1 or BRCA2 (missense variants) that confer a subtle effect on protein function.

As with most previous studies that have examined the significance of family history, inclusion of other breast cancer risk factors did not influence our results (2, 31). However, there may be unrecognized family history (gene) × environment interactions. It is important to point out that this collection of families is highly valuable for studies of gene × environment interactions because of the high proportion of the study population that have a family history of breast cancer (55% by selection as a biological relative of a breast cancer proband).

Limitations of the present study must be considered when interpreting the results. Because this was a historical cohort study, all cases of cancer were incident in relation to the baseline period of 1952. However, at the time of the interview, all were technically prevalent cases. One must typically be concerned about the potential for survival bias in these situations. In the present study, we were able to obtain virtually complete follow-up on all family members, regardless of vital status or relationship to the proband. Thus, the primary question posed here regarding the risk of cancer to biological relatives of the probands compared to the reference population of marry-ins is not likely to be compromised. Moreover, at least with regard to BRCA1 and BRCA2, there does not appear to be an association between mutation status and survival (32). Another limitation is the fact that we did not attempt to validate the occurrence of cancers other than those of the breast. Previous research has shown that for some sites, especially of the female reproductive system, accuracy may be low (33). Thus, there is less reason to be confident about our findings regarding ovarian and endometrial cancer. We were able to obtain some amount of risk factor information on all members of the cohort at risk, even those who were deceased. The limitation, however, is that less detailed risk factor information can be collected from surrogates. A final limitation, especially when considering other phenotypes associated with BRCA1/2 such as gastric cancer, is the lack of data on male relatives. Unfortunately, no information was collected on males in this data set.

In summary, we have successfully completed a historical cohort study of cancer occurrence in 426 families ascertained between 1944 and 1952 in Minnesota. Subsequent risk of breast cancer was elevated compared to the marry-in reference group, but no significant risk elevations were observed for other cancer sites. Future studies are planned to use this unique resource to test hypotheses regarding gene × environment interactions.

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