Cancer Risk Estimates for Family Members of a Population-based Family Registry for Breast and Ovarian Cancer[1]

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Abstract

Population-based breast and ovarian cancer family registries can facilitate studies to evaluate genetic and environmental factors in the etiology of these malignancies. The purpose of this study is to describe what is, as far as we know, the first population-based breast and ovarian cancer family registry and to estimate breast and ovarian cancer risk in relatives of breast and ovarian cancer probands. Population-based consecutive incident cases of breast and ovarian cancer were invited to participate in the University of California, Irvine breast and ovarian family registry. In this study, we report data on 1567 breast cancer and 328 ovarian cancer probands. The operational components of this family registry include enrollment of probands, family history interviewing, confidentiality, pathology, verification and review, biospecimen bank, statistical/genetic analysis, and special studies on positional cloning of known genes. All of the components are tracked through the University of California, Irvine Genetic Research Information System. In non-Hispanic-white breast cancer probands, relative risk (RR) of breast cancer in mothers and sisters is significantly elevated [RR = 1.7 and 95% confidence interval (CI) = 1.4–2.0 and RR = 2.8 and 95% CI = 2.3–3.3, respectively]. In families of ovarian cancer probands, mothers are at increased risk of ovarian cancer (RR = 4.6; 95% CI, 2.1–8.7). RR of breast cancer in mothers of Hispanic breast cancer probands is significantly elevated (RR = 4.9; 95% CI, 2.6–8.5). No elevation of breast or ovarian cancer risk was observed among relatives of Asian probands. In general, there is a decrease in RR among mothers and sisters with increase in age of onset of probands. In second-degree relatives and first cousins, the breast cancer hazards ratios increase with increase in the number of affected first-degree relatives and decrease with increase in age at onset of the proband.

Introduction

As new knowledge and tools in molecular genetics become available, the hereditary component of breast cancer in relation to specific genetic alterations as well as gene-environment interactions can be assessed. This assessment can best be accomplished by using large population-based registries of families at high risk for breast cancer. Cancer family registries can facilitate present and future genetic epidemiology studies to characterize the frequency distribution of genes in the population, to estimate cancer risk in mutation carriers, and to identify environmental factors that modify expression of susceptibility genes. The strong need for family registry resources for studies of the genetic epidemiology of cancer has been recognized by the National Cancer Institute (1) through its establishment of the Cooperative Family Registries for Breast Cancer Studies in six sites in late 1995.

A major risk factor for breast cancer is family history of the disease (2–12). Studies have shown consistently that a history of breast cancer in a first-degree relative increases a woman's risk of breast cancer compared to women without such a family history. If both the mother and a sister have had breast cancer, the risk is further increased (particularly if either the mother or sister was diagnosed at a young age, less than 50 years). Identification of *BRCA1* and *BRCA2* mutations associated with autosomal dominant breast and ovarian cancer predisposition (13, 14) has confirmed what was previously suggested using segregation analysis (15, 16). Hereditary breast cancer is estimated to account for 5–10% of all breast cancers in the United States (13, 15). Early studies estimated that germ-line mutations of the *BRCA1* gene appear to be a predisposing factor in up to 80% of families with early onset breast and ovarian cancer and in 45% of families with site-specific breast cancer (17). Similarly, germ-line mutations in the *BRCA2* gene estimated from early studies appeared to be a predisposing factor in approximately 25–30% of site-specific breast cancer, particularly in males (14). However, more recent studies performed on families that may not be suitable for linkage analysis but are typical of families referred to clinics because of strong history of cancer in their relatives suggest that *BRCA1* mutations account for only 10–20% of inherited breast cancers and that *BRCA2* mutations account for half this fraction of families (18). There have been a number of other genes with very rare mutations that explain a small proportion (<1%) of

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hereditary breast cancer, such as *TP53* (19), whereas other breast cancer susceptibility gene(s) may yet be identified.

More than half a million American women are estimated to be carriers of a breast cancer susceptibility gene; these women may have between 55% and 85% probability of developing breast cancer and perhaps additional cancers at other sites over their lifetime (15, 17, 20–23). For these women, a prevention and early detection strategy is an essential aspect of managing their risk. In breast cancer, it is estimated that the proportion of cases attributable to a breast and ovarian cancer susceptibility gene decreases dramatically with age [33% of cases were 20–29 years of age compared to only 2% of cases at 70–79 years (20)]. The age-specific risk of ovarian cancer in carriers was shown to be 15 times higher than that in noncarriers (20).

In this study, we present the design and methods used to develop what is, as far as we know, the first population-based breast and ovarian cancer family registry for genetic epidemiology studies. This family registry is designed to investigate the hereditary component of breast and ovarian cancer and gene-environment interactions in their etiology. In this report, we present descriptive results on the family registry with regard to familial characteristics with classification by age at onset of the proband, race/ethnicity, histology, and multiple primaries. Risk estimates of breast and ovarian cancer in family members of breast and ovarian cancer probands are described with respect to their relationship to the proband, age at onset, parity, and number of affected first-degree relatives. Previous studies have investigated the distribution of various risk factors by using case-control studies in which family history was defined based on the cancer status among first-degree relatives of the proband. In this study, we use information from a population-based family registry study on first-degree relatives, second-degree relatives, and first cousins.

Materials and Methods

The population under study includes all breast and ovarian cancer cases diagnosed in Orange County, California, during the 1-year period beginning March 1, 1994 (IRB# HS91-137). Eligible probands were identified through the existing population-based cancer registry. The necessary data for possible enrollment into the hereditary breast cancer study were generated by the cancer registry and transmitted to the GRIS[3] developed by our group for genetic epidemiological studies.

Identification of Breast and Ovarian Cancer Patients Using the Population-based Cancer Registry

Breast and ovarian cancer probands were ascertained through the population-based cancer registry of the CSPOC. Description of CSPOC and details of data collection methods have been reported previously (24–26).

For ascertainment of breast cancer, patients were identified through CSPOC within 6 months of diagnosis. However, we incorporated a rapid reporting system to identify ovarian cancer cases within 4 weeks of diagnosis. Patient identification (name, address, and phone number), birth date, race/ethnicity, sex, date of diagnosis, cancer site, histological type, diagnostic/pathology confirmation, stage of disease, and physician information were recorded for each case to link with the GRIS described below.

Eligible Probands. In the current study, all population-based consecutive incident cases of breast and ovarian cancer with age at diagnosis less than or equal to 75 years diagnosed between March 1, 1994 and February 28, 1995 were eligible for inclusion in the UCI breast and ovarian cancer family registry. In this study, we report data on 1567 breast cancer cases and 328 ovarian cancer cases for a total of 1895 cases. A description of the cases by race/ethnicity shows that 84.8% were non-Hispanic white, 8.2% were Hispanic, 0.6% were African-American, and 6.4% were Asian. The age distribution of cases was as follows: (*a*) 9% below age 40 years; (*b*) approximately 25% in each 10-year interval from 40–69 years; and (*c*) 16% in the 70–75-year age interval.

Treating physicians were notified of our intent to contact their patients to participate in the study. Patients were then contacted by way of an introductory letter followed by a telephone call to invite them to participate in the study. A family history was obtained from the probands through a telephone interview. Of the 1567 breast cancer probands, 202 (12.9%) were patients whom we were unable to contact, and 258 (16.5%) were patients who declined to participate. For ovarian cancer, 51 (15.5%) were patients whom we were unable to contact, and 52 (15.5%) were patients who declined to participate.

Among the 202 breast cancer probands whom we were unable to contact, 5 (2.5%) were unable to be contacted due to physician refusal, and 63 (31.2%) died before contact. Among the 51 ovarian cancer probands whom we were unable to contact, 2 (3.9%) were unable to be contacted due to physician refusal, and 33 (64.7%) died before contact.

Among the 258 breast cancer probands who declined to participate, the most common reasons given for nonparticipation were "not interested" [86 probands (33.3%)], "time commitment" [48 probands (18.6%)], "bad health" [27 probands (10.5%)], and "emotional reasons" [24 probands (9.3%)]. Similarly, among the 52 ovarian cancer probands who declined to participate, the most common reasons given for nonparticipation were "not interested" [13 probands (25.0%)], "time commitment" [13 probands (25.0%)], "bad health" [5 probands (9.6%)], and "emotional reasons" [7 probands (13.5%)].

Breast cancer proband participants and nonparticipants did not differ significantly with respect to age at diagnosis, race/ethnicity, or grade of the disease. There was no difference between participants and nonparticipants with respect to the proportion of those with *in situ*, localized, and regional disease at diagnosis. However, the proportion of distant disease was higher among nonparticipants (7.0%) compared to participants (2.4%). In general, the proportion of distant disease accounts for only 3.7% of all breast cancer. There was an age difference between participants and nonparticipants among ovarian cancer probands, with older cases being less likely to participate. Participants and nonparticipants among ovarian cancer probands did not differ significantly with respect to race/ethnicity and grade and stage of the disease. Tables 1 and 2 present the distribution of race/ethnicity, age, and cancer site in participating and nonparticipating breast and ovarian cancer probands.

Interviews elicited family history information on all first- and second-degree relatives and first cousins of the proband. Unaffected relatives were enumerated by date of birth, gender, vital status, and date of death, if applicable. For cancer-affected family members, information on the type of cancer, date of diagnosis, and place of diagnosis was also collected. In the

[3] The abbreviations used are: GRIS, Genetic Research Information System; UCI, University of California, Irvine; RR, relative risk; CSPOC, Cancer Surveillance Program of Orange County; CI, confidence interval.

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Table 1 Distribution of race/ethnicity, age, and cancer site in participating and nonparticipating breast probands

	Participants (n = 1332)	Nonparticipants (n = 563)	Total (n = 1895)
Female Breast Cancer Probands			
Race/ethnicity			
Non-Hispanic white	951 (86.7%)	375 (82.1%)	1326 (85.3%)
Hispanic	76 (6.9%)	41 (9.0%)	117 (7.5%)
African American	5 (0.5%)	7 (1.5%)	12 (0.8%)
Asian	65 (5.9%)	34 (7.4%)	99 (6.4%)
Age (yrs)			
<40	82 (7.5%)	36 (7.9%)	118 (7.6%)
40–49	290 (26.4%)	99 (21.7%)	389 (25.0%)
50–59	287 (26.2%)	111 (24.3%)	398 (25.6%)
60–69	258 (23.5%)	114 (24.9%)	372 (24.0%)
70–75	180 (16.4%)	97 (21.2%)	277 (17.8%)
Grade			
Well	129 (11.8%)	43 (9.4%)	172 (11.1%)
Moderate	330 (30.1%)	134 (29.3%)	464 (29.8%)
Poor	286 (26.0%)	116 (25.4%)	402 (25.9%)
Unknown	352 (32.1%)	164 (35.9%)	516 (33.2%)
Stage			
In situ	165 (15.1%)	62 (13.6%)	227 (14.6%)
Local	585 (53.3%)	214 (46.8%)	799 (51.4%)
Regional	312 (28.4%)	142 (31.1%)	454 (29.2%)
Distant	26 (2.4%)	32 (7.0%)	58 (3.7%)
Unknown	9 (0.8%)	7 (1.5%)	16 (1.1%)
Subtotal	1097 (70.6%)	457 (29.4%)	1554
Male Breast Cancer Probands	10 (76.9%)	3 (23.1%)	13

Table 2 Distribution of race/ethnicity, age and cancer site in participating and nonparticipating ovarian probands

Ovarian cancer probands	Participants (n = 1332)	Nonparticipants (n = 563)	Total (n = 1895)
Race/ethnicity			
Non-Hispanic white	186 (82.7%)	82 (79.6%)	268 (81.7%)
Hispanic	26 (11.5%)	11 (10.7%)	37 (11.3%)
Asian	13 (5.8%)	10 (9.7%)	23 (7.0%)
Age (yrs)			
<40	40 (17.8%)	16 (15.5%)	56 (17.1%)
40–49	53 (23.6%)	17 (16.5%)	70 (21.4%)
50–59	53 (23.6%)	14 (13.6%)	67 (20.4%)
60–69	51 (22.7%)	36 (35.0%)	87 (26.5%)
70–75	28 (12.4%)	20 (19.4%)	48 (14.6%)
Grade			
Well	20 (8.9%)	7 (6.8%)	27 (8.2%)
Moderate	38 (16.9%)	22 (21.4%)	60 (18.3%)
Poor	83 (36.9%)	33 (32.0%)	116 (35.4%)
Unknown	84 (37.3%)	41 (39.8%)	125 (38.1%)
Stage			
Local	69 (30.7%)	27 (26.2%)	96 (29.3%)
Regional	34 (15.1%)	12 (11.7%)	46 (14.0%)
Distant	113 (50.2%)	58 (56.3%)	171 (52.1%)
Unknown	9 (4.0%)	6 (5.8%)	15 (4.6%)
Subtotal	225 (68.6%)	103 (31.4%)	328

1,332 families of participating probands, there were 6,195 first-degree relatives (parents and siblings), 14,527 second-degree relatives (grandparents, aunts, uncles, and half-siblings), and 14,119 third-degree relatives (cousins).

Data Processing and Management. The GRIS database developed by our group is a multi-user, menu-driven system designed for interviewer, research, and management personnel to evaluate progress and data quality. A verification table and a pedigree diagram summarizing the family history interview were produced for each proband and used for follow-up to complete missing data on their relatives. Interviewers also used the GRIS system to verify, expand, and manage information on families as new data were collected. GRIS automated merge functions to create personalized study cards and physician and patient letters as needed. In addition to the family history interview, participants completed a food frequency questionnaire and an epidemiological risk factor questionnaire. The response rates for the food frequency and epidemiological risk factor questionnaires were 81% and 77%, respectively. The results of these questionnaires are not included in this report.

Vital Statistics. For deceased relatives in families, we obtained death certificates to assess the presence or absence of cancer in the four grandparents and in relatives who were reported to have died before age 60 years. Information on the places and dates of death for relatives was obtained from the proband or from the next of kin of deceased individuals.

Biospecimen Bank: Pathology and Tumor Tissue Samples. Reported malignancies for the study in probands and family members were verified by obtaining pathology reports, tumor tissue samples, clinical records, and death certificates; a signed authorization form from the patient or next of kin accompanied these requests. For probands, we verified all tumors by pathology. In particular, among probands, we collected 689 (51.7%) tissue blocks, and an additional 460 tissue blocks (34.5%) have been requested. We verified 257 first-degree relatives (76.0%) with breast or ovarian cancer, 328 second-degree relatives (64.4%) with breast or ovarian cancer, and 107 first cousins (54.3%) with breast or ovarian cancer. Among the 257 verified tumors within first-degree relatives, 56 (21.8%) were verified by pathology, 70 (27.2%) were verified by death certificate, 20 (7.8%) were verified by personal interview of the affected relative, and 111 (43.2%) were verified by interview of another family member in addition to the proband. Among the 328 verified tumors within second-degree relatives, 13 (4.0%) were verified by pathology, 77 (23.5%) were verified by death certificate, 10 (3.0%) were verified by personal interview of the affected relative, and 228 (69.5%) were verified by interview of another family member in addition to the proband. Among the 107 verified tumors within first cousins, 11 (11.3%) were verified by pathology, 11 (11.3%) were verified by death certificate, 2 (1.9%) were verified by personal interview of the affected relative, and 83 (77.6%) were verified by interview of another family member in addition to the proband.

Statistical Methods

Descriptive statistics were computed with SAS statistical procedures (SAS Institute, Inc.). Comparisons of proportions were made using Fisher's exact test with a two-sided significance level of 0.05. The numbers of cancers expected in female relatives of probands were calculated using age-specific incidence rates in Orange County for 1984–1994. Because of the January 1, 1984 starting date of the Cancer Surveillance Program of Orange County, expected numbers of cancers in female relatives of probands were calculated using age-specific incidence rates in Connecticut for the time period prior to 1984. (Age-specific incidence rates for breast and ovarian cancer in Connecticut in 1984–1994 were similar to those in Orange County for the same time period.) The cumulative hazards of breast and ovarian cancer were calculated for each family member and summed to determine the expected numbers of cancers in mothers, sisters, mater-

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Table 3 Distribution of familial[a] cases by proband's cancer status

	Type of proband		
	Breast Cancer $n = 247$	Ovarian Cancer $n = 45$	Total $n = 292$
No. of families with first-degree relatives with breast or ovarian cancer			
1	215 (87.1%)	41 (91.1%)	256 (87.7%)
2	27 (10.9%)	4 (8.9%)	31 (10.6%)
2+	5 (2.0%)	0 (0.0%)	5 (1.7%)
No. of families with first-degree relatives with breast cancer only			
0	19 (7.7%)	11 (24.4%)	30 (10.3%)
1	200 (81.0%)	32 (71.1%)	232 (79.5%)
1+	28 (11.3%)	2 (4.5%)	30 (10.2%)
No. of families with first-degree relatives with ovarian cancer only			
0	218 (87.2%)	32 (71.1%)	250 (85.6%)
1	29 (11.8%)	13 (28.9%)	42 (14.4%)
No. of families with at least one first-degree relative <50 years diagnosed with breast cancer			
0	179 (72.5%)	34 (75.6%)	213 (72.9%)
1	68 (27.5%)	11 (24.4%)	79 (27.1%)
No. of families with at least one first-degree relative diagnosed with breast and at least one first-degree relative diagnosed with ovarian cancer			
0	237 (95.9%)	43 (95.6%)	280 (95.9%)
1	10 (4.1%)	2 (4.4%)	12 (4.1%)

[a] Probands with at least one first-degree relative with the specified phenotype.

nal and paternal grandmothers, and maternal and paternal aunts. In addition, we right-censored at age 85 years for all individuals. CIs were calculated using the exact Poisson distribution. Analyses of the RR of breast and ovarian cancer in family members of probands were restricted to the families in which age at diagnosis of the proband was less than or equal to 75 years of age and in which dates of birth, death, and diagnosis were known in relatives of the proband. Subsets of those for whom expected numbers of cancers were calculated were similar to the entire breast cancer family registry with respect to family history of cancer. In addition, we excluded 29 families in which either the probands were adopted with no knowledge of family history or the family history was incomplete on one side of the family.

The Cox proportional hazards model was used to estimate hazards ratios for probands' mothers and sisters. The dependent variable in the proportional hazards model was years to onset of breast or ovarian cancer in first-degree relatives. Independent variables tested included the age at diagnosis of the proband and whether each relative had any additional family member besides the proband with breast or ovarian cancer. Interaction terms between variables were also considered.

Results

Familial Status of Breast and Ovarian Cancer Probands

The probands were classified as follows with respect to family history: (*a*) sporadic, no first-degree affected relatives of the proband; and (*b*) familial, at least one first-degree relative affected with breast or ovarian cancer. The definition of first-degree relative includes father, mother, sister, or brother. Of the 1303 probands with complete family history (1084 breast cancer probands and 219 ovarian cancer probands), 22.4% were in the familial category. The remainder (77.6%) reported no history of breast or ovarian cancer among first-degree relatives. Among the sporadic families (in both breast and ovarian cancer families), approximately 20% had a history of one second-degree relative with breast or ovarian cancer, and 5% had a history of at least two second-degree relatives with breast or ovarian cancer. Table 3 summarizes the number of families by the number of first-degree relatives with breast or ovarian cancer ($n = 292$). Among familial probands, there were five families (1.7%) with four or more members with breast or ovarian cancer and two families (0.7%) with five or more members with breast or ovarian cancer (four plus the proband). Prevalence of a history of ovarian cancer in a first-degree relative was significantly higher among ovarian cancer probands compared to breast cancer probands ($P = 0.005$). Similarly, prevalence of a first-degree relative with breast cancer was significantly higher in breast cancer families compared to ovarian cancer families ($P = 0.027$).

Table 4 shows the distribution of familial cases by proband status (female breast cancer, ovarian cancer, and male breast cancer). The data are also shown separately for probands who had a personal history of multiple primaries of breast, ovarian, or other cancer. The proportion of familial cases in breast cancer probands with multiple primary malignancies of the breast was significantly greater than that in probands with a single primary cancer ($P < 0.009$; Table 4). When we stratified by the age at diagnosis of the proband, the above-mentioned association was true only among young probands (<50 years). Positive family history was not significantly different among non-Hispanic whites compared to other race/ethnicities (Table 4).

The distribution of family history of breast and ovarian cancer in relationship to histology is shown in Table 5. Probands with *in situ* carcinoma had a higher familial rate (28.9%) than probands with invasive carcinoma (21.7%); this difference was statistically significant ($P = 0.045$). *In situ* lobular carcinoma probands had a higher familial rate (42.9%) compared to the familial rate of probands with nonlobular histological types of *in situ* carcinoma (23.5%). However, this difference was not statistically significant.

Risk of Breast and Ovarian Cancer in Family Members of Probands

Family Members of Breast Cancer Probands. The proportion of mothers of non-Hispanic white female breast cancer probands who were affected with breast cancer was 12.8%, and

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Table 4 Distribution of familial cases by proband's cancer status and race/ethnicity

	Familial[a]	Sporadic[b]	Total
Classified by proband's cancer status			
Female breast cancer probands			
Single primary cancer	211 (22.2%)	741 (77.8%)	952 (88.5%)
Prior history of breast cancer	17 (38.6%)	27 (61.4%)	44 (4.0%)
Prior history of ovarian cancer	1 (20.0%)	4 (80.0%)	5 (0.5%)
Prior history of other cancer	16 (21.3%)	59 (78.7%)	75 (7.0%)
Subtotal	245 (22.8%)	831 (77.2%)	1076
Ovarian cancer probands			
Single primary cancer	40 (20.7%)	153 (79.3%)	193 (88.1%)
Prior history of breast cancer	1 (11.1%)	8 (88.9%)	9 (4.1%)
Prior history of ovarian cancer	0 (0.0%)	1 (100%)	1 (0.5%)
Prior history of other cancer	4 (25.0%)	12 (75.0%)	16 (7.3%)
Subtotal	45 (20.5%)	174 (79.5%)	219
Male breast cancer probands	2 (20.0%)	8 (80.0%)	10
Total	292 (22.5%)	1012 (77.5%)	1305
Classified by proband's race/ethnicity:			
Female breast cancer probands			
Non-Hispanic white	221 (23.7%)	712 (76.3%)	933 (86.7%)
Hispanic	16 (21.0%)	60 (79.0%)	76 (7.1%)
African American	0 (0.0%)	5 (100%)	5 (0.5%)
Asian	8 (12.9%)	54 (87.1%)	62 (5.8%)
Ovarian cancer probands			
Non-Hispanic white	40 (22.1%)	141 (77.9%)	181 (82.3%)
Hispanic	3 (11.5%)	23 (88.5%)	26 (11.9%)
Asian	2 (16.7%)	10 (83.3%)	12 (5.4%)
Classified by proband's age at diagnosis			
Female breast cancer probands			
<50 yrs	70 (19.0%)	299 (81.0%)	369 (34.3%)
50+ yrs	175 (24.7%)	532 (75.3%)	707 (65.7%)
Ovarian cancer probands			
<50 yrs	17 (18.9%)	73 (81.1%)	181 (41.1%)
50+ yrs	28 (21.7%)	101 (88.3%)	129 (58.9%)

[a] At least one first-degree affected relative with breast or ovarian cancer.
[b] No first-degree affected relatives of the proband.

the proportion of mothers of non-Hispanic white female breast cancer probands who were affected with ovarian cancer was 1.4%. In addition, 10.8% of sisters of breast cancer probands were affected with breast cancer, and 1.0% were affected with ovarian cancer. In mothers and sisters of non-Hispanic white breast cancer probands with age at diagnosis equal to or less than 75 years, the RR of breast cancer compared to general population risk was significantly elevated in mothers (1.7; 95% CI, 1.4–2.0) and in sisters (2.8; 95% CI, 2.3–3.3; Table 6). The RR of ovarian cancer in mothers and sisters was lower than that for breast cancer (1.0 and 1.7, respectively). No difference was observed in breast cancer risk among paternal and maternal second-degree relatives.

The increased risk for breast cancer in sisters compared to mothers might have been due to the reduced risk of breast cancer by increasing parity, because mothers in our study had at least one daughter (the proband). However, when we stratified by parity, age at diagnosis of the proband (<50 years and 50+ years), and history of breast cancer in a mother of the relative, the risk of breast cancer in less parous mothers of the proband with an affected mother was 13.1 compared to 4.1 in more parous mothers, whereas the risk in less parous and more parous mothers of the proband with no affected mother was similar (1.9 *versus* 1.8). This effect was not observed among sisters of the proband (Table 7).

The RR of breast cancer in mothers of Hispanic probands was significantly higher than that in mothers of non-Hispanic white probands [4.9 (95% CI, 2.6–8.5) and 1.7 (95% CI, 1.4–2.0), respectively]. RR in sisters of Hispanic probands was 1.6 compared to 2.8 in sisters of non-Hispanic white probands. Among second-degree relatives of Hispanic probands, the RR of breast cancer was not elevated. RR of breast cancer in mothers or sisters of Asian probands was not significantly elevated.

Family Members of Ovarian Cancer Probands. Among mothers of non-Hispanic white ovarian cancer probands, 10.2% were affected with breast cancer, and 5.1% were affected with ovarian cancer. Among sisters, 7.3% were affected with breast cancer, and 1.0% were affected with ovarian cancer.

In families of non-Hispanic white ovarian cancer probands with age at diagnosis ≤75 years, mothers were at increased risk of ovarian cancer (Table 6); the estimated RR is 4.6 (95% CI, 2.1–8.7). When we stratified by age at onset of the proband, the RR of ovarian cancer in mothers among younger probands (<45 years) was 8.6 (95% CI, 1.8–25), whereas the RR was 4.0 (95% CI, 1.5–8.7) among older probands. RR of breast cancer in mothers was estimated to be 1.5. The RR of ovarian and breast cancer in sisters was 1.6 and 1.8, respectively. In the 26 families of ovarian cancer probands who were Hispanic, there were 2.0 observed ovarian cancers in mothers compared to 0.17 expected. Among the 12 Asian families, there were no observed ovarian cancers among mothers of the proband.

Female Relatives with Multiple Primaries. In considering the familial association between breast and ovarian cancer, one group of interest was families of probands with both breast and ovarian cancer. Such a group should be enriched in carriers of genes predisposing to breast or ovarian cancer, so one would expect higher RRs in relatives of these probands. There were 14 families with probands diagnosed with breast and ovarian cancer. Among their 36 first-degree relatives, there were 2.0 observed breast cancers compared to 1.5 cases expected. However, among the 89 first-degree relatives of probands with multiple primary breast cancers, there were 16 observed breast cancers compared to 4.8 cases expected (RR, 3.3; 95% CI, 1.9–5.4).

Female First-Degree (Mothers and Sisters), Second-Degree (Grandparents and Aunts), and First Cousins of Breast Cancer Probands. Table 8 compares hazards ratios of breast cancer among second-degree relatives and first cousins of breast cancer probands. Because second-degree relatives and first cousins were not part of the "familial" definition, hazards ratios were tabulated by familiality status (as in sporadic *versus* familial). We further classified the familial cases into those who had no first-degree relative < 50 years old with breast cancer and those who had at least one first-degree relative < 50 years old with breast cancer. In general, there was a gradation of hazards ratios among relatives, with hazards ratios decreasing with increasing age of the proband, and hazards ratios increasing with increasing degree of familiality.

Table 9 presents hazards ratios for relatives of breast cancer probands with various combinations of family history and proband's age at onset. For example, the hazards ratio for a relative with at least two affected first-degree relatives of a non-Hispanic white breast cancer proband with age at onset between 45 and 54 years of age was 8.5 (95% CI, 6.0–12.0) compared to a relative with no affected first-degree relatives and age at onset of the proband of more than 65 years of age. In addition, there was an increasing trend in risk of breast cancer with increasing number of affected first-degree relatives

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Table 5 Distribution of family history and age at diagnosis by histology of proband's cancer, among female breast and ovarian cancer probands

	Familial	Sporadic	Total	Age (Mean ± SD) (yrs)
Breast cancer				
In situ				
Ductal carcinoma	21 (25.3%)	62 (74.7%)	83	55.3 ± 11.0
Comedocarcinoma	9 (29.0%)	22 (71.0%)	31	54.4 ± 12.7
Lobular carcinoma	9 (42.9%)	12 (57.1%)	21	51.6 ± 8.6
Other histological types	7 (29.2%)	17 (70.8%)	24	59.5 ± 11.6
Subtotal	46 (28.9%)	113 (71.1%)	159	55.3 ± 11.2
Invasive				
Ductal carcinoma	150 (22.9%)	506 (77.1%)	655	55.3 ± 11.5
Lobular carcinoma	11 (15.1%)	62 (84.9%)	73	59.9 ± 10.1
Ductal and lobular	17 (27.4%)	45 (72.6%)	62	57.6 ± 12.0
Adenocarcinomas	7 (18.9%)	30 (81.1%)	37	55.4 ± 11.1
Other histological types	15 (16.7%)	75 (83.3%)	90	53.8 ± 13.1
Subtotal	200 (21.8%)	718 (78.2%)	917	55.7 ± 11.6
Total	246 (22.8%)	831 (77.2%)	1076	55.6 ± 11.6
Ovarian cancer				
Mucinous	5 (25.0%)	15 (75.0%)	20	44.9 ± 15.1
Serous	20 (17.4%)	95 (82.6%)	115	53.2 ± 13.6
Clear cell	3 (18.8%)	13 (81.3%)	16	49.5 ± 9.4
Endometrioid	7 (30.4%)	16 (69.6%)	23	52.1 ± 13.5
Other histological types	10 (22.2%)	35 (77.8%)	45	56.4 ± 13.1
Total	45 (20.5%)	174 (79.5%)	219	52.7 ± 13.6

Table 6 RR of breast and ovarian cancer in non-Hispanic white female relatives of probands who were diagnosed at ≤75 years of age

Relationship to proband (no.)	Proband's cancer status[a]								
	Breast or ovarian cancer			Breast cancer			Ovarian cancer		
	Obs	Exp	O/E (95% CI)	Obs	Exp	O/E (95% CI)	Obs	Exp	O/E (95% CI)
Breast cancer probands									
Mothers (928)	127	78.7	1.6 (1.3–1.9)	114	67.1	1.7 (1.4–2.0)	12	11.7	1.0 (0.5–1.8)
Sisters (1113)	128	49.3	2.6 (2.2–3.1)	119	42.7	2.8 (2.3–3.3)	11	6.6	1.7 (0.8–3.0)
Grandmothers (1516)	67	69.5	1.0 (0.8–1.2)	54	58.4	0.9 (0.7–1.2)	6	11.1	0.5 (0.2–1.2)
Aunts (2722)	274	239.3	1.1 (1.0–1.3)	229	204.3	1.1 (1.0–1.3)	26	35.1	0.7 (0.5–1.1)
Cousins (3914)	152	158.3	1.0 (0.8–1.1)	138	138.1	1.0 (0.8–1.2)	14	20.2	0.7 (0.4–1.2)
Ovarian cancer probands									
Mothers (178)	27	13.4	2.0 (1.3–2.9)	17	11.5	1.5 (0.9–2.4)	9	2.0	4.6 (2.1–8.7)
Sisters (208)	17	9.6	1.8 (1.0–2.8)	15	8.4	1.8 (1.0–3.0)	2	1.2	1.6 (0.2–5.9)
Grandmothers (309)	16	13.8	1.2 (0.7–1.9)	13	11.6	1.1 (0.6–1.9)	2	2.2	0.9 (0.1–3.3)
Aunts (510)	46	44.7	1.0 (0.8–1.4)	36	38.2	0.9 (0.7–1.3)	8	6.5	1.2 (0.5–2.4)
Cousins (697)	19	26.9	0.7 (0.4–1.1)	16	23.4	0.7 (0.4–1.1)	3	3.4	0.9 (0.2–2.6)

[a] Obs, observed; Exp, expected; O/E, observed/expected.

(test for trend, $P = 0.0001$). Similarly, there was an increasing trend in ovarian cancer risk with increasing number of affected first-degree relatives (test for trend, $P = 0.0002$). Moreover, the hazards ratio of breast cancer was 2.1 (95% CI, 1.5–3.0) in a relative with a history of ovarian cancer among her first-degree relatives, whereas the hazards ratio of ovarian cancer was 3.8 (95% CI, 1.6–8.7) in a relative with history of ovarian cancer among her first-degree relatives.

Discussion

Population-based Family Registry for Breast and Ovarian Cancer. The family registry of breast and ovarian cancer described in this report offers several benefits to research regarding the hereditary component of breast and ovarian cancer, the role of gene-environment interactions in their etiology, and a basis on which to develop programs in cancer counseling, prevention, and control and future clinical trials of gene therapy. In the family registry at UCI, we have completed registration of more than 1,400 families with breast or ovarian cancer. On average, each family contains 36 individuals, with a yield of over 50,000 relatives. The availability of an information system that tracks all relatives and progress on each family with respect to blood sampling, retrieval of tissue blocks and death certificates, obtaining risk factor information by questionnaires, and follow-up is vital. At the initial stages of the UCI family registry and in the absence of a completed information system, it was difficult to track families and individual members of families as the number of probands and families increased. However, once the GRIS was developed, we were able to track each individual in the registry. It became clear to us that a sophisticated information system integrating all the modules described in "Materials and Methods" was necessary to make the family registry optimally functional for genetic epidemiology studies. For example, implementation of a bar code system linked to the GRIS for both blood and tissue blocks improved the accuracy and efficiency of processing, archiving,

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Table 7 RR of breast cancer in mothers and sisters of non-Hispanic white breast cancer probands, by type of relative, type of proband, age of proband, and parity status of the relative

	Mothers	Sisters
Breast cancer probands		
Parity of relative		
0		2.2 (1.2–3.7)
1	2.1 (1.2–3.4)	3.2 (2.1–4.8)
2	1.9 (1.3–2.6)	2.8 (1.8–4.0)
3	1.6 (1.1–2.4)	3.7 (2.5–5.2)
3+	1.5 (1.0–2.0)	2.0 (1.2–3.2)
Proband < 50 yrs		
Parity 0–1	2.1 (0.4–6.2)	4.7 (1.5–11.0)
Parity 1+	2.2 (1.5–3.9)	3.3 (1.3–6.8)
Proband 50+ yrs		
Parity 0–1	2.2 (1.1–4.0)	2.6 (1.8–3.7)
Parity 1+	1.8 (1.3–2.3)	2.7 (2.1–3.4)
Relatives with affected mother		
Parity 0–1	13.1 (1.6–47.3)	5.1 (2.0–11.0)
Parity 1+	4.1 (2.0–7.5)	5.4 (3.0–9.0)
Relatives with unaffected mother		
Parity 0–1	1.9 (1.0–3.3)	2.6 (1.8–3.6)
Parity 1+	1.8 (1.4–2.2)	2.5 (1.9–3.1)

Table 8 Hazards ratios of breast cancer in female second- and third-degree relatives of non-Hispanic white breast cancer probands, by familial status, by age at diagnosis of the proband, and by type of relative, from Cox proportional hazards regression

Proband's age at diagnosis (yrs)	Family history index		
	Familial[a]		Sporadic[b]
	Yes 1st <50 yr	No 1st <50 yr	
Grandparents			
<50	4.7 (1.9–11.3)	2.3 (1.0–5.3)	1.6 (0.9–2.6)
50+	2.6 (1.1–6.2)	0.9 (0.4–2.1)	1.0
Aunts			
<50	2.4 (0.9–6.4)	2.9 (1.7–4.9)	1.2 (0.8–1.7)
50+	1.3 (0.8–2.2)	1.7 (1.2–2.3)	1.0
Cousins			
<50	2.8 (0.7–11.7)	2.7 (1.2–5.9)	1.0 (0.6–1.8)
50+	1.9 (1.1–3.3)	0.8 (0.5–1.3)	1.0

[a] At least one first-degree affected relative with breast or ovarian cancer.
[b] No first-degree affected relatives of the proband.

Table 9 Hazards ratios of breast or ovarian cancer in relatives of non-Hispanic white breast cancer probands, results of Cox proportional hazards model

	Risk of breast cancer		
	No. of first-degree relatives with breast cancer		
	0	1	2
Age at onset of proband (yrs)			
<45	2.0 (1.5–2.8)	2.8 (1.7–4.7)	1.0 (0.1–7.2)
45–54	1.2 (0.9–1.5)	3.4 (2.5–4.7)	8.5 (6.0–12.0)
55–64	1.0 (0.8–1.3)	1.9 (1.3–2.7)	3.4 (2.4–6.0)
65+	1.0	1.8 (1.2–2.5)	3.2 (1.9–5.3)

	Risk of breast cancer	Risk of ovarian cancer
No. of first-degree relatives with breast cancer		
0	1.0	1.0
1	2.0 (1.7–2.5)	2.3 (1.3–3.9)
2	3.1 (2.2–4.3)	2.3 (0.9–3.9)
3+	6.7 (4.9–9.2)	
Test for trend	$P = 0.0001$	$P = 0.0002$
No. of first-degree relatives with ovarian cancer		
0	1.0	1.0
1	2.1 (1.5–3.0)	3.8 (1.6–8.7)

and follow-up of biological specimens by family, date, location, and genotyping laboratory.

The Familial Component of Breast and Ovarian Cancer. The proportion of probands who reported a history of breast or ovarian cancer in at least one first-degree relative was approximately 23%. To date, there are 67 (5%) "high-risk" families in the family registry; these are families with two affected first-degree relatives in addition to the proband or with at least one first-degree relative and two second-degree relatives on the same side of the family. Because of the dynamic nature of the family registry, the number of high-risk families described above reflects what was available in this study as of the writing of the manuscript. Among the more than 184,000 new cases of breast cancer to be diagnosed in the nation this year, we estimate that 9,200 (5%) will have a potentially hereditary form of the disease. Family history was studied in approximately 2,000 patients in an ongoing care program for breast cancer patients in the Stockholm area (27); these investigators reported that 6.7% of patients had a hereditary form of the disease. In Canada, it has been estimated that 5% of breast cancer cases have a hereditary basis (28). In 1986, Lynch and Lynch (29) reported that among 328 consecutive breast cancer patients seen in an oncology clinic, 9% had disease consistent with hereditary breast cancer. Thus, our results are consistent with these studies. However, it should be noted that our results are likely to be more applicable to the general population because this study included a population-based series in contrast to cases from an oncology clinic, where high-risk patients are likely to be overrepresented.

Risk Estimates of Breast and Ovarian Cancers by Ethnicity, Histological Type, and Relationship to the Proband. Because hereditary breast cancers tend to occur at early ages (3, 6, 10, 15, 22, 30–33), there is great potential for loss in person-years of life and for suffering in the families of these young women. The data presented in this study suggest a significant excess RR of breast cancer in mothers and sisters of breast cancer probands [1.7 (95% CI, 1.4–2.0) and 2.8 (95% CI, 2.3–3.3), respectively]. Our data also show that in families of ovarian cancer probands, mothers were at increased risk of ovarian cancer, with an estimated RR of 4.6 (95% CI, 2.1–8.7). In addition, we observed an increase in ovarian cancer risk with decreasing age at onset of the proband. This decreasing trend was also observed in relatives of breast cancer probands. This finding is consistent with the results of familial risk by Claus (10, 15).

Other factors that may be associated with increased familial risk in breast cancer were also observed in our data. Probands who had multiple primaries of breast and ovarian cancer showed a significantly higher familial rate compared to probands with a single primary cancer. This is consistent with a number of studies showing an association between increased frequency of multiple primary tumors and familial cancers (34–36). Familial cases with multiple affected relatives were important as an indication of the contribution of highly penetrant genes to familial clustering of the disease. In addition, the familial rate by race/ethnicity followed the same patterns as age-adjusted incidence rates, where non-Hispanic whites had a

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higher familial rate than that of other race/ethnic groups. However, our data showed the RRs of breast and ovarian cancer in mothers of Hispanic probands to be elevated and similar to those in mothers of non-Hispanic white probands. In particular, RR of breast cancer in mothers of Hispanic probands was significantly higher than the population risk among Hispanics (RR, 4.9; 95% CI, 2.6–8.5).

There have been several reports of a positive relationship between ductal carcinoma *in situ* and family history of breast cancer (37–39). The population-based family registry breast cancer data reported here show similar breast cancer familial rates in probands with ductal carcinoma *in situ* and with invasive breast cancer. Studies of lobular carcinoma *in situ* have been inconsistent (40). In a 1980 study by Erdreich *et al.* (41), none of 31 lobular carcinoma *in situ* patients reported a positive family history. The RR associated with family history of breast cancer was not statistically significant in the large population-based case-control study reported by Weiss *et al.* (38) in 1996. However, in 1972, Haagensen (42) had reported a higher frequency of mothers having a history of breast cancer in patients with lobular carcinoma *in situ* compared to patients with invasive breast cancer. Similarly, an increased frequency of sisters with breast cancer among women with lobular carcinoma *in situ* has been reported (43). Using data from the Cancer and Steroid Hormone Study, Claus *et al.* (5) reported that patients with lobular carcinoma *in situ* were significantly more likely to have a mother and/or sister affected with breast cancer (23.3%) compared to patients with all other histological types (2.9–11.8%). Similar to these latter results, in our study, the relationship between family history and histology was strongest for lobular carcinoma *in situ* (42.9% *versus* 23.5% when compared to family history in probands of other *in situ* carcinomas). Although the proportion of probands with *in situ* carcinoma reporting a positive family history was higher than that of probands with invasive carcinoma, this difference was not statistically significant and may have been due to heightened surveillance or screening in those with a positive family history.

Conclusions. Our study showed: (*a*) in non-Hispanic white breast cancer probands, RR of breast cancer in mothers and sisters was significantly elevated [RR = 1.7 (95% CI, 1.4–2.0) and 2.8 (95% CI, 2.3–3.3), respectively]; (*b*) in families of ovarian cancer probands, mothers were at increased risk of ovarian cancer (RR, 4.6; 95% CI, 2.1–8.7); (*c*) RR of breast cancer in mothers of Hispanic breast cancer probands was significantly elevated (RR, 4.9; 95% CI, 2.6–8.5); however, no elevation of breast or ovarian cancer risk was observed among relatives of Asian probands; (*d*) there was a decrease in RR among mothers and sisters with increase in age of onset of probands; and (*e*) in second-degree relatives and first cousins, the breast cancer hazards ratios increased with increase in the number of affected first-degree relatives and decreased with increase in age at onset of the proband.

The investment in this population-based family registry of breast and ovarian cancer will support further etiological studies of breast and ovarian cancer because of extensive characterization of patients and family members, validation of the familial risk, verification of tumors in families, and a biospecimen bank containing both DNA and RNA from blood samples and tumor tissue samples. Furthermore, the population-based family registry of breast and ovarian cancer will be ideal for programs in cancer prevention and control and genetic predisposition testing of *BRCA1*, *BRCA2*, and other breast cancer susceptibility genes.

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