Cancer Risk Estimates for BRCA1 Mutation Carriers Identified in a Risk Evaluation Program

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Background: **Increasing numbers of BRCA1 mutation carriers are being identified in cancer risk evaluation programs. However, no estimates of cancer risk specific to a clinic-based population of mutation carriers are available. These data are clinically relevant, because estimates based on families ascertained for linkage studies may overestimate cancer risk in mutation carriers, and population-based series may underestimate it. Wide variation in risk estimates from these disparate ascertainment groups makes counseling in risk evaluation programs difficult. The purpose of this study was to estimate BRCA1-related cancer risks for individuals ascertained in a breast cancer risk evaluation clinic.** ***Methods:*** **Cumulative observed and age-adjusted cancer risk estimates were determined by analyzing 483 BRCA1 mutation carriers in 147 families identified in two academic breast and ovarian cancer risk evaluation clinics. Cancer risks were computed from the proportion of individuals diagnosed with cancer during a 10-year age interval from among the total number of individuals alive and cancer-free at the beginning of that interval. Age-of-diagnosis comparisons were made using two-sided Student's *t* tests.** ***Results:*** **By age 70, female breast cancer risk was 72.8% (95% confidence interval [CI] = 67.9% to 77.7%) and ovarian cancer risk was 40.7% (95% CI = 35.7% to 45.6%). The risk for a second primary breast cancer by age 70 was 40.5% (95% CI = 34.1% to 47.0%). We also identified an increased risk of cancer of the colon (two-fold), pancreas (threefold), stomach (fourfold), and fallopian tube (120-fold) in BRCA1 mutation carriers as compared with Surveillance, Epidemiology, and End Results (SEER) Program population-based estimates.** ***Conclusion:*** **The estimates for breast and ovarian cancer risk in BRCA1 mutation carriers is higher than population-based estimates but lower than estimates based on families ascertained for linkage studies. These cancer risk estimates may most closely approximate those faced by BRCA1 mutation carriers identified in risk evaluation clinics. [J Natl Cancer Inst 2002;94: 1365–72]**

Mutations in BRCA1, a tumor suppressor gene located on 17q12–21 (MIM 113705, *(1)*] are associated with markedly increased risks for breast and ovarian cancer *(2,3).* As commercial testing for BRCA1 mutations has gained acceptance, increasing numbers of BRCA1 mutation carriers are being identified in cancer risk evaluation programs. Published estimates of cancer

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See "Notes" following "References."

risk attributable to BRCA1 mutations vary widely, based on the population of inference, and to date, no cancer risk estimates for BRCA1 mutation carriers identified from risk evaluation clinics have been published. The highest cancer risk estimates are derived from families used for linkage analysis, collected specifically for high risk of breast and ovarian cancer, and thus likely to overestimate risk for a clinic-based population. Risks for these families are estimated at 85% for breast cancer and 60% for ovarian cancer *(4,5).* Lower cancer risk estimates come from population-based studies, with cancer risk estimates for BRCA1 mutation carriers in the range of 35%–50% for breast cancer and 15% for ovarian cancer *(6–9).* However, families that present to a risk evaluation clinic on the basis of family history are likely to have characteristics intermediate to these populations. To obtain a more applicable estimate of cancer risk faced by BRCA1 mutation carriers identified during clinical evaluation for cancer risk, we undertook this study in BRCA1 mutation carriers referred to our cancer risk evaluation programs.

Subjects and Methods

All families seeking breast cancer risk counseling at the University of Michigan (January 1991 through July 1994) and at the University of Pennsylvania (August 1994 through December 2001) with a documented deleterious BRCA1 mutation in the family were included (147 families). The accompanying Breast Cancer Linkage Consortium (BCLC) study *(10)* used 96 of these 147 families and included 2120 people from those pedigrees, with individuals from our clinic populations making up approximately 15% of the BCLC study. However, because of requirements for specific age-related data, we used only 381 females from the 147 families. Thus, almost all the individuals in this study also are in the BCLC study, but only a small fraction of those in the BCLC study are analyzed here. These clinics were specifically designated as breast cancer risk assessment services; thus, these families may have more affected individuals with breast cancer than those ascertained through a general oncology clinic. Approximately 25% of individuals seen in these clinics underwent genetic testing for germline BRCA1 and BRCA2 mutations, and approximately 15% of the tested individuals have detectable disease-associated mutations. In families with BRCA1 mutations identified by this clinical service, the average age at breast cancer diagnosis is 42 years. The number of breast cancer cases per family varies widely, but in those families with detected mutations, the proportion of females 21 years old and older with breast cancer is approximately 40%. Data recorded included mutation, year of birth, year of death, sex, any known cancer, and the year of diagnosis for all cancers. All information was obtained by personal interview or by mailed questionnaire. This study was approved by the Institutional Review Boards of both institutions.

BRCA1 mutation carriers were identified either on the basis of direct genetic testing or as presumed carriers. Presumed carriers were defined as being in the line of descent between two tested mutation carriers or between a mutation carrier and an individual with breast or ovarian cancer (Fig. 1).

Cancer risk was determined by calculating the proportion of individuals diagnosed with each cancer during their lifetime or until their current age. The observed rate of cancer incidence was calculated as Σ(NC/NR) for each decade of life, where NC is the number of cases observed during that decade, and NR is the number of individuals at risk in the same age range. Age-adjusted risk was calculated by multiplying the number of each cancer occurring during any decade by the proportion of individuals at risk during the same decade, Σ[(NR/TR) * (NC/NR)] for each decade of life, where NR/TR (TR indicates total number of individuals at risk) is the proportion of the entire population that is at risk during that decade. Lifetime rates were calculated to age 110 to ensure that all deceased individuals were correctly censored. For determination of breast cancer risk, women diagnosed with more than one breast cancer (ipsilateral or contralateral) were included only once, using age at first diagnosis. The risk of second primary breast cancer was calculated using age at diagnosis of the second breast cancer. Cancer risk also was calculated based on mutation location (exons 1–10, exon 11, and exons 12–24). A two-sided Student's *t* test was used to compare mean age between tested and presumed carriers. Cumulative age-adjusted cancer risk estimates were computed as the proportion (p) of individuals diagnosed with cancer during a 10-year age interval from among the total number of individuals alive and cancer-free (N) at the beginning of that interval. Ninety-five percent confidence intervals (CIs) for these risks were computed as $p \pm 1.96 \sqrt{[p(1 - p)/N]}$. Relative risks (RRs) and 95% CIs were used to compare the age-specific cancer risk in BRCA1 mutation carriers against age-specific cancer risks obtained from Surveillance, Epidemiology, and End Results (SEER)[1] Program registry data. We assumed that when 95% CIs

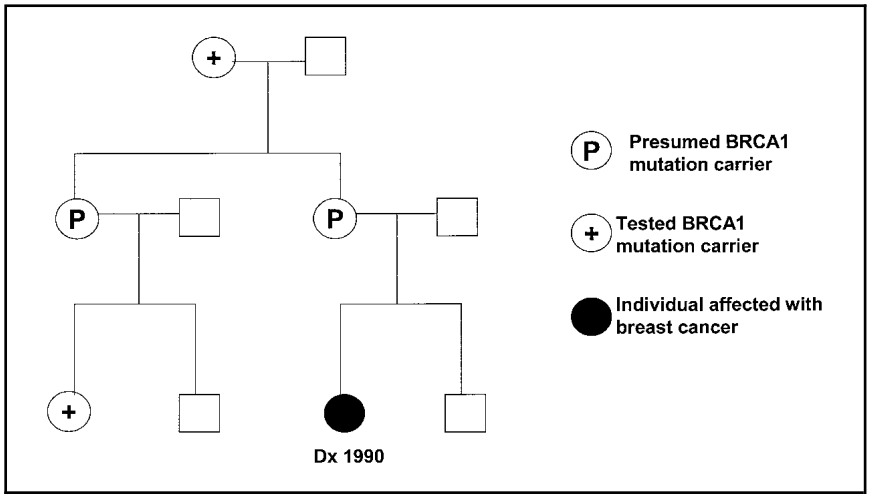

Fig. 1. Sample pedigree. This pedigree demonstrates the identification of BRCA1 mutation carriers who were either tested individuals or presumed carriers seen for counseling in our cancer risk evaluation program.

of one point estimate did not overlap the other point estimate, the differences are statistically significant at $P<.05$. For each cancer, RR was computed as the ratio of the risk in a given 10-year age interval among mutation carriers compared with the reported SEER risk of that cancer in the same age interval.

RESULTS

Population Characteristics

The study included 461 (95%) Caucasian participants among a total of 483 participants. The remainder represented small numbers of African-Americans, Asians, and Native Americans. All patients were either self- or physician-referred for a perceived elevated risk of breast or ovarian cancer. We identified 642 known or presumed mutation carriers from 147 families, representing 58 different mutations in BRCA1. Only family members with information on current age or age of death were included because these data are required for age adjustment of the observed cancer rates. Using these criteria, data on 483 mutation carriers (381 females, 102 males) of 642 eligible participants were analyzed (Table 1). Among the 483 participants, there were 316 tested mutation carriers and 167 presumed carriers. Because exact age of diagnosis was considered as the minimum criterion for considering a family report credible, individuals without an age at diagnosis were included in the analysis but were considered unaffected. Two hundred twenty-seven (60%) of the 381 women in the study had a diagnosis of breast cancer (Table 2). The average age at censoring for all individuals in the analysis was 56 years: 51 years for tested carriers and 63 years for presumed carriers ($P<.001$). One hundred seventy-nine (37%) of 483 participants had Ashkenazi Jewish founder mutations (26% 185delAG, 11% 5382insC). Two hundred fifteen (45%) mutations were in exons 1–10, 149 (31%) were in exon 11, and 119 (25%) were in exons 12–24.

Breast and Ovarian Cancer Risk

The cumulative age-adjusted risk up to age 110 for female breast cancer in this group was 78.3% (95% CI = 74.1% to 82.4%), and the cumulative age-adjusted risk to age 70 was 72.8% (95% CI = 67.9% to 77.7%) (Fig. 2). The SEER lifetime risk estimate for breast cancer is 12.86% *(11)*. Lifetime estimates are defined by SEER to age 95 or older *(11)*. There were four cases of male breast cancer among the 102 male BRCA1 mutation carriers (3.9%), for a cumulative age-adjusted risk of male breast cancer of 5.8% (95% CI = 1.3% to 10.4%). This is 53 times higher than the risk in the general male population, estimated at 0.011% *(11)*.

Table 1. Characteristics of BRCA1 mutation carriers

Characteristics	Female carriers	Male carriers	All carriers
Total no. (tested/presumed)	381 (260/121)	102 (56/46)	483 (316/167)
Age, y			
⩽30	10	3	13
31–40	59	10	69
41–50	108	17	125
51–60	91	20	111
61–70	59	17	76
>70	54	35	89
Mutation position			
Exons 1–11	281	83	364
Exons 12–24	100	19	119

One hundred two (27%) of 376 women had ovarian cancer (Table 2), with an estimated lifetime cumulative age-adjusted risk of 49.9% (95% CI = 44.9% to 55.0%) (Fig. 2), as compared with SEER lifetime risk estimates for ovarian cancer of 1.7% *(11)*. The cumulative age-adjusted ovarian cancer risk to age 70 was 40.7% (95% CI = 35.7% to 45.6%).

Families used for linkage analysis are ascertained through these clinics, and because of concern that these families may bias cancer risk estimates upward, we performed an analysis with families grouped as suitable or not suitable for linkage and compared these data to the overall analysis. There was no statistically significant difference between the cumulative age-adjusted lifetime rate of breast cancer in families used for linkage analysis (86.0%, 95% CI = 79.0% to 93.1%) and that in families not suitable for linkage analysis (76.4%, 95% CI = 71.5% to 81.3%) or that in the sample as a whole (78.0%, 95% CI = 74.1% to 82.5%). It was surprising, however, that the age-adjusted ovarian cancer rate in families used for linkage (35.7%, 95% CI = 26.0% to 45.5%) was statistically significantly lower than both the rate in families not suitable for linkage analysis (54.2%, 95% CI = 48.5% to 60.0%) and that in the sample as a whole (40.1%, 95% CI = 35.2% to 45.0%).

One source of bias in calculating risk estimates that could limit the application of the findings to non-Jewish women would occur if Ashkenazi Jewish women with the founder mutations 185delAG and 5382insC had different cancer risks than non-Ashkenazi Jewish women with BRCA1 mutations. To address this issue, we compared the age-adjusted rate of female breast and ovarian cancer between the individuals of Ashkenazi Jewish descent and the rest of the sample. The age-adjusted rates of breast and ovarian cancer for women with either founder mutation were not statistically significantly different from those in non-Ashkenazi Jewish women. For breast cancer, the risk to age 70 was 76.0% (95% CI = 69.1% to 82.8%) in Ashkenazi Jewish women and 78.0% (95% CI = 72.7% to 83.4%) in non-Ashkenazi Jewish women. For ovarian cancer, the risks were 45.8% (95% CI = 37.8% to 53.7%) and 51.1% (95% CI = 44.7% to 57.6%) for Ashkenazi Jewish women and non-Ashkenazi Jewish women, respectively.

Because unaffected family members may be more likely than those with cancer to have incomplete data, leading to another source of bias, we conducted a separate analysis of excluded individuals. Of the 77 excluded females, 33 had breast cancer, for an observed risk estimate of 42.8% (95% CI = 37.2% to 48.4%), which was statistically significantly lower than the observed cumulative estimate of 57.5% (95% CI = 55.0% to 60.0%) for those from whom we had complete data. Thirteen of the excluded women had ovarian cancer, for an observed rate of ovarian cancer of 16.8% (95% CI = 12.6% to 21.0%), which was not statistically significantly different from the estimate of 24.7% (95% CI = 22.5% to 26.9%) in those with complete data. None of the 63 excluded males had breast cancer. Of note, age-adjusted rates, which we believe are more informative than observed rates, cannot be calculated for the excluded individuals because incomplete age data was the exclusion criterion in all cases.

Other Cancer Risks

In addition to breast and ovarian cancer, four other cancers (colon, pancreatic, gastric, and fallopian tube) occurred statisti-

Table 2. Cumulative lifetime cancer risk in BRCA1 mutation carriers and population cancer risk*

Type of cancer	N†	BRCA1 mutation carriers: Cumulative age-adjusted risk, % (95% CI)	BRCA1 mutation carriers: Relative risk	Population, %
Female				
Breast (to age 70)‡	227	78.3 (74.1 to 82.4)	6.1	12.9
Ovarian (to age 70)‡	102	49.9 (44.9 to 55.0)	29.3	1.7
Uterine	5	2.1 (0.6 to 3.5)		2.7
Cervical	1	0.3 (0.3 to 0.8)		0.8
Fallopian tube	3	3.0 (1.3 to 4.7)	120	0.025§
All cancers other than breast or ovary	38	10.3 (7.2 to 13.3)		
Male				
Breast	4	5.8 (1.3 to 10.4)	58.2	0.1
Prostate	4	6.2 (1.5 to 10.8)		15.9
All cancers other than breast	25	26.1 (17.5 to 34.6)		
Female and male				
Colon	19	11.0 (8.2 to 13.9)	2.0	5.6
Pancreatic	5	3.6 (1.9 to 5.3)	2.8	1.3
Lung	7	3.0 (1.5 to 4.5)		6.2
Melanoma	3	2.5 (1.1 to 3.9)		1.3
Gastric	7	5.5 (3.4 to 7.5)	6.9	0.8
All cancers other than breast or ovarian	63	13.8 (10.7 to 16.9)		

*Population risks are from the Surveillance, Epidemiology, and End Results (SEER) Program, 2000 *(10)*. CI = confidence interval.
†N = the number of individuals with the specified cancer.
‡Rates calculated to age 70 for ease of comparison to the Breast Cancer Linkage Consortium data (for breast and ovarian cancers only).
§Fallopian tube cancer population risk is estimated as 0.5% of all gynecologic cancers from SEER 2000 data *(10)*.

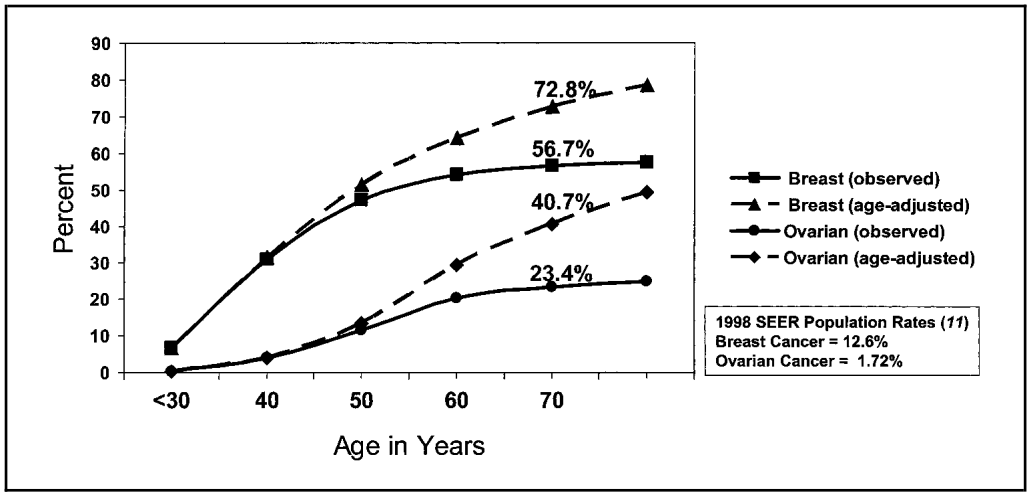

Fig. 2. Risk of breast and ovarian cancer in BRCA1 mutation carriers. The cumulative observed and age-adjusted risk of breast and ovarian cancers is shown. For comparison, population risk from Surveillance, Epidemiology, and End Results (SEER) Program data *(11)* are noted in the inset. Risk estimates are labeled for age 70.

cally significantly more often in BRCA1 mutation carriers than in the general population ($P<.05$). Other cancers evaluated but not present at greater frequencies than in the general population include uterine, cervical, brain, leukemia, bladder, kidney, thyroid, head and neck, and lymphoma. The cumulative age-adjusted lifetime risk of colon cancer among BRCA1 mutation carriers was 11.1% (95% CI = 8.3% to 13.9%), twice that of SEER population estimates of 5.6%. The cumulative age-adjusted lifetime risk of pancreatic cancer was 3.6% (95% CI = 1.9% to 5.3%), three times the estimated 1.3% population risk, and the cumulative age-adjusted lifetime risk of gastric cancer was 5.5% (95% CI = 3.4% to 7.5%), four times the population risk of 0.8%. All population risks are based on SEER estimates *(11)*.

The cumulative age-adjusted lifetime risk of fallopian tube cancer in this clinic-based population was 3.0% (95% CI = 1.3% to 4.7%). Population risk estimates for this cancer are difficult to obtain because it is rare, but using an estimate of the frequency of fallopian tube cancer among all gynecologic malignancies of 0.5% *(12)* and the combined risk of ovarian, uterine, and cervical cancer in the population of 5.2% *(11)*, we estimate the risk of fallopian tube cancer in the general population to be approximately 0.025%. Thus, the risk of fallopian tube cancer in this study population represents a 120-fold increase over the estimated population risk.

In the evaluation of the excluded individuals, 3 (4%) of 77 females and 9 (14%) of 63 males had an additional cancer. Although the numbers are small, and therefore not reliable, other cancer rates in the excluded individuals are lower than the observed rates in those included in the analysis, at 8.1% and 21.6% for females and males, respectively. As noted above, cancer rates in the excluded individuals are not age adjusted.

The observed incidence of prostate cancer among all male BRCA1 mutation carriers was 2.9%. Prostate cancer risk to age

60 was 1.4%, similar to the estimated 1.86% in the general population. The cumulative age-adjusted lifetime risk in mutation carriers was 6.2% (95% CI = 1.5% to 10.8%), statistically significantly lower than the 15.91% lifetime risk of prostate cancer in the general population *(11)* but possibly an underestimate due to the small numbers of older men included in this analysis.

Finally, the cumulative age-adjusted lifetime risk of any cancer diagnosis in this group of BRCA1 mutation carriers, other than breast and ovarian cancer, was 13.8% (95% CI = 10.7% to 16.9%). Of note, the overall risk of cancers other than of the female breast and ovary was statistically significantly higher for men than women, with cumulative age-adjusted lifetime risks of 26.1% (95% CI = 17.5% to 34.6%) and 10.3% (95% CI = 7.2% to 13.3%), respectively.

Risk of Second Cancers

Of 222 women in the study with breast cancer, 49 (22%) had a contralateral or asynchronous ipsilateral breast cancer not thought clinically to represent local recurrence. The cumulative age-adjusted lifetime risk of a second breast cancer diagnosis in this group was estimated at 40.5% (95% CI = 34.1% to 47.0%). Thirty-three (15%) of the 222 women with breast cancer subsequently developed ovarian cancer, for a cumulative age-adjusted lifetime risk of ovarian cancer after a breast cancer diagnosis of 18.8% (95% CI = 13.6% to 23.9%). Eighteen (8%) of 222 women with breast cancer were diagnosed with a subsequent cancer other than breast or ovarian cancer, for a cumulative age-adjusted lifetime risk of 9.7% (95% CI = 5.8% to 13.6%).

Average Age at Cancer Diagnosis

The average age at female breast cancer diagnosis in this study of BRCA1 mutation carriers, as in many others, was 42 years (95% CI = 40 to 44 years), and the average age at ovarian cancer diagnosis was 52 years (95% CI = 50 to 53 years). These ages are 20 and 10 years younger, respectively, than population averages *(13)*. The average age at male breast cancer diagnosis was 53 years (95% CI = 45 to 60 years), compared with 69 years in the general population. The average age at colon cancer diagnosis was 65 years (95% CI = 59 to 71 years), compared with 72 years in the general population. Although the risk of uterine cancer was not increased in this clinic-based population, the average age at uterine cancer diagnosis was 50 years (95% CI = 40 to 60 years), compared with the population average of 66 years. [All population-based ages at diagnosis were taken from *(13)*.]

Cancer Risk by Mutation Location

We did not detect a difference in the cumulative age-adjusted risk of breast cancer based on mutation location within the BRCA1 gene. However, the cumulative age-adjusted lifetime risk of ovarian cancer in women with mutations in exons 12–24 was statistically significantly higher than that in women with mutations in exons 1–11 (Fig. 3). That is, the cumulative age-adjusted lifetime risk of ovarian cancer for women with BRCA1 mutations in exons 1–11 was 43.8% (95% CI = 37.9% to 49.7%) and for women with mutations in exons 12–24 was 75.9% (95% CI = 68.5% to 83.3%). We also compared the risk associated with either Ashkenazi Jewish founder mutation to other mutations in the same portions of the BRCA1 gene and found no statistically significant differences between the two risks. However, when we examined the lifetime risk of ovarian cancer, we found a statistically significantly lower lifetime ovarian cancer risk in carriers of the 185delAG mutation as compared with the 5382insC mutation ($P<.05$), consistent with the genotype–phenotype association seen in the overall analysis when we compared ovarian cancer risk for carriers of mutations in exons 1–11 compared with carriers of mutations in exons 12–24 (Fig. 3).

Discussion

Cancer risk estimates for BRCA1 mutation carriers are specific to population ascertainment. We have estimated cancer risk for mutation carriers in a risk evaluation program with the idea that these estimates may be the most relevant for advising patients in this setting on medical and surgical management. It is not surprising that the cumulative age-adjusted risk of breast cancer in these clinic-based populations (77%) was intermediate between the 85% risk estimated by the BCLC *(4,14)* and the 56% risk estimated in Ashkenazi Jewish volunteers *(6)* (Table 3, Fig. 4). The clinic-based risk estimates derive from individuals cognizant of increased and early cancer incidence in their family, but few of these families are as striking as those required for linkage analysis.

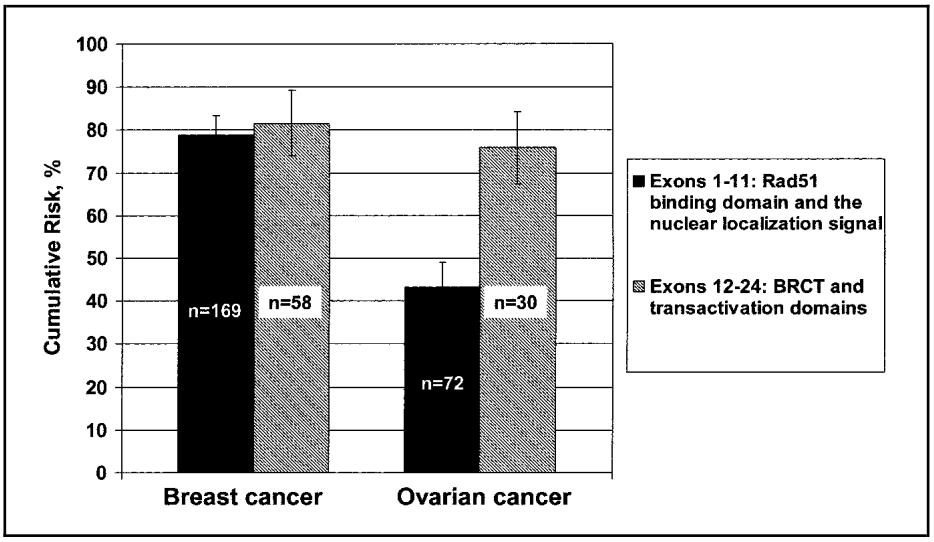

Fig. 3. Breast and ovarian cancer risk by mutation location. Cumulative age-adjusted risk of breast and ovarian cancer by mutation location is shown with 95% confidence intervals (**error bars**). Numbers of individuals included in the analysis are as noted. n = number of affected individuals in each group; BRCT = BRCA1 carboxyl terminus.

Table 3. Summary of selected previous studies of breast and ovarian cancer risk estimates in BRCA1 mutation carriers

Previous studies	Population	Penetrance, %*	
		Breast cancer	Ovarian cancer
Easton et al. *(4)*	Thirty-three families selected for having at least four cases of breast or ovarian cancer diagnosed before age 60 and with evidence of linkage to BRCA1	85	63
Struewing et al. *(6)*	First-degree relatives of 61 BRCA1 mutation carriers identified from 5318 volunteer Ashkenazi Jewish subjects	56 (95% CI ≈ 26 to 85) (data not shown)	16†
Fodor et al. *(8)*	Eight BRCA1 185delAG mutation carriers identified from 268 Ashkenazi Jewish women with breast cancer	36 (95% CI = 18 to 72)†	N/A
Hopper et al. *(7)*	First- and second-degree relatives of nine BRCA1 and nine BRCA2 mutation carriers identified from 388 women diagnosed with breast cancer before age 40	40 (95% CI = 27 to 53)‡	N/A

*Risk to age 70; 95% confidence intervals (CIs) shown in parentheses, if available. N/A = not applicable.
†Penetrance was calculated by using the BRCA1 mutation carrier frequency in an Ashkenazi Jewish population referred for prenatal testing.
‡For BRCA1 and BRCA2 combined.

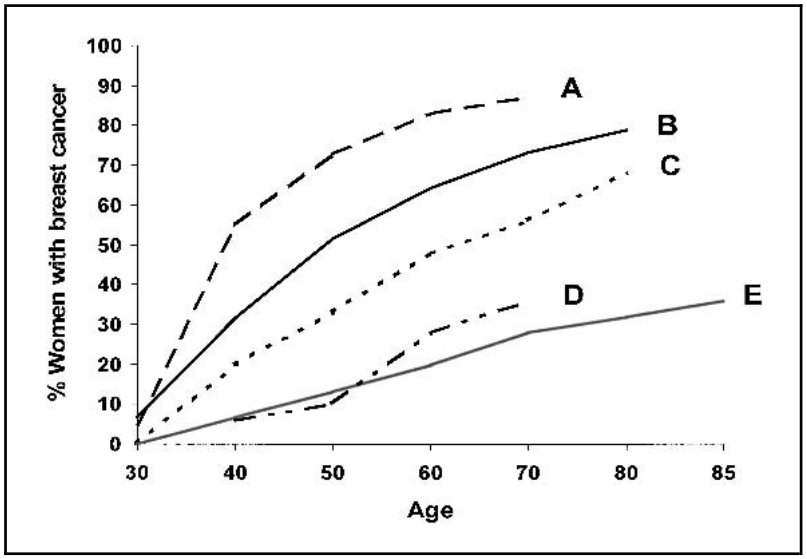

Fig. 4. Estimates of breast cancer risk in a clinic-based ascertainment of BRCA1 mutation carriers. Cumulative risk of cancer to age 70 derived from several studies shows the difference in breast cancer estimates available for BRCA1 mutation carriers depending on ascertainment. **A**) Easton et al. *(4)*, all mutations, linkage families; **B**) Brose et al. (current study), all mutations, risk evaluation clinic families; **C**) Struewing et al. *(6)*, 185delAG, 5382insC, Ashkenazi Jewish volunteers; **D**) Hopper et al. *(8)*, selected mutations, consecutive breast cancer cases; **E**) Fodor et al. *(7)*, 185delAG, 5382insC, consecutive breast cancer cases.

Several features of the study design must be considered when interpreting these estimates. By including presumed and tested carriers, and not systematically including all affected individuals, we minimize bias due to preferential inclusion of tested individuals. However, a bias toward individuals with cancer is an attribute of the clinic population, because both personal and family cancer histories motivate participants to seek cancer risk assessment. This is a particular concern in evaluating risk of other cancers, if increased cancer prevalence other than breast and ovarian cancer is a reason for referral. Our data on reason for referral (self or physician), however, suggest that concerns about cancers other than breast or ovary are raised by less than 5% of our clinic population. Data are not available on how many of the families concerned about other cancers were included in this analysis, but given the low prevalence of those cancers and the low percentage of referrals with other cancers as a concern, it seems unlikely that such families constitute an important bias to estimating other cancer risk. It also is important to consider that this study was performed using a clinic population specifically to provide the most relevant cancer risk estimates to families being evaluated in that setting, rendering "bias" a relative term.

In addition, we calculated age-adjusted risk of cancer by decade to account for the lower numbers of older individuals in the study. This deficit is presumably due to decreased survival in cancer-prone families, the lack of testing availability during most of the older individuals' lives, and our inability to assign them as presumed carriers, given limited information on the preceding generation. Finally, consideration of prophylactic surgery was not included in this analysis. Prophylactic oophorectomy decreases the risk of breast cancer in BRCA1 mutation carriers by approximately 50% *(15)*; therefore, adjusting for oophorectomy would result in higher breast cancer risk than we have reported here.

Another source of bias in our ascertainment and study design is the potential for differential data on affected and unaffected individuals within a family, because family members may be more likely to recall information on individuals with cancer. In this study, exact age at diagnosis was the minimal amount of information required to consider a family report of cancer credible. Thus, if age at diagnosis was not available, an individual was included in the analysis but considered unaffected. However, because we could not evaluate age-adjusted risk if current age or age of death was unavailable, individuals without these data were excluded from the analysis. These criteria are expected to have offsetting effects—we may have considered some affected individuals as unaffected, biasing the results toward lower cancer risk estimates, and excluded some individuals who

may have a lower likelihood of being affected, biasing the results toward higher risk estimates.

As with breast cancer, ovarian cancer risk estimates in this study (40.7%) were intermediate between those derived from families selected for one or more cases of ovarian cancer [63% *(4)*] and from a volunteer population [16% *(6)*]. However, BRCA1 mutation carriers identified from sequential Ashkenazi Jewish breast cancer cases *(16)* and the BCLC study families *(14)* have estimated ovarian cancer risks of 46% and 44%, respectively. The similarity of ovarian cancer risk estimates in these studies and the current study suggests that genetic and environmental modifying factors may be more important for breast cancer than for ovarian cancer, making ovarian cancer risk estimates less variable. Again, our estimates may be slightly lower than the true risk of ovarian cancer in our population because we have not corrected for prophylactic oophorectomy, which is our current recommendation for all women with a BRCA1 mutation after completion of childbearing.

Although male breast cancer is widely associated with BRCA2 mutations *(4)*, the breast cancer risk in men with BRCA1 mutations is often overlooked. A study of 237 families with four or more breast cancers found that 20 (77%) of 26 male breast cancer cases were due to BRCA2 mutations, but just five (19%) were due to BRCA1 mutations *(5)*. The cumulative age-adjusted risk of breast cancer in male BRCA1 mutation carriers in the current study represents a 53-fold increase in risk compared with population rates. Because of relatively small numbers (four of 102 male BRCA1 mutation carriers), the CI is wide, but even the lower 95% CI boundary represents a 10-fold increase over the estimated population risk. The cumulative age-adjusted risk of prostate cancer was not elevated in male BRCA1 mutation carriers in this study; however, the average age of male BRCA1 mutation carriers was 62. Given the average age of prostate cancer diagnosis of 70 years in the general population *(13)*, modest changes in cumulative age-adjusted prostate cancer risk would be unlikely to be detected in this study.

Colon, pancreatic, and gastric cancer were found to occur more frequently in this study of a clinic-based sample than in the general population. Colon cancer risk in BRCA1 mutation carriers has varied between studies, with BCLC data *(14)* suggesting a fourfold increase, whereas other studies *(6)* report no increase over general population risk. The cumulative age-adjusted risk of colorectal cancer in the current study was a moderate but statistically significant twofold increase in risk ($P<.05$). We also estimate a threefold increase in pancreatic cancer risk and a fourfold increase in gastric cancer risk. Only one previous study of BRCA1 mutation carriers from Sweden *(17)* reported an increased risk of gastric cancer in BRCA1 mutation carriers (almost a sixfold increase). Moreover, a series of gastric cancer patients diagnosed before age 35 documented allelic loss flanking BRCA1 in 12 of 27 cases (44%) *(18)*, suggesting a possible mechanistic link between BRCA1 and the development of gastric cancer. Pancreatic cancer has not been noted in previous studies in association with BRCA1 mutations.

We estimate a 120-fold increase in risk for fallopian tube cancer in BRCA1 mutation carriers, based on an estimated incidence in the population of 0.025%. Several case reports *(19–22)* suggest an association between fallopian tube carcinoma and BRCA1 mutations, but ours is the first large study to provide evidence of such an association. Even when using the lower bound of the 95% CI as a conservative estimate, risk of fallopian tube cancer in BRCA1 mutation carriers is 48 times that of the general population. These data strongly support our recommendation that both fallopian tubes should be removed during prophylactic oophorectomy.

Results from genotype–phenotype association studies in BRCA1 mutation carriers are inconsistent. Small differences in cancer risks between mutation locations have been seen in other studies *(23,24)*, but the current study did not show variation in risk of breast cancer by mutation location within the gene, possibly because a larger sample size is needed. Our results do suggest an association between increased ovarian cancer risk and mutations in the 3′ region of BRCA1, which encodes the BRCA1 carboxyl terminus (BRCT) motifs and is required for transcriptional co-activation of p53-dependent promoters *(25)*. However, previous studies *(23,26,27)* have suggested that mutations in the 5′ region of BRCA1 were associated with a higher risk of ovarian cancer. A recent study of incident ovarian cancer cases tested for germline BRCA1 mutations suggested a consistent risk of ovarian cancer association with mutations throughout BRCA1 but an increased risk of breast cancer associated with mutations in the 3′ region of BRCA1 *(24)*. Finally, the largest study to date, by the BCLC *(28)*, suggests an increased risk of ovarian cancer and a decreased risk of breast cancer associated with mutations in the central region of BRCA1 (predominantly exon 11). However, in the BCLC study, ovarian cancers that occurred after the age of 70 were excluded, whereas in our analysis, these cancers contributed to the higher risk of ovarian cancer associated with mutations in the C-terminal region.

Despite the statistical significance of the increased ovarian cancer risk associated with mutations in the 3′ region noted in the current study, in the absence of consistent results from multiple studies, it is difficult to definitively assign differential ovarian cancer risk to any specific gene region. From a clinical perspective, the most conservative approach is to counsel all BRCA1 mutation carriers to undergo prophylactic oophorectomy after completion of childbearing because all estimates of increased risk are greatly in excess of population risks regardless of mutation position, and effective surveillance for ovarian cancer does not exist.

In summary, we have presented estimates for breast and ovarian cancer risk for BRCA1 mutation carriers from a cancer risk evaluation program in North America. These estimates are statistically significantly higher than most population-based estimates ($P<.05$) but lower than early estimates based on families ascertained for linkage studies. In addition, these data support an increased risk of colon, gastric, male breast, and fallopian tube cancer in BRCA1 mutation carriers and provide the first evidence of an increased risk for pancreatic cancer. In this population of BRCA1 mutation carriers, the risk of breast cancer does not vary by mutation location, although, in contrast to previous reports, we report an increase in ovarian cancer risk associated with mutations in the 3′ region of BRCA1. We believe that these data may provide the most relevant cancer risk estimates to date for use in advising women who have undergone genetic testing for BRCA1 mutations in cancer risk evaluation clinics in the United States.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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