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THE RISK OF CANCER ASSOCIATED WITH SPECIFIC MUTATIONS OF *BRCA1* AND *BRCA2* AMONG ASHKENAZI JEWS

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ABSTRACT

Background Carriers of germ-line mutations in *BRCA1* and *BRCA2* from families at high risk for cancer have been estimated to have an 85 percent risk of breast cancer. Since the combined frequency of *BRCA1* and *BRCA2* mutations exceeds 2 percent among Ashkenazi Jews, we were able to estimate the risk of cancer in a large group of Jewish men and women from the Washington, D.C., area.

Methods We collected blood samples from 5318 Jewish subjects who had filled out epidemiologic questionnaires. Carriers of the 185delAG and 5382insC mutations in *BRCA1* and the 6174delT mutation in *BRCA2* were identified with assays based on the polymerase chain reaction. We estimated the risks of breast and other cancers by comparing the cancer histories of relatives of carriers of the mutations and noncarriers.

Results One hundred twenty carriers of a *BRCA1* or *BRCA2* mutation were identified. By the age of 70, the estimated risk of breast cancer among carriers was 56 percent (95 percent confidence interval, 40 to 73 percent); of ovarian cancer, 16 percent (95 percent confidence interval, 6 to 28 percent); and of prostate cancer, 16 percent (95 percent confidence interval, 4 to 30 percent). There were no significant differences in the risk of breast cancer between carriers of *BRCA1* mutations and carriers of *BRCA2* mutations, and the incidence of colon cancer among the relatives of carriers was not elevated.

Conclusions Over 2 percent of Ashkenazi Jews carry mutations in *BRCA1* or *BRCA2* that confer increased risks of breast, ovarian, and prostate cancer. The risks of breast cancer may be overestimated, but they fall well below previous estimates based on subjects from high-risk families. (N Engl J Med 1997; 336:1401-8.)

CURRENT estimates of the risk of breast cancer in a woman who carries a *BRCA1* or *BRCA2* mutation and is from a kindred with multiple cases of breast or ovarian cancer, or both, range from 76 to 87 percent.[1-4] Estimates of the risk of ovarian cancer in a woman from such a kindred range from 32 to 84 percent for carriers of *BRCA1* mutations but are much lower for carriers of *BRCA2* mutations.[2-4] These results were derived from studies of high-risk families and may not apply to all carriers of *BRCA1* or *BRCA2* mutations.

The large size of the *BRCA1* and *BRCA2* genes, the dispersed locations of the more than 140 mutations identified thus far,[5-7] and the lack of functional assays hamper the direct estimation of carrier frequencies and cancer risks in the general population. However, characteristic *BRCA1* and *BRCA2* mutations have been identified in Ashkenazi Jews, a genetically distinct population of Jews whose ancestors lived in central and eastern Europe.[8-12] The combined frequency of the mutations in *BRCA1* involving the deletion of an adenine and guanine (185delAG) and the insertion of a cytosine (5382insC) and the mutation in *BRCA2* involving the deletion of a thymine (6174delT) exceeds 2 percent.[13-15] Thus, within this group, relatively simple assays can identify enough carriers to estimate the risk of cancer in the general population.

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METHODS

Recruitment of Subjects

Jewish men and women over the age of 20 were recruited from the Washington, D.C., area through posters, newspapers, and radio announcements in the general and Jewish media. Steering and advisory committees composed of members of Jewish organizations, breast-cancer advocacy groups, and medical groups reviewed the protocol, consent form, and recruitment procedures. The participants did not receive their individual test results. The study was approved by an institutional review board of the National Institutes of Health.

Collection of Data

The subjects were enrolled at 15 sites over a nine-week period. After giving informed consent, the participants completed a self-administered questionnaire and gave a blood sample. The questionnaire included questions on the country of origin of the subjects' parents and grandparents; the age, vital status, and cancer history of first-degree relatives, grandparents, and half-siblings; and the numbers and selected cancer history of aunts and uncles. Participants were also asked to list relatives who had volunteered or might volunteer for the study. We created family sets using family-history data and information about other relatives who had volunteered. A total of 4873 sets were created: 326 from 771 related subjects and 4547 from subjects with no participating relatives. After the family sets were created, links between the participants' names and assigned study numbers were destroyed.

Laboratory Methods

A description of the laboratory methods used is available through the National Auxiliary Publications Service (NAPS) and the Breast Cancer Information Core site (<http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/>).*

Phlebotomists used finger-stick procedures to collect 100 to 150 μl of blood from each subject, which was then transferred onto collection cards (Isocode, Schleicher and Scheull, Keene, N.H.). DNA was isolated from two 3-mm punches of a blood spot in 96-well trays according to the manufacturer's instructions with a slight modification. Allele-specific oligonucleotide assays were used to detect two mutations in *BRCA1:* 185delAG and the deletion of 11 bp at position 188 (188del11). Allele-specific polymerase-chain-reaction (PCR) assays were used to identify the 5382insC mutation in *BRCA1* and the 6174delT mutation in *BRCA2*.[16] For each mutation, genomic DNA from a person known to be heterozygous for that mutation was included in 96-well PCR trays for each assay.

A second round of isolation of DNA and assays was performed on all samples initially scored as positive and on at least 250 samples initially scored as negative. There were no false negative results and three (2.4 percent) false positive results (two involving 185delAG and one involving 6174delT). Only samples that were positive on retesting were considered positive in the statistical analyses.

Statistical Analysis

Carrier frequencies and exact binomial 95 percent confidence intervals were calculated for the entire group and for subgroups categorized according to the age at diagnosis and family history.

To estimate the risks of breast, ovarian, and prostate cancer among carriers of *BRCA1* and *BRCA2* mutations, we compared the history of cancer among the set of 306 female and 273 male first-degree relatives identified by participants who were found to be carriers with the history among 13,018 female and 13,324 male first-degree relatives identified by participants who were not carriers. If two or more family members volunteered for the study, we selected one to define the carrier status of the family and the set of first-degree relatives, so that no relative was included more than once and the number of informative person-years was maximized. For example, if one of two sibling volunteers carried a mutation, the mother was counted only once, as a first-degree relative of a carrier. The participants' self-reports of cancer were not considered in the risk calculations.

The probability of disease among the first-degree relatives of carriers of a mutation (R_+) can be expressed as

$$R_+ = (p/2 + 1/2)S_1 + (1/2 - p/2)S_0.$$

The probability of disease among the first-degree relatives of noncarriers (R_-) can be expressed as

$$R_- = pS_1 + (1 - p)S_0.$$

In these equations p is the frequency of the mutant allele, S_1 the risk of disease among carriers (penetrance), and S_0 the risk of disease among noncarriers. By solving two equations in two unknowns, S_1 and S_0 can be expressed as functions of what we observed:

$$S_1 = 2R_+ - R_-$$

and

$$S_0 = \frac{1+p}{1-p} R_- - 2\,\frac{p}{1-p} R_+.$$

R_+ and R_- were estimated with Kaplan–Meier curves. Although true cumulative risks cannot decrease with age, our estimates can do so because they represent the difference between two cumulative risks. We used a bootstrap method to estimate the variance of the risk estimates. The reported 95 percent confidence intervals for the risk of cancer are the 25th and 975th ordered values from 1000 random samplings of the data (with replacement), with the family as the unit. We also calculated the risk of breast cancer with various groups of participants excluded: survivors of breast and ovarian cancer, female subjects, and those under the age of 50. To explore the risk of cancers other than breast, ovarian, and prostate cancer, we compared the proportions of carrier and noncarrier families in which at least one case of cancer was reported, using the chi-square test.

RESULTS

Of the 5331 persons who completed the questionnaire and provided a blood sample, 7 were excluded because they were adopted and 6 were excluded for other reasons. Of the remaining 5318 participants, all were genotyped for the 5382insC and 185delAG mutations in *BRCA1;* 5087 gave permission for the future use of their samples, which were analyzed for the 6174delT mutation in *BRCA2;* and 1000 samples were arbitrarily chosen to be assayed for the 188del11 mutation in *BRCA1.* Forty-six percent of the subjects were under the age of 50, and nearly 30 percent were men (Table 1). The participants were highly educated, with over 57 percent reporting a postgraduate degree.

Mutations were found in 120 participants (Table 2). Of these, 61 had *BRCA1* mutations (185delAG in 41 and 5382insC in 20) and 59 had the 6174delT mutation in *BRCA2.* No 188del11 mutations in

*See NAPS document no. 05401 for 5 pages of supplementary material. Order from NAPS, c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) $11.65 for photocopies or $5 for microfiche. Outside the U.S., add postage of $4.50 for up to 20 pages, $5.50 for over 20 pages, or $1.50 for microfiche. There is a $15 invoicing charge on all orders filled before payment.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE SUBJECTS.*

CHARACTERISTIC	NO. OF SUBJECTS (%) (N=5318)
Age (yr)	
21–29	263 (4.9)
30–39	658 (12.4)
40–49	1542 (29.0)
50–59	1293 (24.3)
60–69	767 (14.4)
70–79	593 (11.2)
≥80	196 (3.7)
Unknown	6 (0.1)
Sex	
Female	3742 (70.4)
Male	1576 (29.6)
U.S. native	4947 (93.0)
Married or living as married	4064 (76.4)
Received postgraduate degree	3066 (57.7)
Relative of another subject	771 (14.5)
Personal or family (first-degree relative) history of breast cancer	
Neither	4064 (76.4)
Personal history only	202 (3.8)
Family history only	966 (18.2)
Both	86 (1.6)

*The subjects had a mean of 2.7 female first-degree relatives and 2.7 male first-degree relatives.

BRCA1 were detected in the 1000 arbitrarily chosen samples that were tested. No participant carried more than one of the three mutations, and no subjects were identified who were homozygous for the 185delAG mutation. The methods of detection we used could not rule out homozygosity for the 5382insC and 6174delT mutations. Younger age at diagnosis among survivors of breast or ovarian cancer and a family history of breast cancer in first-degree relatives were associated with higher carrier frequencies (Table 2).

Figure 1A shows the Kaplan–Meier estimates of the reported incidence of breast cancer among first-degree female relatives of the subjects. From these data the risk of cancer and 95 percent confidence interval were estimated for all carriers combined (Fig. 1B) and for carriers according to the mutation identified (Fig. 1C). The estimated risk of breast cancer at the age of 50 among carriers was 33 percent (95 percent confidence interval, 23 to 44 percent), as compared with 4.5 percent (95 percent confidence interval, 4.0 to 5.0 percent) among noncarriers. The estimated risks among carriers and noncarriers at the age of 70 were 56 percent (95 percent confidence interval, 40 to 73 percent) and 13 percent (95 percent confidence interval, 12 to 14 percent), respectively.

TABLE 2. CARRIER FREQUENCIES FOR *BRCA1* OR *BRCA2* MUTATIONS AMONG THE SUBJECTS.*

GROUP	NO. TESTED	MUTATION			
		185delAG	5382insC	6174delT†	TOTAL‡
		no. (%) with mutation			
Female survivors of breast or ovarian cancer	302	10 (3.3)	6 (2.0)	11 (3.6)	27 (8.9 [6.0–12.7])
Age at diagnosis <50 yr§	143	7 (4.9)	5 (3.5)	8 (5.6)	20 (14)
Age at diagnosis ≥50 yr	153	3 (2.0)	1 (0.7)	3 (2.0)	7 (4.6)
Women with no prior history of breast or ovarian cancer	3440	21 (0.6)	11 (0.3)	30 (0.9)	62 (1.8 [1.4–2.3])
First-degree relative with breast or ovarian cancer					
Yes	786	13 (1.7)	8 (1.0)	9 (1.1)	30 (3.8)
No	2648	8 (0.3)	3 (0.1)	21 (0.8)	32 (1.2)
Men	1576	10 (0.6)	3 (0.2)	18 (1.2)	31 (2.0 [1.3–2.8])
First-degree relative with breast or ovarian cancer					
Yes	275	4 (1.5)	2 (0.7)	8 (2.9)	14 (5.1)
No	1301	6 (0.5)	1 (0.1)	10 (0.8)	17 (1.3)
Total	5318	41 (0.8 [0.6–1.0])¶	20 (0.4 [0.2–0.6])	59 (1.2 [0.9–1.5])‖	120 (2.3 [1.9–2.7])

*Values in brackets are 95 percent confidence intervals.

†A total of 295 survivors of breast or ovarian cancer, 3273 women with no prior history of breast or ovarian cancer, and 1519 men were tested for the 6174delT mutation.

‡These rates were calculated by including the entire sample in the denominators, ignoring the possibility of 6174delT carriers among those not tested for this mutation.

§Six subjects whose age at diagnosis was unknown were excluded.

¶Two of the subjects in this group were related to each other.

‖Five of the subjects in this group were related to one another.

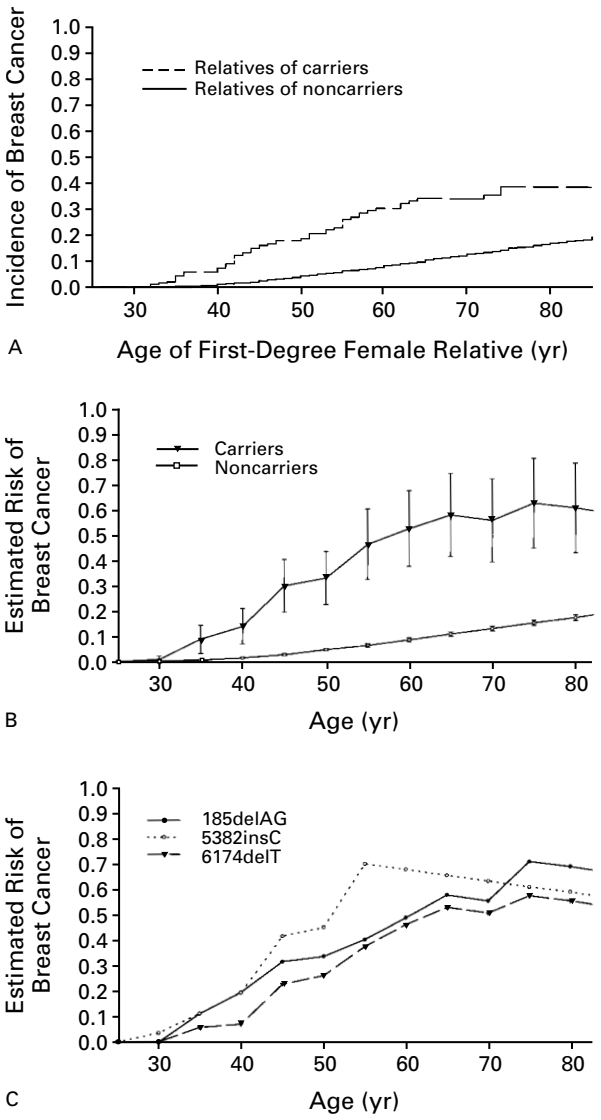

Figure 1. Kaplan–Meier Estimates of the Incidence or Risk of Breast Cancer.

Panel A shows the reported incidence of breast cancer among first-degree female relatives of subjects who carried a *BRCA1* or *BRCA2* mutation and those of subjects who did not. Panel B shows the estimated risk of breast cancer and 95 percent confidence intervals among carriers and noncarriers of a *BRCA1* or *BRCA2* mutation. The difference in risk between the two groups was statistically significant by the age of 35. Panel C shows the estimated risk of breast cancer among carriers of each of the three mutations. The 95 percent confidence intervals are not shown but are about 50 percent wider than the upper curve in Panel B and are widely overlapping.

Excluding the family-history information of subjects who were survivors of breast or ovarian cancer lowered the risk estimate at the age of 70 to 54 percent; excluding all female subjects reduced it to 43 percent; and excluding all subjects under the age of 50 lowered it to 42 percent.

The risk of ovarian cancer was also significantly elevated among carriers of *BRCA1* or *BRCA2* mutations (Fig. 2A). The estimated risk was 7 percent (95 percent confidence interval, 2 to 14 percent) by the age of 50 and 16 percent (95 percent confidence interval, 6 to 28 percent) by the age of 70. Among noncarriers the risk of ovarian cancer was 0.4 percent (95 percent confidence interval, 0.2 to 0.6 percent) by the age of 50 and 1.6 percent (95 percent confidence interval, 1.2 to 2.0 percent) by the age of 70. The estimated risk by the age of 70 was higher among carriers of the 5382insC mutation (22 percent) than among those with the 6174delT mutation (18 percent) or the 185delAG mutation (12 percent), but the differences between groups were not statistically significant (Fig. 2B).

The estimated risk of prostate cancer among carriers of a *BRCA1* or *BRCA2* mutation was low before the age of 50, but it was 16 percent (95 percent confidence interval, 4 to 30 percent) at the age of 70, as compared with 3.8 percent (95 percent confidence interval, 3.3 to 4.4 percent) among noncarriers (Fig. 3A). The risk among carriers of *BRCA1* mutations (25 percent) was higher than that among carriers of the *BRCA2* mutation (5 percent) at the age of 70, but the difference was smaller by the age of 80 (Fig. 3B).

Colon cancer was reported less frequently among the families of subjects who had a *BRCA1* or *BRCA2* mutation than among the families of noncarriers (Table 3). Of 16 subjects who reported having a male relative with breast cancer, 1 carried the 6174delT mutation. A comparison of the rates of all cancers (except nonmelanoma skin cancer) reported in families with two or more carriers is shown in Table 3.

Of the 120 subjects who carried a *BRCA1* or *BRCA2* mutation, 31 did not report a family history of breast or ovarian cancer among first- or second-degree relatives. Among the subjects and their first-degree relatives, there were an average of 3.3 women in the families without a history of breast or ovarian cancer, as compared with 3.7 in the families with such a history. Among carriers with no family history of breast or ovarian cancer in a first-degree relative, 18 percent had three or more first-degree female relatives over the age of 40.

DISCUSSION

From these studies of Jewish subjects, we estimate that the risk of breast cancer among carriers of one of three *BRCA1* and *BRCA2* mutations is 33 percent by the age of 50 and 56 percent by the age of

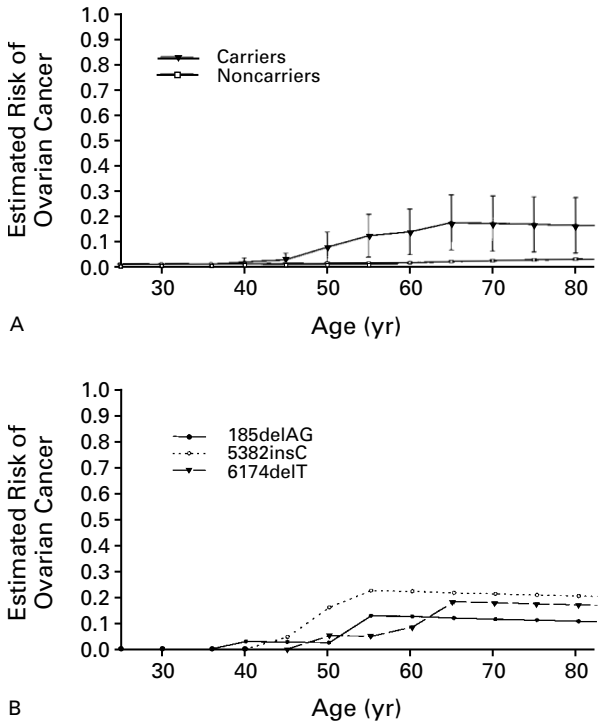

Figure 2. Estimates of the Risk of Ovarian Cancer.

Panel A shows the estimated risk of ovarian cancer and 95 percent confidence intervals among carriers and noncarriers of *BRCA1* or *BRCA2* mutations. The differences were statistically significant by the age of 45. Panel B shows the estimated risk of ovarian cancer among carriers of each mutation. Although not shown, the 95 percent confidence intervals are widely overlapping.

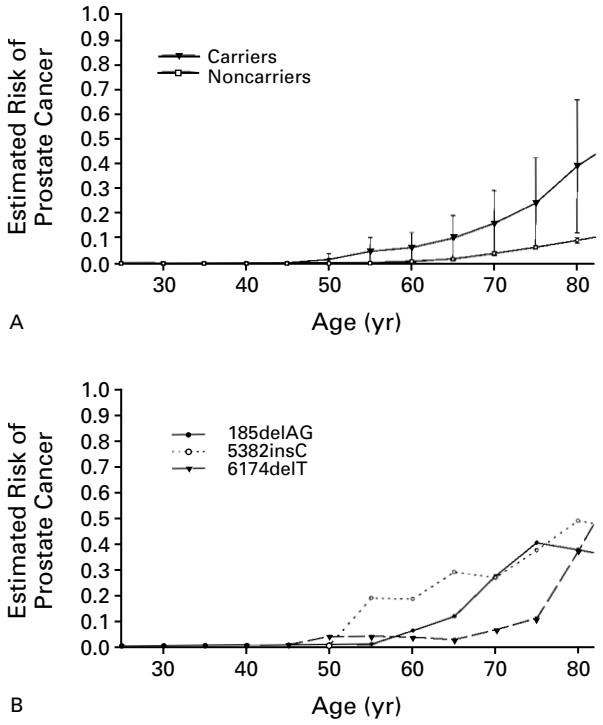

Figure 3. Estimates of the Risk of Prostate Cancer.

Panel A shows the estimated risk of prostate cancer and 95 percent confidence intervals among carriers and noncarriers of *BRCA1* or *BRCA2* mutations. The differences were statistically significant by the age of 67. Panel B shows the estimated risk of prostate cancer among carriers of each mutation. Although not shown, the 95 percent confidence intervals are widely overlapping.

70 (95 percent confidence interval, 40 to 73 percent). These estimates fall well below most prior estimates of the risk of cancer among carriers of *BRCA1* or *BRCA2* mutations from families with breast cancer, but they concern particular *BRCA1* and *BRCA2* mutations and may not apply to carriers of other mutations. The estimated risk among carriers of the 6174delT mutation in *BRCA2* was slightly lower than that among carriers of the 185delAG mutation in *BRCA1,* and this difference was more pronounced up to the age of 50 (26 percent vs. 34 percent). Previous analyses of small series of Jewish women with early-onset breast cancer suggested that the risk of early-onset disease was much lower among those with the 6174delT mutation than among those with the 185delAG mutation.[11,14,15,17] Our results suggest that the difference, if real, is small and decreases in later life, underscoring the uncertainties inherent in the early stages of this research. The apparent risk of cancer was the highest among carriers of the 5382insC mutation in *BRCA1,* but it was based on small numbers and the differences in risk associated with the three mutations were not statistically significant.

The estimated risk of ovarian cancer, based on small numbers, was 16 percent by the age of 70 among carriers of a mutation. Surprisingly, the estimated risks were highest among carriers of 5382insC, lowest among carriers of 185delAG, and intermediate among those with the 6174delT mutation in *BRCA2.* Earlier data suggested that the risk of ovarian cancer was higher for *BRCA1* than for *BRCA2* mutations[3] and higher for mutations in the 5′ end of *BRCA1.*[18] The 6174delT mutation is within a portion of the *BRCA2* gene that may be associated with a high risk of ovarian cancer.[19] Studies of larger series may clarify the relative risk of ovarian cancer for different mutations in *BRCA1* and *BRCA2.*

We found a significantly elevated estimated risk of prostate cancer among carriers of *BRCA1* or *BRCA2* mutations. This suggests that prostate cancer is part of the phenotype for these carriers and supports previous observations.[2,20,21] The risk was higher among carriers of *BRCA1* mutations, but the

TABLE 3. PERCENTAGES OF CARRIERS AND NONCARRIERS OF *BRCA1* OR *BRCA2* MUTATIONS WITH A FAMILY HISTORY OF SELECTED CANCERS.*

HISTORY OF CANCER IN FIRST-DEGREE RELATIVES†	185delAG (N=40)	5382insC (N=20)	6174delT (N=54)	ANY MUTATION (N=114)	NONCARRIERS (N=4759)‡
			number (percent)		
Breast cancer (female relative)	18 (45)§	12 (60)§	21 (39)§	51 (45)§	937 (20)
Ovarian cancer	3 (8)¶	3 (15)§	5 (9)§	11 (10)§	118 (2)
Prostate cancer	5 (12)	5 (25)§	6 (11)	16 (14)§	364 (8)
Lung cancer	3 (8)	0	8 (15)¶	11 (10)	337 (7)
Colon cancer	2 (5)	1 (5)	6 (11)	9 (8)	509 (11)
Pancreatic cancer	2 (5)	1 (5)	4 (7)	7 (6)	146 (3)
Lymphoma	2 (5)	1 (5)	3 (6)	6 (5)	147 (3)
Uterine cancer	1 (2)	1 (5)	2 (4)	4 (4)	108 (2)
Multiple myeloma	1 (2)	1 (5)¶	2 (4)¶	4 (4)§	36 (1)
Thyroid cancer	1 (2)	1 (5)	2 (4)	4 (4)	70 (1)
Leukemia	0	1 (5)	2 (4)	3 (3)	161 (3)
Kidney cancer	1 (2)	0	2 (4)	3 (3)	91 (2)
Hodgkin's disease	0	0	3 (6)§	3 (3)	43 (1)
Stomach cancer	2 (5)	1 (5)	0	3 (3)	125 (3)
Bladder cancer	1 (2)	0	1 (2)	2 (2)	106 (2)
History of any cancer	32 (80)§	18 (90)§	43 (80)§	93 (82)§	2915 (61)

*Only cancers reported by two or more carriers were included in the analysis.

†If more than one type of cancer was reported in a relative, each is shown.

‡This is the reference group for chi-square comparisons of the prevalence ratio.

§$P<0.01$ for the comparison with the noncarriers.

¶$P<0.05$ for the comparison with the noncarriers.

estimates for each mutation rose considerably after the age of 60, reaching 16 percent by the age of 70 and 39 percent by the age of 80. A previous study[2] showed a higher-than-normal incidence of colon cancer among carriers of *BRCA1* mutations, but we did not find that in this study. Very few subjects reported having male relatives with breast cancer, and the only carrier reporting having such relatives had the 6174delT mutation in *BRCA2*, which has previously been associated with male breast cancer.[3,12,21,22]

A family history of several rare cancers in first-degree relatives was reported more frequently among subjects with mutations than among those with no identified mutations. Both pancreatic cancer and lymphoma were reported about twice as frequently in the former group, but the differences between groups were not significant. Multiple myeloma was reported more frequently among the families of carriers, and Hodgkin's disease and lung cancer were more common among families with carriers of the 6174delT mutation. Although based on small numbers, these associations point to cancers that may warrant further investigation with respect to *BRCA1* and *BRCA2*.

In our study population, 2.3 percent were carriers of a *BRCA1* or *BRCA2* mutation, a rate that is very close to previous results in studies of Ashkenazi Jews.[13-15] We analyzed 1000 samples and did not detect 188del11, a *BRCA1* mutation found to be common in one study[23] but not in other studies[4,7,11,24,25] of this ethnic group. Subjects with a family history of breast or ovarian cancer were more likely to have a mutation, but 31 carriers did not report a history of breast or ovarian cancer among first- or second-degree relatives. A few such persons would be expected because, especially in small families, by chance there may be no female carriers.

Small family size does not entirely explain the absence of a family history of breast and ovarian cancer among carriers of a *BRCA1* or *BRCA2* mutation, however, because 18 percent of the carriers with no family history of breast or ovarian cancer had three or more first-degree female relatives over the age of 40. The observations in this and other studies[11,24,26] of carriers without a family history of breast cancer contrast with the estimated risk of breast cancer of approximately 85 percent among high-risk pedigrees, suggesting that there may be considerable variability in the risk of cancer among carriers. This variation may be due to chance, to genetic and environmental modifying factors, or to both. The study of families with an apparently low risk of can-

cer may help elucidate such modifiers, allowing more refined estimates of an individual person's risk of cancer.

The most important limitation of our study is the disproportionate number of subjects who reported a family history of breast cancer and, to a lesser degree, of other cancers. This bias would tend to inflate the estimates of the risk of cancer for both carriers and noncarriers. Our estimated risks would be unbiased if the study subjects had the same frequency of a family history of cancer as nonparticipants. Because the frequency of a family history of cancer in our subjects is probably higher than that in nonparticipants, our estimates are likely to be higher than those for the total Jewish population. Among women with no prior history of breast or ovarian cancer, 19 percent of those who were under the age of 50 and 23 percent of those who were 50 or older reported having a first-degree relative with breast cancer, as did 16 percent of the men in the study. These rates are almost twice the rates for control Jewish women in two small case–control studies[27,28] (and Brinton L: personal communication) and are considerably higher than those from a recent study in which the reported rate of a family history of breast cancer seemed especially low.[29] The subjects' reports of a history of familial cancer were not verified in our study or in these other studies.[27-29] As compared with the rates of cancer among whites from population-based Surveillance, Epidemiology, and End Results registries,[30] our risk estimates for noncarriers were 68 percent higher for breast cancer, 48 percent higher for ovarian cancer, and 5 percent higher for prostate cancer.

Precisely how much the bias introduced by the use of volunteers inflated our risk estimates as they apply to the entire Jewish population is unknown, but analysis of subgroups of the data in which the bias is less pronounced indicates the potential magnitude of the effect. At the age of 70, the risk of breast cancer was 56 percent among all subjects, 54 percent after the exclusion of women who had survived breast or ovarian cancer, 43 percent after the exclusion of female subjects, and 42 percent when subjects under the age of 50 were excluded. These analyses suggest that the true risk of breast cancer may be 50 percent or lower, an estimate that is both quantitatively and qualitatively lower than most prior estimates.

All the subjects came from a limited geographic region where the relative frequency of specific mutations may differ from that in other Jewish communities. Also, there may be unknown genetic or environmental factors among the Ashkenazi population that affect the extrapolation of these risk estimates to other populations carrying the same mutations. We screened for only four specific mutations, but there may be other, as yet undetected *BRCA1* or *BRCA2* mutations among Ashkenazi Jews. The analysis of a large number of people with the same mutations is advantageous with regard to allelic homogeneity, but the degree to which our risk estimates apply to carriers of other *BRCA1* and *BRCA2* mutations is unknown. Knowing the country of origin of the subjects' grandparents did not differentiate carriers from noncarriers. Fewer than 50 subjects reported exclusively Sephardic ancestors; but since for many of these subjects the reported countries of origin of all ancestors were in central and eastern Europe, no participants were excluded on the basis of Jewish ethnic group.

This community-based study is a departure from previous investigations of genetic predisposition to cancer in high-risk families. The commitment of the Jewish population allowed us to recruit many volunteers with little or no family history of breast cancer. But the technical ease of identifying large numbers of carriers of a *BRCA1* or *BRCA2* mutation forces us to confront the ethical issues raised by testing for genetic predisposition for cancer, such as the insurability and employability of persons identified as carriers and their relatives and the psychological and social consequences of the test results.[31-34]

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