ARTICLES

Cancer Incidence in BRCA1 Mutation Carriers

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Background: **Germline BRCA1 mutations confer a substantial lifetime risk of breast and ovarian cancer, but whether cancer at other sites is increased is less clear. To evaluate the risks of other cancers in BRCA1 mutation carriers, we conducted a cohort study of 11 847 individuals from 699 families segregating a BRCA1 mutation that were ascertained in 30 centers across Europe and North America.** *Methods:* **The observed cancer incidence was compared with the expected cancer incidence based on population cancer rates. Relative risks (RRs) of each cancer type in BRCA1 carriers relative to risks for the general population were estimated by weighting individuals according to their estimated probability of being a mutation carrier. All statistical tests were two-sided.** *Results:* **BRCA1 mutation carriers were at a statistically significantly increased risk for several cancers, including pancreatic cancer (RR = 2.26, 95% confidence interval [CI] = 1.26 to 4.06, *P* = .004) and cancer of the uterine body and cervix (uterine body RR = 2.65, 95% CI = 1.69 to 4.16, *P*<.001; cervix RR = 3.72, 95% CI = 2.26 to 6.10, *P*<.001). There was some evidence of an elevated risk of prostate cancer in mutation carriers younger than 65 years old (RR = 1.82, 95% CI = 1.01 to 3.29, *P* = .05) but not in those 65 years old or older (RR = 0.84, 95% CI = 0.53 to 1.33, *P* = .45). Overall, increases in the risk for cancer at sites other than the breast or ovary were small and evident in women (RR = 2.30, 95% CI = 1.93 to 2.75, *P* = .001) but not in men (RR = 0.95, 95% CI = 0.81 to 1.12, *P* = .58).** *Conclusions:* **In carriers of BRCA1 mutations, the overall increased risk of cancer at sites other than breast and ovary is small and is observed in women but generally not in men. BRCA1 mutations may confer increased risks of other abdominal cancers in women and increased risks of pancreatic cancer in men and women. [J Natl Cancer Inst 2002;94:1358–65]**

Germline mutations in the BRCA1 gene are associated with elevated risks of breast and ovarian cancer *(1,2)*. The absolute risk of cancer by the age of 70 years conferred by a BRCA1 mutation is reported to be between 45% and 87% for breast cancer and between 36% and 66% for ovarian cancer [e.g., *see (3–7)*]. The extent to which BRCA1 mutation carriers are at an increased risk of other cancers has, however, been less clear.

One study *(3),* based on 33 breast and/or ovarian cancer families in which the disease was linked to the BRCA1 locus, found a statistically significant elevation in the risk of cancers other than breast or ovarian cancer, with particular increases in the risks for prostate cancer and colon cancer. Subsequent studies [e.g., *see (8–10)*] attempted to identify associations with other cancer types or to replicate these results, particularly for prostate cancer, but no consensus has emerged. To provide more precise estimates of the risks of other cancers in BRCA1 carriers, we have performed a much larger study, based on 11 847 individuals in 699 families, ascertained from 30 centers across Europe and North America.

MATERIALS AND METHODS

Seven hundred families were ascertained by members of the Breast Cancer Linkage Consortium (BCLC) from 30 centers in Western Europe and North America. The studies in each participating center were approved by the relevant local institutional review board. Individuals undergoing mutation screening gave written informed consent. The criteria for inclusion in the study were that the family had a history of breast and/or ovarian cancer and that at least one individual was known to carry a pathogenic BRCA1 mutation. A single family segregating two distinct mutations (185delAG and 5382insC) was excluded, leaving 699 families in the analysis. Twenty-five of these 699 families were previously included in the analysis of 33 families by Ford et al. *(3)*. The ethnic origin of the families was not specifically recorded, but the families were all from countries where the majority of the population is Caucasian. The cohort consisted of tested mutation carriers, patients with ovarian cancer, male patients with breast cancer, women diagnosed with breast cancer before the age of 60 years, and first-degree relatives of individuals in any of these categories. The following information was obtained by each center for individuals in the cohort: ages at all cancer diagnoses; code from the International Classification of Diseases (ICD), revision 9 *(11),* and whether or not the diagnosis had been confirmed (by pathologic review, pathologist's report, cancer registry record, clinical record, or death certificate); age at last contact or death; and age at operation for women who had undergone a prophylactic mastectomy or oophorectomy. Wherever possible (and for at least one person per family), date of birth was obtained; dates of birth were estimated from the pedigree structure if this information was missing. For the majority of families, follow-up was until the end of 1999. Individuals born before 1890, or with insufficient follow-up information, were excluded. The cohort contained 7106 women and 4741 men, including 1928 women with breast cancer (and 11 men with breast cancer), 876 women with ovarian cancer, and 9253 individuals (4730 men, 4523 women) unaffected with these cancers. Of the cohort of 11 847 people, 18.9% (2245) were tested BRCA1 mutation carriers, 9.3% (1106) were tested noncarriers, and the remaining 71.7% (8496) had not been tested for mutations.

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See "Appendix" for list of consortium members who contributed to this study.
See "Notes" following "References."

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For all men and for women without a breast or ovarian cancer, follow-up started at the date of birth or on January 1, 1960, whichever occurred later, and continued until the date of cancer diagnosis, death, their 80th birthday, or the date of last contact, whichever occurred first. We truncated all observation before January 1, 1960, because earlier population cancer incidence rates are not generally available. For individuals with a breast or ovarian cancer, entry into the cohort was assumed to begin at the first diagnosis of breast or ovarian cancer or on January 1, 1960, whichever occurred later. Exit was as for the rest of the cohort, but with a cancer diagnosis being the first cancer subsequent to the initial breast or ovarian cancer. Thus, women with a non-breast/ovarian cancer before their first breast/ovarian cancer were excluded, because they did not contribute to follow-up. During the follow-up period, 300 individuals were diagnosed with breast cancer, 145 with ovarian cancer, and 744 (392 men, 352 women) with another cancer type; 10 136 (4338 men, 5798 women) individuals died or were censored without a diagnosis of cancer. The total number of person-years of follow-up was 295 850 (26.12 per individual).

Risks to mutation carriers relative to the general population (i.e., relative risks [RRs]) were evaluated with the standardized incidence ratio, which is simply the ratio of observed cases to expected cases in the cohort. The expected number of cases was calculated with the program PYRS (version 1.21) (12). Population rates were from the "Cancer Incidence in Five Continents" publications (13–17) and from information provided by the International Agency for Research on Cancer and were specific to country, calendar period, sex, and 5-year age group.

To optimize the amount of information available for analysis and to avoid the bias that would have been incurred by studying only those individuals who had undergone a mutation test, untested individuals were included, weighted by their estimated probability of carrying a mutation. These probabilities were estimated with the program MENDEL (http://www.biomath.medsch.ucla.edu/faculty/klange/software.html) (18), based on an individual's history of breast and/or ovarian cancer, his or her family history of breast and/or ovarian cancer, and the mutation status of their relatives, as we previously described (19). The age-specific incidences of breast and ovarian cancer for carriers were fixed at those previously estimated with a subset of the same dataset (20). Incidence rates for noncarriers were taken from the most recent edition of "Cancer Incidence in Five Continents" (17), averaged over all countries represented in the study. The weighted RR, λ, took the form:

$$\lambda = \frac{\sum_i w_i O_i}{\sum_i w_i E_i}, \qquad [1]$$

where O_i is the observed number of cancers in individual i (i.e., 1 if individual i is affected and 0 if individual i is unaffected), E_i is the expected number of cancers (in person-years) in individual i under the null hypothesis, and w_i is the estimated carrier probability for individual i. For tested carriers, w_i is 1 and for tested noncarriers, w_i is 0. RRs were computed, by sex, for each of 28 cancer sites. The RR to noncarriers in the cohort, ϕ, was also computed by replacing the w_i by $(1 - w_i)$, the probability of an individual not carrying a mutation, in equation 1.

Two-sided statistical significance levels for the RRs were estimated by simulation that was performed with Splus (version 3.4; http://www.insightful.com). The simulated number of cases in individual i was drawn from the Poisson distribution with a mean of E_i, under the null hypothesis of no increased risk to carriers. This process was repeated 1000 times to obtain the proportion of simulations resulting in an RR more extreme than that observed.

The RR to carriers and noncarriers were estimated, jointly, in two ways. First, we derived pseudo-maximum likelihood estimates by ignoring the dependence between individuals within the same family. (This procedure provides estimates that are consistent but not fully efficient.) These estimates were obtained iteratively with the EM algorithm (21). The estimated carrier probability for each untested individual was iteratively updated in light of his/her own cancer incidence at the given site and the current RR estimate, and the updated carrier probabilities were then used to produce the revised RR estimates with equation 1. Asymptotic 95% confidence intervals (CIs) were obtained from the variance–covariance matrix, as described previously (19). In most cases, joint estimation of λ and φ, the RR to noncarriers, led to estimates of φ that were not statistically significantly different from 1. To simplify the analyses (and to gain some precision), the estimates of λ presented in the "Results" section were derived under the restriction that φ was fixed at 1, unless otherwise specified.

For those cancers with some evidence of an elevated risk in mutation carriers, we also computed full maximum likelihood estimates and used MENDEL (18) to perform the pedigree analysis. For each family, the likelihood was computed from the observed and expected number of cancers at the site of interest in each family member, along with the occurrence of breast and ovarian cancer within the family and each individual's carrier status. The incidence rates for breast and ovarian cancer were fixed, as in the previous analysis, and the noncarrier RR was fixed at 1. In practice, the estimates from the two methods were very similar; we have therefore presented only the results from the pseudo-maximum likelihood method.

Separate analyses were also performed stratified by age group (<65 years or ≥65 years), region (Europe or North America), and the number of patients with breast and/or ovarian cancer in the family (families with three or more patients were compared with smaller families). The 25 families that had been included in the previous BCLC study (3) were analyzed separately to see if they were typical of BRCA1 families.

The cumulative risks of cancer by age t (in the absence of other causes of death), $F(t)$, were estimated with the standard formula (based on the usual assumption that the number of cancers in an individual carrier at age t follows a Poisson distribution):

$$F(t) = 1 - \prod_{j=0}^{t} \exp(-\mu_j \lambda_j), \qquad [2]$$

where λ_j is the RR in age group j in carriers relative to the general population, and μ_j is the corresponding population incidence rate. Separate RR estimates were used for those carriers aged younger than 65 years and 65 years old or older. Population incidence rates, μ_j, were those for England and Wales from 1988 through 1992, except for prostate cancer, where separate popu-

lation rates (and RR estimates) were used for North America and Europe. For cervical cancer, the risks to carriers aged 65 years or older were taken to be the same as those in the general population, because the RR estimate did not converge for the older age group. All statistical tests were two-sided.

RESULTS

Table 1 shows the observed and expected numbers of cancers at 28 sites for tested BRCA1 mutation carriers, tested noncarriers, and untested family members; estimated RRs to carriers (λ); and statistical significance levels computed by simulation. We also performed analyses in which RRs to both carriers and noncarriers (ϕ) were estimated jointly. However, for all sites except liver and other cancers, the 95% CI for ϕ included 1 and, in particular, the estimated ϕ for all cancers was close to 1 (RR = 0.83, 95% CI = 0.72 to 0.95). We have therefore presented the estimated carrier RRs with ϕ fixed at 1, unless otherwise stated.

The overall cancer risk (excluding breast cancer) to male carriers was very close to that expected (RR = 0.95, 95% CI = 0.81 to 1.12, P = .58). For female carriers, however, the cancer risk at sites other than breast or ovary was markedly elevated (RR = 2.30, 95% CI = 1.93 to 2.75, P = .001). This increased risk was still highly statistically significant even when allowing for the slightly greater than expected risk in female noncarriers

(carrier RR = 2.25, 95% CI = 1.87 to 2.70; noncarrier RR = 1.09, 95% CI = 0.92 to 1.30). Increased RRs that were statistically significant at the 5% level were observed for cancers of the colon (RR = 2.03, 95% CI = 1.45 to 2.85, P<.001), liver (RR = 4.06, 95% CI = 1.77 to 9.34, P = .004), pancreas (RR = 2.26, 95% CI = 1.26 to 4.06, P = .004), uterine body (RR = 2.65, 95% CI = 1.69 to 4.16, P<.001), cervix (RR = 3.72, 95% CI = 2.26 to 6.10, P<.001), other cancers (RR = 7.40, 95% CI = 5.14 to 10.66, P<.001), and cancers of unknown site (RR = 3.45, 95% CI = 2.35 to 5.07, P<.001).

The cohort included 65 people with cancers that were assigned to the category of "other cancers" in tested carriers (12 cases) or untested relatives (53 cases) (there was one more case in a noncarrier). Forty-seven of these 65 cases occurred in women (23 of which were confirmed diagnoses) compared with 8.6 cases expected (female carrier RR = 9.64, 95% CI = 6.36 to 14.61, P<.001; noncarrier RR = 2.60, 95% CI = 1.55 to 4.35, P<.001). The most frequent "other cancer" sites in women were peritoneal (13 cases), "abdomen not otherwise specified" (10 cases), "unspecified intestinal tract" (nine cases), "other female genital organ" (four cases), vagina (two cases), vulva (two cases), unspecified site (two cases), and "secondary and unspecified malignant neoplasm of the lymph nodes" (three cases). RRs for these "other cancers" were similar for women younger than 65 years and for women 65 years old or older (for women

Table 1. Observed (Obs) and expected (Exp) numbers of cancers in BRCA1 families and estimated relative risks (RRs) and 95% confidence intervals (CIs) to carriers

Cancer site (ICD code)*	Carriers		Noncarriers		Untested		Carrier RR (95% CI)†	P value‡
	Obs	Exp	Obs	Exp	Obs	Exp		
Buccal cavity and pharynx (140–9)	0	3.42	1	2.56	16	23.76	0.15 (0.06 to 0.40)	.014
Esophagus (150)	1	1.01	0	0.74	6	8.88	0.98 (0.38 to 2.56)	.94
Stomach (151)	5	2.58	2	1.99	33	24.80	1.56 (0.91 to 2.68)	.12
Colon (153)	14	7.36	6	6.17	76	48.77	2.03 (1.45 to 2.85)	<.001
Rectum (154)	0	4.11	1	3.29	13	29.16	0.23 (0.09 to 0.59)	<.001
Liver (155)	0	0.65	0	0.47	17	5.03	4.06 (1.77 to 9.34)	.004
Gallbladder and bile ducts (156)	0	0.66	1	0.53	7	4.73	1.87 (0.59 to 5.88)	.24
Pancreas (157)	2	1.94	0	1.60	24	14.53	2.26 (1.26 to 4.06)	.004
Larynx (161)	3	1.39	0	1.06	7	10.13	1.06 (0.45 to 2.49)	.84
Lung (162)	5	13.05	0	10.78	85	95.51	0.76 (0.54 to 1.07)	.14
Bone (170)	0	0.35	0	0.30	2	1.99	0.05 (0.00 to 1.63)	.68
Connective tissue (171)	2	0.77	0	0.63	2	4.28	1.27 (0.40 to 4.02)	.54
Melanoma (172)	3	3.78	3	3.03	16	15.94	1.11 (0.58 to 2.15)	.7
Uterine body (179, 181–2)	11	3.94	5	3.42	31	18.65	2.65 (1.69 to 4.16)	<.001
Cervix (180)	8	2.86	0	2.22	28	11.82	3.72 (2.26 to 6.10)	<.001
Prostate (185)	11	7.70	5	6.20	47	55.85	1.07 (0.75 to 1.54)	.72
Testis (186)	1	0.79	0	0.63	10	5.43	2.10 (0.70 to 6.33)	.16
Bladder (188)	3	3.78	0	3.01	11	29.16	0.48 (0.24 to 0.96)	.01
Kidney (189)	2	2.53	1	2.05	5	16.25	0.43 (0.16 to 1.14)	.036
Brain (191–2)	2	2.27	1	1.88	21	13.11	1.70 (0.85 to 3.42)	.12
Thyroid (193)	0	1.70	1	1.38	7	6.79	0	.10
Hodgkin's disease (201)	0	1.66	3	1.35	7	8.23	0	.15
Other lymphoma (200, 202)	4	4.39	2	4.05	3	34.13	0.23 (0.09 to 0.60)	<.001
Myeloma (203)	0	0.87	1	0.73	5	6.06	0.58 (0.12 to 2.72)	.53
Leukemia (204–8)	1	2.69	0	2.25	21	16.84	0.88 (0.37 to 2.14)	.83
Other cancers§	12	2.21	1	1.84	53	11.54	7.40 (5.14 to 10.66)	<.001
Unknown site (199)	8	3.07	0	2.55	55	25.60	3.45 (2.35 to 5.07)	<.001
All cancers‖	98	80.03	34	65.03	612	527.83	1.34 (1.19 to 1.51)	<.001
Male	38	44.66	16	34.38	338	365.44	0.95 (0.81 to 1.12)	.58
Female	60	35.37	18	30.65	274	162.39	2.30 (1.93 to 2.75)	.001

  *ICD = International Classification of Disease (11).

  †Estimating using EM algorithm, fixing noncarrier RR = 1. Blank field = confidence interval not computed because RR = 0.

  ‡Simulated two-sided statistical significance levels. All statistical tests were two-sided.

  §Includes cancers of the peritoneum, intestinal tract, nasal sinuses, pleura, other genital organs, eye, and several ill-defined sites.

  ‖All cancers other than breast cancer, ovarian cancer, or nonmelanoma skin cancer.

aged <65 years, RR = 10.12, 95% CI = 6.35 to 16.12; for women aged ≥65 years, RR = 8.25, 95% CI = 3.29 to 20.67). In contrast, there was no evidence of an increased risk of other cancers in men (carrier RR = 2.10, 95% CI = 0.74 to 5.90; noncarrier RR = 3.36, 95% CI = 1.27 to 8.90).

Incidence rates for peritoneal cancers were not available for all the populations in this study. However, we derived an RR estimate for this site that was based on rates from 1983 through 1987 for Caucasians from the SEER (Surveillance, Epidemiology and End Results)[1] Program *(16)* (RR = 44.64, 95% CI = 24.86 to 80.15, *P*<.001).

In addition to the cancer sites summarized in Table 1, seven cancers of the fallopian tube (ICD 183.2) were reported in the cohort, of which six were confirmed. Cancer of the fallopian tube is usually combined with ovarian cancer in published incidence rates, but an approximate RR was obtained by use of incidence rates provided by the East Anglian Cancer Registry (U.K.) for 1995 through 1998 (RR = 49.94, 95% CI = 22.48 to 110.94, *P*<.001).

The estimated RR to mutation carriers was greater for those younger than 65 years than for those 65 years old or older (Table 2). The RR estimates for those 65 years old or older were not statistically significantly different from 1.0 (for both sexes combined, RR = 0.99, 95% CI = 0.81 to 1.20). The cancer risks in men younger than 65 years old were also very similar to those expected (RR = 1.05, 95% CI = 0.85 to 1.31, *P* = .64), so that the only marked overall increased risk was in women younger than 65 years (RR = 2.62, 95% CI = 2.15 to 3.18, *P*<.001). RRs were higher for those younger than 65 years for pancreatic cancer (RR = 3.10, 95% CI = 1.43 to 6.70, *P* = .008), cervical cancer (RR = 3.84, 95% CI = 2.33 to 6.33, *P*<.001), and uterine cancer (RR = 3.40, 95% CI = 2.13 to 5.44, *P*<.001). We also observed some evidence of an increased risk of prostate cancer for those for men younger than 65 years (RR = 1.82, 95% CI = 1.01 to 3.29, *P* = .05) but not for those 65 years old or older (RR = 0.84, 95% CI = 0.53 to 1.33, *P* = .45).

The overall RR to female carriers was higher in European families (RR = 2.91, 95% CI = 2.32 to 3.66) than in North American families (RR = 1.47, 95% CI = 1.09 to 1.98, *P*<.001 for the difference). The RR to female noncarriers was statistically significantly greater than 1 for European women (RR = 1.36, 95% CI = 1.09 to 1.98) but not for North American women. In both continents, the observed risk in male carriers was similar to the expected risk. Overall confirmation rates were similar in both continents for women (37.1% [83 of 224] of all non-breast/ovarian cancers in European families were confirmed, compared with 40.6% [52 of 128] of those in North American families),

but a higher proportion of cancers in men was confirmed in North America than in Europe (39.4% [76 of 193] versus 22.1% [44 of 199]). The greater than expected risk of uterine cancer was seen only in European families (European RR = 3.89, 95% CI = 2.24 to 6.75 versus North American RR = 1.12, 95% CI = 0.50 to 2.52, *P* = .013 for difference). In contrast, the increased risk of cervical cancer was larger in North American families, although not statistically significantly so, and there was a statistically significantly increased risk to noncarriers in North America (European RR for carriers = 2.50, 95% CI = 1.32 to 4.73; North American RR for carriers = 4.86, 95% CI = 1.99 to 11.87, *P* = .2 for difference; North American RR for noncarriers = 2.79, 95% CI = 1.23 to 6.35). The RR for prostate cancer in men younger than 65 years was higher in European carriers (RR = 2.53, 95% CI = 1.10 to 5.82, *P* = .026) than in North American carriers (RR = 1.44, 95% CI = 0.62 to 3.32), although the difference was not statistically significant (*P* = .37). The risk of prostate cancer was not increased for those 65 years old or older in either continent (European RR = 1.14, 95% CI = 0.57 to 2.27; North American RR = 0.61, 95% CI = 0.30 to 1.24).

Estimated cumulative cancer risks (based on the RR estimates) are shown in Table 3 for all cancers and for each cancer site for which there was evidence of a greater than expected risk. Cumulative risks were calculated in the absence of other causes of death and were based on population rates for England and Wales. By the age of 50 years, the estimated cumulative risk of any cancer other than breast or ovarian was 6.16% in female carriers and 2.65% in male carriers. These risks increased to 23.27% and 16.89%, respectively, by the age of 70 years. The estimated cumulative risks of cervical cancer and of other uterine cancers in female carriers were approximately 4% and 2%, respectively, by the age of 70 years, and the risk of pancreatic cancer was approximately 1% for both sexes. The absolute risk of prostate cancer by the age of 70 years was approximately 3%, based on European RRs and population rates for England and Wales, but nearly 8%, based on North American RRs and U.S. population rates.

DISCUSSION

This study is by far the largest to date to examine risks of cancer in BRCA1 mutation carriers at sites other than the breast and ovary. By virtue of its size, this study had the statistical power to detect more moderate risks than any of the previous studies and, hence, has been able to quantify the magnitude of the excess risk more precisely. Statistically significantly in-

Table 2. Relative risks (RRs) and 95% confidence intervals (CIs) of cancer to BRCA1 mutation carriers, by age group

Cancer site	<65 years old		≥65 years old		
	RR (95% CI)	*P**	RR (95% CI)	*P**	*P* for difference*
Pancreas	3.10 (1.43 to 6.70)	.008	1.54 (0.63 to 3.76)	.28	.2
Cervix†	3.84 (2.33 to 6.33)	<.001			
Uterus	3.40 (2.13 to 5.44)	<.001	0.65 (0.12 to 3.40)	.67	.06
Prostate	1.82 (1.01 to 3.29)	.05	0.84 (0.53 to 1.33)	.45	.04
All cancers, male‡	1.05 (0.85 to 1.31)	.64	0.86 (0.68 to 1.08)	.085	.2
All cancers, female‡	2.62 (2.15 to 3.18)	<.001	1.57 (1.08 to 2.27)	.013	.02

*Two-sided significance levels obtained by simulation.

†Cervical cancer RR estimate did not converge above the age of 65 years.

‡All cancers other than nonmelanoma skin cancer, breast cancer, or ovarian cancer.

Table 3. Cumulative risk for cancer in BRCA1 mutation carriers*

Cancer site	Cumulative risk, % (95% CI)	
	Age 50 years	Age 70 years
Pancreas		
Male	0.12 (0.09 to 0.17)	1.16 (0.83 to 1.61)
Female	0.12 (0.09 to 0.18)	1.26 (0.92 to 1.72)
Uterus	0.38 (0.33 to 0.43)	2.47 (2.02 to 3.04)
Cervix	2.16 (1.90 to 2.46)	3.57 (3.16 to 4.04)
Prostate		
Europe	0.04 (0.03 to 0.06)	2.64 (1.95 to 3.57)
North America	0.12 (0.07 to 0.21)	7.67 (4.77 to 12.20)
All cancers†		
Male	2.65 (2.16 to 3.26)	16.89 (14.52 to 19.61)
Female	6.16 (5.73 to 6.62)	23.27 (21.73 to 24.89)

*CI = confidence interval.

†All cancers other than nonmelanoma skin cancer, breast cancer, or ovarian cancer.

creased risks of colon, liver, pancreatic, uterine, and cervical cancers, other cancers, and cancers of unknown site were observed. It is important to note, however, that the estimated RR was less than fourfold for each of these sites. Indeed, the overall estimated risk to male carriers is very close to that expected in the general population. For women carrying a BRCA1 mutation, the estimated risk of developing a cancer other than breast or ovarian cancer by the age of 70 years was roughly twofold that of the general population (i.e., 1 in 5 versus 1 in 10). A substantial proportion of the increased risk is attributable to unspecified abdominal cancers or cancers of unknown primary site, many of which can be explained as misdiagnoses of ovarian or peritoneal cancers; the cumulative risk of cancer by the age of 70 years for each of the specific sites with a statistically significantly increased risk was less than 4% in each case. Aside from the three main sites at which statistically significantly increased risks were observed (cervix, uterus, and pancreas), the excess risk to defined sites appears to be small (RR to female carriers = 1.27, 95% CI = 0.95 to 1.69).

A critical assumption in this study is that families were ascertained independently of the occurrence of any cancer type other than breast or ovarian. Although these criteria were strictly adhered to by each center, it is of course possible that other cancers may have led to a family's being referred for counseling. Overall, no increased risk to noncarriers was observed (RR = 0.83, 95% CI = 0.72 to 0.95), indicating that any ascertainment bias is likely to be small, although there was a slightly elevated risk to women from European centers (RR = 1.36, 95% CI = 1.09 to 1.69). As a further check on the validity of this assumption, we performed analyses subdivided by numbers of breast or ovarian cancers in the family. The rationale for these analyses is that any referral bias would be more likely in families with few breast and/or ovarian cancers. Families with three or more women with ovarian cancer or with breast cancer diagnosed before the age of 60 years were referred to as large (499 large families), whereas those with fewer than three such women were referred to as small (200 small families). For men, there was no difference in the risk between the groups (P = .5), but for women the RR was somewhat higher in the small families (RR for small families = 3.37, 95% CI = 2.10 to 5.43; RR for large families = 2.17, 95% CI = 1.79 to 2.62; P = .09 for the difference). However, the RR for the large families (for whom

referral bias is unlikely to have been a major factor) was very close to that for the whole dataset (RR = 2.30, 95% CI = 1.93 to 2.75; Table 1), confirming that any ascertainment bias is likely to be small.

The increased risks for brain and liver cancer may well be explicable as misreported metastases from other sites, given that the proportion of cancers confirmed is low (21% [5 of 24] brain cancers and 11% [2 of 17] liver cancers compared with 34.3% [255 of 744] overall). In the analysis in which RRs to both carriers and noncarriers are estimated, the estimated RRs for stomach cancer were similar in carriers (1.37) and noncarriers (1.35), suggesting that the observed excess may be a consequence of overreporting, independent of BRCA1 status.

We found a twofold increased RR for pancreatic cancer. This RR was similar in men and women but declined with age. This increased risk is interesting in light of the well established increase in risk of pancreatic cancer in BRCA2 mutation carriers (22–25). However, the risk for pancreatic cancer in BRCA1 carriers appears to be more moderate than the risk in BRCA2 carriers; the BCLC study (19) estimated an RR of 3.5 for BRCA2 carriers. Tonin et al. (26) reported that 11 of 91 Ashkenazi Jewish breast cancer families with a founder BRCA1 mutation contained a member with pancreatic cancer, compared with five of 120 Ashkenazi Jewish families without a founder BRCA1 or BRCA2 mutation. In addition, there have been several other anecdotal reports of pancreatic cancers in BRCA1 families [e.g., see (4,27,28)].

The interpretation of the twofold increased RR of colon cancer is more problematic. The increased risk was still statistically significant after adjustment for an increased risk in noncarriers. However, there was a marked deficit in the number of rectal cancers, and when the two sites were considered together, the observed risk was much closer to the expected risk (RR = 1.25, 95% CI = 0.91 to 1.72, P = .16), suggesting that some rectal cancers may have been inaccurately reported as colon cancers. In addition, no excess risk of colorectal cancer was observed in men (RR = 0.93, 95% CI = 0.60 to 1.44, P = .8), but a statistically significantly increased risk was found in women, even for the two sites combined (RR = 1.94, 95% CI = 1.21 to 3.10, P = .006), suggesting that some of this increased risk may be from ovarian cancers misdiagnosed as colon cancers. The earlier BCLC study (3) reported a fourfold increased RR for colon cancer in BRCA1 carriers. Since then, one BRCA1 family with seven cases of breast cancer, one case of ovarian cancer, and seven cases of colon cancer has been reported (29), but there has been no further strong evidence that colon cancer is part of the BRCA1 phenotype (30).

The analysis of this cohort provides weak evidence for a modestly elevated risk for prostate cancer at younger ages in BRCA1 mutation carriers (RR = 1.82 for those younger than 65 years, 95% CI = 1.01 to 3.29, P = .05) but no evidence of an elevated risk in those 65 years old or older. When the analysis was restricted to the European centers, where the effects of screening would be much less important, the estimated RR for prostate cancer in those younger than 65 years was somewhat larger (RR = 2.53, 95% CI = 1.10 to 5.82, P = .026). However, this risk is still modest in comparison with the risk in BRCA2 carriers; the BCLC study (19) estimated an RR of approximately 5 overall, increasing to more than 7 in men younger than 65 years.

The original BCLC BRCA1 analysis *(3)* of 33 families reported an RR for prostate cancer of 3.33, but the results of more recent studies have been conflicting. Some studies in Ashkenzi Jewish populations found modest evidence for BRCA1's involvement in prostate cancer *(4,9,31,32),* but others found no evidence *(33–35).* Studies in non-Jewish populations have found little or no evidence of an increased risk for prostate cancer in BRCA1 mutation carriers *(8,10,36).*

We observed statistically significantly increased risks of cervical and other uterine cancers in BRCA1 mutation carriers. Again, it is possible that some of these cancers may result from the misreporting of ovarian cancer. Another possibility is that the increased number of endometrial cancers may be associated with tamoxifen use, which may increase the risk of endometrial cancer *(37–39).* Tamoxifen is a widely prescribed treatment for breast cancer, but its use in unaffected women has largely been restricted to recent chemoprevention trials. Comprehensive information on tamoxifen use was not available in this study, but the large majority of endometrial cancer cases occurred before 1990 and, hence, predate the chemoprevention trials. Restricting the analysis to women unaffected with breast cancer did not materially change the results (RR = 3.13, 95% CI = 1.73 to 5.67, *P*<.001), suggesting that the use of tamoxifen is unlikely to have been a major confounder.

Several groups have pursued a possible association between BRCA1 mutations and uterine papillary serous carcinoma (UPSC), a particularly virulent form of uterine cancer that accounts for 5%–10% of uterine cancer cases. UPSC is histologically similar to papillary serous carcinoma of the peritoneum and to papillary serous ovarian cancer, the most common histologic form of ovarian cancer in BRCA1 mutation carriers *(31).* An Israeli study *(40)* found that two of nine Ashkenazi Jewish women with UPSC carried a BRCA1 mutation, but other studies [e.g., *see (41)*] have not replicated this observation.

The greater than expected risk of cervical cancer in mutation carriers was observed in the European centers and in the North American centers. No statistically significantly increased risk was observed in European noncarriers, but the North American centers did show an increased risk in noncarriers. The rate of pathologic confirmation was markedly higher in the European centers (62.5% [10 of 16] versus 25.0% [5 of 20]), suggesting that some of the increased risk in North America may result from misspecifying screening-detected cervical intraepithelial neoplasia as invasive cancer.

The highly statistically significantly increased risk of cancer of the fallopian tube is consistent with previous case reports [e.g., *see (26,42–44)*]. The estimated RR was comparable to that for ovarian cancer and is equivalent to an absolute risk of 1.6% by the age of 80 years. It can be difficult to distinguish fallopian tube cancer from ovarian cancer, particularly at advanced stages, and because it is more likely that an ambiguous tumor would be described as ovarian cancer, it is possible that the risk for fallopian tube cancer is underestimated. Clearly, this risk for fallopian tube cancer needs to be borne in mind when prophylactic surgery is considered.

The RR estimate for peritoneal cancer was also comparable to that for ovarian cancer. Peritoneal cancers are thought to develop from the peritoneal surfaces of the abdomen and pelvis and have the same histologic appearance as papillary serous ovarian carcinomas. BRCA1 mutations have been reported specifically in women with papillary serous carcinoma of the peritoneum *(45,46).* There have also been several reports of peritoneal cancers occurring in women after they have had an oophorectomy, including those with a family history of ovarian cancer [e.g., *see (47,48)*]. Of the 13 female patients in our cohort, one had had a prophylactic oophorectomy a year before her peritoneal cancer was diagnosed.

In conclusion, these results establish important differences in the site-specific cancer risks associated with BRCA1 and BRCA2 mutations that may reflect essential functional differences. BRCA2 mutations are associated with increased risks for male breast cancer, prostate cancer, and pancreatic cancer and are associated with possible increased risks for gallbladder cancer, stomach cancer, and melanoma *(19).* Thus, there are important management implications for male BRCA2 carriers. In contrast, the major increased risks in BRCA1 carriers, aside from that for breast cancer, are for ovarian cancer and other gynecologic or abdominal cancers in women. The overall cancer risk and associated mortality to women who carry a BRCA1 mutation is considerably increased, but there is little increased risk to men who carry a BRCA1 mutation. Such risk estimates can guide the future management of BRCA1 carriers.

APPENDIX

The following are the contributing centers and the names of the principal investigators. The number of families about whom information was contributed by each center is given in brackets:

Cancer Research U.K. Genetic Epidemiology Unit, Cambridge, U.K. (coordinating center): D. Easton, D. Thompson, L. McGuffog; University of Pennsylvania, Philadelphia: B. Weber [97]; Institut Curie, Paris, France: S. Gad, D. Stoppa-Lyonnet [76]; University of Vienna, Vienna, Austria: V. Korn, R. Kroiss, G. Langbauer, D. Muhr, T. Wagner [48]; Creighton University, Omaha, NE, and International Agency for Research on Cancer, Lyon, France: D. Goldgar, G. Lenoir, H. T. Lynch, S. Narod, O. Sinilnikova [46]; Cancer Research U.K. Human Cancer Genetics Research Group, Cambridge: S. Gayther, B. Ponder, A. Taylor [43]; Erasmus Medical Centre and Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands: J. G. M. Klijn, H. Meijers-Heijboer [42]; National Institute of Oncology, Budapest, Hungary: E. Olah [35]; Institut Paoli Calmettes, Marseille, France: H. Sobol, F. Eisinger [34]; University of Lund, Sweden: A. Borg, O. Johannsson, N. Loman, H. Olsson [32]; Deutsches Krebsforschungszentrum, Heidelberg, Germany, and University of Würzburg, Würzburg, Germany: J. Chang-Claude, U. Hamann, B. H. F. Weber [31]; Karolinska Hospital, Department of Molecular Medicine, Stockholm, Sweden: B. Arver, A. Lindblom [31]; Institute of Cancer Research, Sutton, U.K.: R. Eeles, D. Ford, J. Peto, M. Stratton, [25]; University of Utah, Salt Lake City: L. Cannon-Albright, S. L. Neuhausen [23]; Helsinki University Central Hospital, Helsinki, Finland: H. Eerola, H. Nevanlinna [20]; Centre Jean Perrin, Clermont-Ferrand: Y. Bignon [17]; National Cancer Institute, Milan, Italy: S. Manoukian, B. Pasini, M. A. Pierotti, P. Radice [15]; Duke University Medical Center Comprehensive Cancer Center, Durham, NC: A. Futreal [15]; University of Leiden and Foundation for the Detection of Hereditary Tumours, Leiden, The Netherlands: C. J. Cornelisse, P. Devilee, H. Vasen [13]; Centre René Gauducheau, Nantes, France: C. M. Maugard [9]; Lothian Breast Cancer Family Clinic, Edinburgh and Tayside Breast Cancer Family Clinic, Dundee, Scotland: J. Campbell, L. McCleish, M. Stell [8]; Max-Delbrück-Centrum für Molekulare Medizin, Tumorgenetik, Berlin, Germany: S. Scherneck, S. Seitz [8]; Imperial Cancer Research Fund, Leeds, U.K.: D. T. Bishop, G. Crockford [7]; Fundación Jiménez Diaz, Madrid, Spain: J. Benitez, A. Osorio [6]; McGill University, Montreal, Canada: S. Narod (currently at University of Toronto) [6]; National Cancer Institute, Bethesda, MD: J. Struewing [6]; Heinrich-Heine Uni-

versität, Düsseldorf, Germany: M. W. Beckmann, B. Kuschel [5]; University of Aberdeen, Aberdeen, U.K.: N. Haites, A. Schofield [1]; Centre for Cancer Epidemiology, Manchester, U.K.: G. Evans [1].

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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.