

Cancer Incidence in a Population of Jewish Women at Risk of Ovarian Cancer

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Purpose: To evaluate the incidence and clinical characteristics of ovarian and other cancers in a cohort of women at risk of developing ovarian cancer.

Patients and Methods: The Gilda Radner Ovarian Cancer Detection Program in Los Angeles, CA, was established in 1991 to study the efficacy of screening in the early detection of ovarian cancer. We present findings from a historical cohort of 290 Jewish women who were offered *BRCA* testing for three common founder mutations (*BRCA1* 185delAG and 5382insC and *BRCA2* 6174delT).

Results: In 10 years, 17 cancers were observed (1,111 per 100,000 per year), including six breast and eight ovarian or related cancers. A high proportion of cancers of peritoneal origin was observed. The majority (86%) of women with incident breast or ovarian/peritoneal cancer carried a mutation in the *BRCA1* gene. The

overall cancer incidence among carriers of mutations in the *BRCA1* gene was estimated to be 5,450 per 100,000 per year, corresponding to a cumulative incidence of 47.5% at 10 years. In contrast, the cumulative incidence of cancer among noncarriers was 2.5% ($P < 10^{-8}$). After adjustment for sampling, the risks to *BRCA1* mutation carriers at 10 years were estimated to be 21% for ovarian/peritoneal/tubal cancer, 16% for breast cancer, and 36% for all cancers.

Conclusion: The excess risk of breast and ovarian cancer in Jewish women with a family history of ovarian cancer is largely attributable to mutations in *BRCA1*. Intensive surveillance by use of CA-125 and ultrasound does not seem to be an effective means of diagnosing early-stage ovarian cancer in this high-risk cohort.

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THE STRONGEST RISK factor for ovarian cancer is the presence of an inherited mutation in one of the two ovarian cancer susceptibility genes, *BRCA1* or *BRCA2*. It is estimated that more than 10% of women in North America with invasive ovarian cancer carry a *BRCA1* or *BRCA2* mutation.¹ Other risk factors include a family history of ovarian cancer, a previous diagnosis of breast cancer, and Ashkenazi Jewish ethnicity.² The highest recorded rates of ovarian cancer have been reported among Israeli Jews born in Europe or North America.³ The majority of these women are of Ashkenazi origin. The prevalence of founder germline *BRCA* mutations in the Jewish population contributes to the high cancer rate. Two mutations in *BRCA1* (185delAG and 5382insC) and one in *BRCA2* (6174delT) have a

combined frequency of one in 45 Ashkenazi Jews.⁴⁻⁶ Several groups have estimated the prevalence of *BRCA1* and *BRCA2* mutations in Jewish ovarian cancer patients.⁷⁻¹⁰ In a study of 208 unselected North American Jewish ovarian cancer patients, the frequency of *BRCA* mutations¹¹ was 41.3%. In a recent large study, 244 (29%) of 840 women with ovarian or peritoneal cancer in Israel had a founder mutation in *BRCA1* or *BRCA2*.¹²

Regular ovarian surveillance is recommended for carriers of *BRCA* mutations, including rectovaginal pelvic examination, serum CA-125, and transvaginal sonography at annual or biannual intervals.¹³ However, there are few data that indicate that screening of high-risk women will reduce mortality from ovarian cancer.¹⁴

The cumulative lifetime risk of developing ovarian cancer to age 70 years associated with a *BRCA1* or *BRCA2* mutation has been estimated^{1,6,15} to be in the range of 16% to 60%, and the risk of breast cancer is estimated^{1,15-17} to be in the range of 28% to 87%. These estimates were based on the inspection of pedigrees of high-risk families from cross-sectional studies and may be subject to ascertainment and recall biases. Because of the wide ranges in risk, genetic counseling is difficult, and accurate estimates are desirable. In principle, cohort studies of healthy women who carry *BRCA* mutations are ideal for estimating the risk of cancer by the direct observation of cancer incidence.

Participants of the Gilda Radner Ovarian Cancer Detection Program in Los Angeles, CA, were considered to be at increased risk of developing ovarian cancer, on the basis of their family histories of ovarian cancer, breast cancer, or

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both or a previous diagnosis of breast cancer. Many of these women have now been observed for 5 or more years, and many have undergone genetic testing. This cohort provides a unique opportunity to estimate cancer risk among female carriers of *BRCA1* or *BRCA2* mutations.

PATIENTS AND METHODS

The Gilda Radner Ovarian Cancer Detection Program

In July 1991, the Gilda Radner Ovarian Cancer Detection Program was established at the Cedars-Sinai Medical Center in Los Angeles, CA. The goals of this ovarian cancer screening program have been described.¹⁸ Briefly, women 35 years and older with a family history of ovarian, breast, colon, or endometrial cancer or with a personal history of breast cancer were eligible to participate at no cost. Screening with transvaginal ultrasonography with color Doppler imaging, as well as tumor marker testing, was performed biannually until July 1995. After 1995, the protocol was amended to annual screening interventions. Five tumor markers (CA-125, LASA, DM70K, UGP, and HER-2/*neu*) were used; however, only CA-125 has been accepted in clinical practice and is discussed here.

Study Population

This study focuses on the subgroup of healthy Jewish participants in the Gilda Radner Ovarian Cancer Detection Program at the Cedars-Sinai Medical Center in Los Angeles, CA. Women who attended the program for only one appointment were not considered participants, nor were those observed for less than 1 year.

From 1991 to 2000, 1,261 women were enrolled onto the Gilda Radner program. A total of 475 subjects (38%) were Jewish (self-reported). Of these, 83 women were excluded because they did not provide 1 full year of follow-up. Some of these included women who elected to undergo oophorectomy and were therefore discharged from the screening program at the time of surgery.

Our study cohort included women with a family history of ovarian cancer (any age) or breast cancer (younger than 50 years) in a first- or second-degree relative. Sixty-one women were excluded from the study on the basis of the family history criteria. Forty-one women with a past diagnosis of breast cancer were also excluded because of the possible effect of treatment on subsequent cancer risk. As a result, 290 potential subjects were eligible for analysis.

Study procedures were approved by the institutional review boards of the Cedars-Sinai and Women's College Hospitals. In 1998, women received a letter explaining the goals of the study with an invitation to participate in genetic testing. Women who agreed to participate contacted the Gilda Radner program directly. Women who agreed to genetic testing provided a blood specimen for DNA extraction. Participants were offered the results of the genetic testing by genetic counselors and physicians associated with the research program (1999 to 2000). The women were asked to provide details regarding cancer, surgery, and cancer occurrences in the family.

Mutation Detection

Human genomic DNA was isolated from 10 to 20 mL of peripheral blood. DNA specimens were sent to the molecular laboratory of the Princess Margaret and Women's College Hospitals in Toronto, Canada. *BRCA* analysis included screening for three common mutations (*BRCA1* 185delAG and 5382insC and *BRCA2* 6174delT). The rapid

fluorescent multiplexed polymerase chain reaction analysis method was used to detect founder mutations in the *BRCA1* and *BRCA2* genes.¹⁹ All mutant bands detected by polymerase chain reaction were confirmed with direct sequencing. To be comprehensive and to avoid missing any mutations, women with incident cancers of the breast or ovary who did not carry one of the three Jewish founder mutations were offered complete screening of *BRCA1* and *BRCA2* by direct sequencing of all coding regions through Myriad Genetic Laboratories (Salt Lake City, UT).

We were able to genotype two women who had died. One patient with non-Hodgkin's lymphoma was genotyped by using previously stored DNA specimens. Histologic slides were used to test one subject with peritoneal cancer who died in 1994. Testing of histologic slides was performed as previously described.¹⁹

Case Definitions

All cancers in the cohort were confirmed by review of medical records, operative reports, and pathology slides, as well as the ultrasound, tumor marker, and family history information. Participants in the Gilda Radner Ovarian Cancer Detection Program receive annual reminders about their appointments, including a request to update us about any changes to the status of their health.

Peritoneal serous papillary carcinoma was defined according to the criteria of the Gynecologic Oncology Group²⁰: (1) the ovaries are normal in size or enlarged by a benign process; (2) the extraovarian sites of carcinoma are of significantly greater volume than the tumor present on either ovary; (3) the ovarian tumor component is nonexistent, is confined to the ovarian surface with or without stromal invasion measuring less than 5 × 5 mm, or is within the ovarian substance but measuring less than 5 × 5 mm; and (4) the histologic characteristics indicated serous papillary carcinoma of any grade. All pathologic findings and tissue blocks of ovarian cancer patients (including peritoneal cancer patients) were reviewed independently by two experts. Fallopian tube cancer in one patient was confirmed by surgical pathology review.

Statistical Analysis

Women were considered to be at risk for breast cancer from the time of their first clinic appointment to the date of the last appointment, breast cancer diagnosis, or death. Women were considered to be at risk of developing ovarian or peritoneal cancer from the time of the first appointment to the date of last contact, ovarian or peritoneal cancer diagnosis, bilateral oophorectomy, or death. Kaplan-Meier survival analysis was performed to estimate the cumulative incidence of cancer in the cohort. For subgroup analyses of cumulative incidence of cancer in carriers and noncarriers, women who were not tested were excluded. The log-rank test was used to assess the statistical significance of differences in survival curves. The relative risks (RR) of cancer were estimated by use of the Cox proportional hazards model.²¹

RESULTS

Jewish Cohort

The study cohort comprised 290 Jewish women. The mean age of the women at first contact was 44.8 years and was 40.4 years for carriers of mutations in *BRCA1/2*. Forty-three women (14.8%) had prophylactic bilateral salpingo-oophorectomy at a time from 1 to 9 years after study

Table 1. Characteristics of 290 Jewish Gilda Radner Participants

Variable	Total		Tested		Not Tested	
	No.	%	No.	%	No.	%
Jewish cohort	290	100	213	73.4	77	26.6
Age at first contact						
< 40 years	100	34.5	80	37.6	20	26
40-49 years	125	43.1	89	41.8	36	46.8
50-59 years	40	13.8	27	12.7	13	16.9
60-69 years	20	6.9	15	7	5	6.5
≥ 70 years	5	1.7	2	0.9	3	3.9
Family history						
Ovarian in first-degree	205	70.6	158	74.2	47	61
Ovarian in second-degree	38	13.1	28	13.1	10	13
Breast in first-degree	30	10.3	22	10.3	8	10.4
Breast in second-degree	5	1.7	5	2.3	—	—
Missing	12	4.1	—	—	12	15.6
Prophylactic oophorectomy	43	14.8	34	16	14	18.2

entry. Indications for surgery were given as abnormal ultrasound findings (20 of 43), prevention of ovarian cancer (16 of 43), increased CA-125 (four of 43), breast cancer diagnosis (two of 43), and uterine bleeding (one of 43). The mean follow-up was 5.3 ± 2.2 years for all study participants, and was 7.2 ± 1.7 years for carriers of mutations in *BRCA1/2*, with a maximal follow-up time of 10 years. Two women died, one as a result of peritoneal cancer (incident) and one as a result of non-Hodgkin's lymphoma (incident).

DNA specimens were available for 213 (73.4%) of the 290 eligible Jewish women. We were unable to obtain blood samples from the other 77 women in the cohort. Forty-eight women for whom no sample was obtained had not participated in the Gilda Radner program since 1996, and eight women were discharged after prophylactic oophorectomy. The remaining 29 women did not respond to a mailed invitation to participate in genetic testing or declined to participate. The similar characteristics of women who underwent genetic testing as compared with those who were not tested are listed in Table 1.

A total of 33 founder mutations (15.5%) were found among 213 Jewish program participants, including 31 in *BRCA1* (27 in 185delAG and four in 5382insC) and two in *BRCA2* (6174delT) (Table 2). Twelve of the 14 women who developed breast or ovarian cancer during the course of the program were carriers of a germline mutation in the *BRCA1* gene. Two women with incident breast and ovarian cancers were offered comprehensive screening of *BRCA1* and *BRCA2* mutations with Myriad Genetic Laboratories after testing negative for the three common Ashkenazi Jewish mutations. No mutations were found for these two women.

Ten women had other cancers diagnosed before enrolling in the program, including a preinvasive breast cancer (lobular carcinoma-in-situ) and thyroid, cervical, and seba-

ceous gland (eye) cancer. Six women had skin cancer (basal cell carcinomas) (Table 2). Of the 10, seven women (70%) were tested, and three women with skin cancer were not tested. The thyroid cancer patient was found to carry the *BRCA1* 5382insC mutation.

Ovarian/Peritoneal/Tubal Cancer Risk

Since 1991, eight incident cases of invasive ovarian or related cancers (eg, peritoneal or fallopian tube primary tumors) were observed among the 290 women in the study cohort. These included five cases of primary peritoneal cancer, two cases of ovarian cancer, and one case of peritoneal/fallopian tube cancer. The mean age of cancer diagnosis was 47.7 years (range, 38 to 56 years). Seven *BRCA1* 185delAG mutations were identified. A mutation was not detected for one patient who was diagnosed with stage I ovarian carcinoma (patient no. 3). A total of 1,439 years of follow-up were available for analysis of ovarian cancer risk, with a mean follow-up of 5.0 ± 2.2 years. The cumulative incidence of ovarian/peritoneal cancer among the 31 *BRCA1* carriers was 28% at 10 years and was much greater than the incidence for the 180 noncarriers, which was less than 1% during the entire study period (RR = 32; 95% confidence interval [CI], 4.0 to 260) (Fig 1a).

The characteristics of the eight patients with ovarian/peritoneal/tubal cancer are listed in Table 3. We have previously reported on six of these patients²²; two additional patients are described here (patient nos. 11 and 12).

Six of the eight patients presented with stage IIIc disease, one with stage Ic, and one with stage IIc. Three of the eight women had at least one abnormally increased CA-125 level (> 35 U/mL) during routine screening before surgery (patient nos. 5, 7, and 9); all of these were diagnosed with stage IIIc disease. Patient no. 5 had two abnormally in-

Table 2. Frequency of Mutations Among 290 Jewish Gilda Radner Participants

Variable	Total (n)	Tested (n)	Positive for Mutation					
			BRCA1		BRCA2		Either	
			No.	%	No.	%	No.	%
Jewish cohort	290	213	31	14.6	2	0.9	33	15.5
Prophylactic oophorectomy*	43	34	10	29.4	1	2.9	11	32.4
Prevalent cancer								
Breast LCIS	1	1	—	—	—	—	—	—
Thyroid	1	1	1	—	—	—	1	—
Skin (basal cell carcinoma)	6	3	—	—	—	—	—	—
Cervical	1	1	—	—	—	—	—	—
Sebaceous gland (eye)	1	1	—	—	—	—	—	—
Total	10	7	1	14.3	0	—	1	14.3
Incident cancer								
Breast†	6	6	5	83.3	—	—	5	83.3‡
Ovarian	2	2	1	50	—	—	1	50‡
Fallopian tube/peritoneal	1	1	1	100	—	—	1	100
Peritoneal	5	5	5	100	—	—	5	100
Non-Hodgkin's lymphoma	1	1	—	—	—	—	—	—
Cervical	1	1	—	—	—	—	—	—
Bone cancer (osteosarcoma)§	1	1	1	—	—	—	1	—
Total	17	17	13	76.5	0	—	13	76.5

Abbreviation: LCIS, lobular carcinoma-in-situ.

*Six had prophylactic oophorectomy after receiving BRCA results.

†One was diagnosed synchronously with melanoma.

‡Complete BRCA1 and BRCA2 testing was performed (Myriad Genetic Laboratories, Salt Lake City, UT).

§One had basal cell carcinoma previously.

creased CA-125 levels at 1 and 2 months before surgery. Patient no. 7 had a modestly increased CA-125 level and was found to have synchronous primary cancers of the fallopian tube and peritoneum. Patient no. 9 had persistently increased CA-125 levels for 18 months, starting from her first visit to the program. She was monitored monthly for three visits and biannually for the last two visits. Because the CA-125 level was not increasing and the ovaries appeared normal on transvaginal ultrasonography, this was suspected to be caused by a benign gynecologic abnormality in a premenopausal woman.²² Patient no. 10 was diagnosed during pregnancy; she had normal screening CA-125 and ultrasound findings before pregnancy. Ultrasound findings were abnormal in two of the eight patients (nos. 3 and 7). Five of the eight women presented with abdominal pain or discomfort. All had normal ultrasound findings, three had a nonincreased screening CA-125 (patient nos. 6, 10, and 11), four were diagnosed with stage IIIc disease (nos. 6, 9, 10, and 12), and one was diagnosed with stage IIc disease (patient no. 11). Two patients (nos. 11 and 12) discontinued their participation in the Gilda Radner program several years before their diagnoses but continued to receive annual ovarian cancer screening with CA-125 and transvaginal ultrasound elsewhere. Patient no. 11 had a moderately increased CA-125 and presented with intermittent pelvic

pain and ascites less than 2 months before her diagnosis. Patient no. 12 had normal ultrasound findings less than 2 months before she presented with pelvic pain and ascites; her CA-125 at the time of diagnosis was abnormally high.

All six cases of peritoneal serous papillary carcinoma occurred among carriers of the 185delAG mutation. The cumulative risk of peritoneal cancer among carriers of the 185delAG mutation was estimated to be 20% at 10 years.

Breast Cancer Risk

Six cases of breast cancer were observed during the follow-up period. The mean age of breast cancer diagnosis was 45.2 years (range, 42 to 69 years) (Table 4). DNA samples were available for all of these, and five (83%) were positive for a BRCA1 mutation (four 185delAG and one 5382insC). All four incident breast cancer cases diagnosed at younger than age 50 carried the BRCA1 185delAG mutation. The woman found to carry the BRCA1 5382insC mutation was diagnosed at age 56 years, and one woman who tested negative for the three founder mutations was diagnosed at age 69 years. A total of 1,521 years of follow-up were available for analysis, with a mean follow-up time of 5.3 ± 2.1 years. The incidence of breast cancer among carriers of BRCA mutations was much greater than the incidence among noncarriers (RR = 18; 95% CI,

Table 3. Characteristics of Eight Women in Whom Ovarian, Peritoneal, or Fallopian Tube Cancers Developed

Case No.	Cancer Site	Histology	Stage, Nuclear Grade	Age at Onset (years)	Mutation Status*	No. of Visits	Last Five CA-125 Values (U/mL)	Time Since Screen at GR to Diagnosis (months)	TVS Findings	Indication	Vital Status
3	Ovarian	PS	Ic, 2	48	—	10	10, 5, 7, 8, 14	1.4	Right ovary, 2.4-cm cyst; left ovary, 4.4- and 2.3-cm complex cysts	TVS, RI	Alive
5	Peritoneal	PS	IIIc, 3	55	+	10	12, 14, 18, 670, 1,020	1.2	Normal ovaries	CA-125	Alive
6	Peritoneal	PS	IIIc, 3	55	+	3	18, 11, 22	5.9	Normal ovaries	Pain	Deceased
7	Fallopian tube and peritoneal	PS	IIIc, 3	39	+	10	19, 28, 51, 36, 50	3.4	Normal ovaries; left ovary, 3-cm complex mass adjacent	TVS	Alive
9	Peritoneal	PS	IIIc, 3	45	+	5	197, 38, 127, 161, 125	15.6	Normal ovaries	Ascites; positive cytologic findings	Alive
10	Peritoneal	PS	IIIc, 3	38	+	2	10, 7	17.2	Normal ovaries	Ascites; omental cake on obstetric sonogram	Alive
11	Ovarian	PS	IIc, 2	55	+	7	29, 23, 17, 12, 10, (11, 55)†	31 (1.5)†	Normal ovaries	Pain and ascites	Alive
12	Peritoneal	PS	IIIc, 3	42	+	2	37, 15, (5,000+)†	70 (1)†	Normal ovaries	Pain and ascites	Alive

Abbreviations: PS, papillary-serous; TVS, transvaginal sonography; RI, resistance index measured on Doppler imaging at the last visit before diagnosis; GR, Gilda Radner.

*+ = germline *BRCA1* 185delAG mutation; — = no mutation was found with complete *BRCA1* and *BRCA2* testing.

†Screened outside of the Gilda Radner program; information shown in parentheses.

2.1 to 157). The 10-year risk of breast cancer for mutation-positive participants was 21%, compared with a cumulative risk to noncarriers of less than 1% (Fig 1B).

Overall Cancer Risk

Other incident cancers in the cohort included one case of bone cancer (osteosarcoma) in a *BRCA1* 185delAG carrier, one case of cervical cancer in a noncarrier, and one case of non-Hodgkin's lymphoma in a noncarrier (Table 1). Overall, the incidence of any cancer among carriers of *BRCA* mutations was 14 times greater than that for noncarriers (RR = 14; 95% CI, 4.4 to 42). The 10-year risk of any cancer for mutation-

positive participants was 47.5%. The cumulative 10-year risk for noncarriers was 2.5% (Fig 1C). In summary, 13 (76.5%) of the 17 women with incident cancer carried a *BRCA1* mutation (including five of six women with breast cancer and seven of eight women with ovarian/peritoneal/tubal cancer), and four women were noncarriers.

DISCUSSION

Since 1991, the Gilda Radner Ovarian Cancer Detection Program at the Cedars-Sinai Medical Center in Los Angeles has observed women at risk of ovarian cancer. The majority (87.5%) of Jewish women in the program who developed

Table 4. Characteristics of Six Women Who Developed Breast Cancer

Case No.	Cancer Site	Age at Onset (years)	Histology	Tumor Size (cm)	Lymph Nodes Positive	Detection Method	Mutation Status	Oophorectomy	Vital Status
13	Breast	69	Ductal	0.8	0/25	Mammogram	—	3 years before	Alive
14	Breast	45	Ductal	< 1.5	3/15	Self	185delAG	—	Alive
15	Breast	46	Ductal	1.5	N/A	Self	185delAG	2 years after	Alive
16	Breast	49	Ductal	1.5	3/14	Self	5382insC	Pending (5 years after)	Alive
17	Breast and melanoma	42	Ductal	1.1	0/19	Self	185delAG	2 years after	Alive
18	Breast	56	Ductal	1.5	0/25	N/A	185delAG	At time of diagnosis	Alive

Abbreviation: N/A, not available.

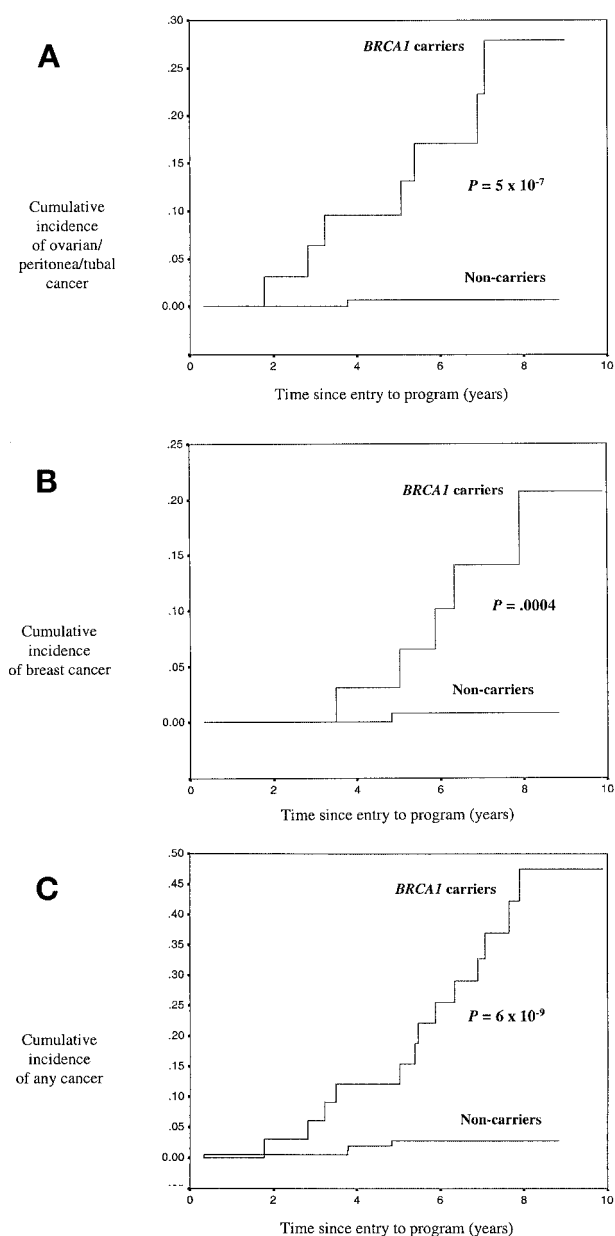


Fig 1. Cumulative cancer incidence for Jewish participants of the Gilda Radner Ovarian Cancer Detection Program. (A-C) Percentage of women developing cancer since inception of the program in 1991 by time. Censored observations included date of cancer diagnosis, prophylactic surgery, death, or last appointment.

these cancers were found to be carriers of the *BRCA1* 185delAG mutation. Only two Jewish women who developed ovarian or breast cancer during the course of the program did not carry a *BRCA1* mutation; one was diagnosed with stage I ovarian cancer at age 48 years, and the other was diagnosed with breast cancer at age 69 years.

No *BRCA2* mutations were found among the cancer patients (Table 2). However, the age of onset of ovarian cancer in carriers of mutations in the *BRCA2* gene is older than for carriers of mutations in *BRCA1*.¹ The majority of *BRCA2*-associated ovarian cancers are diagnosed between the ages of 50 and 70 years, whereas *BRCA1*-associated ovarian cancers occur 4 to 5 years sooner than is usual for patients with ovarian cancer.¹ In our study, the mean age of the study participants at entry was 44.8 years. Because ovarian cancer in carriers of *BRCA2* mutations is diagnosed at a mean age of 62 years, we would have required additional follow-up to observe cancers in this cohort.¹¹

In this population, intensive screening resulted in the diagnosis of only one early-stage ovarian cancer. We identified seven stage II or III ovarian, fallopian tube, or peritoneal serous papillary carcinomas, which had spread beyond the ovary at the time of diagnosis. Furthermore, four of the eight cancers presented in symptomatic women who had normal screening tests. Five of these had undergone screening ≤ 6 months before the diagnosis.

Papillary serous carcinoma of the peritoneum is histologically indistinguishable from papillary serous ovarian cancer, and it is often multifocal in origin.²² The risk of peritoneal cancer is significant for carriers of germline mutations in the *BRCA1* gene.²⁰ In this study, the diagnosis of peritoneal serous papillary carcinoma is in accordance with the guidelines by the Gynecologic Oncology Group.²⁰ The ovaries were present at the time of diagnosis; however, the extent of involvement at extraovarian sites was significantly greater, and the ovarian tumor component was either nonexistent or confined to the ovarian surface. It is important to discriminate peritoneal cancer from epithelial ovarian cancer because papillary serous carcinoma of the peritoneum may not be amenable to prevention by salpingo-oophorectomy. The majority of the ovarian-type cancers observed in our cohort were determined to be of peritoneal origin and, we believe, would not have been prevented through prophylactic salpingo-oophorectomy.

Previously, a small study of 17 women with primary cancers of the peritoneum identified three *BRCA1* mutations (18%), including two Jewish patients with the *BRCA1* 185delAG mutation.²³ In our study, seven of eight patients with ovarian-related cancer, including all six with primary cancers of the peritoneum, were *BRCA1* 185delAG mutation carriers (Table 3). On the basis of the six cases of peritoneal cancer, we estimated the cumulative risk of peritoneal cancer among *BRCA1* carriers to be 20% at 10 years. Carriers of mutations in the *BRCA1* gene should be counseled about the persistent risk of peritoneal cancer after prophylactic surgical removal of the ovaries.²⁰

One patient (no. 7) was diagnosed with synchronous primary cancers of the fallopian tube and peritoneum. Carcinoma of the fallopian tube is also a phenotypic variant of *BRCA1* and *BRCA2*.²⁴⁻²⁷ In a recent study of 44 unselected cases of fallopian tube cancer in the province of Ontario, six germline *BRCA* mutations (9.1%) were detected, including two *BRCA2* mutations.²⁸ Carriers should be counseled about the risk of cancer of the fallopian tube, and prophylactic salpingectomy should accompany oophorectomy.

These data provide one of the first risk estimates for *BRCA* carriers on the basis of a population of asymptomatic women who were observed prospectively. Generally, cross-sectional studies have been used to estimate the risk of cancer to female carriers of mutations in *BRCA1* or *BRCA2*, relying mainly on the proband's recall of cancer occurrence in the family. A cohort study design, such as the one presented here, is preferred in the estimation of risks or rates of disease in a population, in which new occurrences of the disease are observed and confirmed by the investigators.²¹ Recently, prospective data on female *BRCA1* or *BRCA2* mutation carriers participating in a breast cancer surveillance program in the Netherlands was presented.^{29,30} Meijers-Heijboer et al²⁹ studied 139 *BRCA1* or *BRCA2* mutation carriers and reported eight incident cases of breast cancer in their cohort with a mean follow-up of 3 years, resulting in a 2.5% increase in breast cancer risk per year. The risk estimates presented here (eg, 2.1% breast cancer risk per year) are based on a longer mean follow-up of 7 years for *BRCA1/2* mutation carriers. However, our estimates are likely to be high because of our study design. Because we had access to paraffin-embedded tumor specimens, we were able to test a higher proportion of women who developed cancer (100%) than women in the cohort who were not diagnosed with incident cancers (71.8%). Among women without incident cancers who were tested, the prevalence of *BRCA* mutations was 10.2% (20 of 196). If we assume the same mutation rate for the healthy women who were not tested, we would expect there to be an additional eight carriers; ie, the number of carriers in the cohort would increase by 24%, from 33 to 41. Therefore, it is likely that we have overestimated the cancer incidence rates among carriers by approximately 24%. Adjusting for sampling bias, the estimated risks for female carriers of germline mutations in the *BRCA1* gene at 10 years are 21% for ovarian/peritoneal/tubal cancer (15% for peritoneal cancer alone), 16% for breast cancer, and 36% for any cancer.

The lower risk of breast cancer in *BRCA* mutation carriers observed in our study as compared with the data from the Netherlands^{29,30} may be explained by random variation, by different populations, by mutation position, or by study

design. Gayther et al³¹ proposed that germline mutations in the 5' region of the *BRCA1* gene are associated with a greater risk of ovarian cancer than mutations in the 3' region. In support of this, we identified a greater number of exon 2 185delAG mutations (in the 5' end of the gene) among the study subjects than 5382insC mutations (a 3' mutation). The 185delAG mutation accounted for 27 of 33 mutations identified in the cohort and for 12 of 13 of the mutation-positive cancer patients. The 3' *BRCA1* exon 20 5382insC mutation was detected in one incident breast cancer patient diagnosed at age 44 and in one thyroid cancer patient diagnosed at age 36. The 5382insC mutation is much less common than the 185delAG mutation in the Jewish population.⁴ By using a case-control approach, we have previously estimated an RR of 37 for ovarian cancer for the 185delAG mutation and of 21 for the 5382insC mutation.¹¹

Because of the small number of cancers observed in the cohort, it was not possible to calculate age-specific risks. Our estimates are based on a population of Jewish women with a family history of ovarian cancer or breast cancer. It is not yet clear to what extent these risks are generalizable to carriers of other *BRCA1* mutations, to those without a family history, or to those from a different ethnic group. In particular, the risk of peritoneal carcinomatosis was high in this cohort, but these cases seem to be caused by a single *BRCA1* mutation. It may be that mutations in other regions of the *BRCA1* gene are associated with a lower risk. It has not yet been established that carriers of *BRCA2* are at increased risk of peritoneal cancer.

In contrast to the *BRCA1/2* mutation carriers presented by Meijers-Heijboer et al²⁹ and Brekelmans et al,³⁰ our study did not include a breast cancer screening protocol; however, women were advised to arrange breast cancer screening outside of the Gilda Radner Program. Magnetic resonance imaging was not available to our participants, and mammography was routinely recommended. Four of the six women with breast cancer reported that they detected the breast lump themselves, and one woman (who did not have a mutation) had a breast tumor detected by mammography (Table 3). Information on the detection method of breast cancer for one case was not available.

Screening by ultrasound and CA-125 did not result in the identification of early-stage ovarian cancer in the Gilda Radner program. We believe that genetic testing is an option for the Ashkenazi Jewish woman at high familial risk for ovarian cancer, because the majority of Jewish women who have a family history and who develop breast or ovarian cancer will be carriers of *BRCA* mutations. These women may benefit from prophylactic bilateral salpingo-oophorectomy, including the reduction in the risk of subsequent breast cancer with the removal of the ovaries by decreasing levels of circulating

estrogen.^{32,33} However, given the high proportion of cancers with peritoneal origins observed in our study, it is not clear to what extent the risk of cancer will be reduced by oophorectomy. Future follow-up studies of women with mutations who have undergone an oophorectomy will be critical to clarify this risk.

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