

Breast and Ovarian Cancer Risks Due to Inherited Mutations in *BRCA1* and *BRCA2*

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Risks of breast and ovarian cancer were determined for Ashkenazi Jewish women with inherited mutations in the tumor suppressor genes *BRCA1* and *BRCA2*. We selected 1008 index cases, regardless of family history of cancer, and carried out molecular analysis across entire families. The lifetime risk of breast cancer among female mutation carriers was 82%, similar to risks in families with many cases. Risks appear to be increasing with time: Breast cancer risk by age 50 among mutation carriers born before 1940 was 24%, but among those born after 1940 it was 67%. Lifetime risks of ovarian cancer were 54% for *BRCA1* and 23% for *BRCA2* mutation carriers. Physical exercise and lack of obesity in adolescence were associated with significantly delayed breast cancer onset.

Breast cancer is the most common malignancy among women, with a lifetime risk of more than 10%. Ovarian cancer is rarer, with a lifetime risk of 1.8%, but it is among the most lethal cancers (*1*). Most breast and ovarian cancers are sporadic (that is, not inherited), but

some are the result of inherited predisposition, principally due to mutations in the tumor suppressor genes *BRCA1* and *BRCA2*. Women born with mutations in *BRCA1* or *BRCA2* are at significantly higher risk of developing breast and ovarian cancer than are women in the general population, but the magnitude of risk to these women is controversial [reviewed in (*2*)]. In families with multiple cancer cases, which were used to clone the *BRCA1* and *BRCA2* genes, the estimated lifetime risk of breast cancer is >80%, and the lifetime risk of ovarian cancer is 40 to 65% for *BRCA1* carriers and 20% for *BRCA2* carriers (*3*). Subsequent estimates of risk were based on families of singly ascertained breast cancer patients, using family history and statistical models of risk as a surrogate for molecular analysis of relatives. These risk estimates were significantly lower (*4-16*). The goal of this project was to combine ascertainment of probands not selected for high incidence of cancer with genetic analysis of relatives throughout families with mutations, including in the risk assessment only female relatives with confirmed *BRCA1* or *BRCA2* mutations.

Probands were consenting patients with incident, invasive breast cancer, regardless of age or family history of cancer, diagnosed between September 1996 and December 2000 by participating physicians at one of 12 major cancer centers in the greater New York City area (*17*). The cohort was composed specifically of Ashkenazi Jewish patients, because this population harbors three ancient *BRCA1* and *BRCA2* mutant alleles with a combined population frequency of 2.5% (*4, 5, 8, 18*) and includes very few rare family-specific *BRCA1* or *BRCA2* mutations (*19*). Therefore, in the Jewish population, accurate *BRCA1* and *BRCA2* status can be obtained for large numbers of breast cancer patients by screening only a limited number of mutation

sites. Nevertheless, the results are likely to be generalizable to women with any pathogenic *BRCA1* and *BRCA2* mutations who have similar lifestyles.

Of the 1008 female probands with incident, primary, invasive breast cancer, 104 (10.3%) carried an ancient mutation in *BRCA1* or *BRCA2*. Frequencies of the individual mutations were 42 (4.2%) *BRCA1*.185delAG, 25 (2.5%) *BRCA1*.5382insC, and 37 (3.7%) *BRCA2*.6174delT, similar to values previously reported in this population (*4, 5, 6, 8, 12*). As anticipated, inherited breast cancer was associated both with young age at breast cancer onset and with family history of breast or ovarian cancer (Table 1). However, the expected association of inherited predisposition with family history masks an observation with important clinical implications. Namely, exactly half of the patients with inherited mutations (52 of 104) were from low-incidence families with no breast or ovarian cancer among mothers, sisters, grandmothers, or aunts. In nearly all these low-incidence families, *BRCA1* and *BRCA2* mutations proved to be inherited from fathers. We subsequently tested whether low incidence was equivalent to low risk.

From families of probands with a *BRCA1* or *BRCA2* mutation, living adult relatives were enrolled and genotyped, regardless of the relatives' own cancer histories or places of residence (*17*). Genotypes of deceased relatives were determined from genotypes of their children or by isolating DNA from tissues archived by pathology departments. Independently, cancer history was obtained for relatives by interview or from hospital records and confirmed by pathology report or (occasionally) by death certificate. After genotypes were determined, clinical and genetic data were merged. Using Kaplan-Meier analyses, cumulative risks by age of breast cancer and of ovarian cancer were determined for female relatives carrying any of the three ancient *BRCA1* or *BRCA2* mutations (*20*). Only relatives with confirmed *BRCA1* or *BRCA2* mutations were included in the risk analysis. If all sisters in a sibship could not be genotyped with certainty (either directly or by reconstruction from their surviving relatives), the entire sibship was omitted from the risk analysis. All probands were excluded from the risk analysis, because they were selected in consequence of their breast cancer.

Risks of breast cancer to relatives with *BRCA1* or *BRCA2* mutations were 20% by age 40, 55% by age 60, and >80% by age 80 (Fig. 1A) (Table 2). There was no significant difference in risk by specific mutation, although risks associated with *BRCA2* were lower prior to age 65 years. In contrast, risks of ovarian cancer were significantly greater (log rank $P = 0.002$) among women with *BRCA1* mutations compared to women with *BRCA2* mutations (Fig. 1B) (Table 2).

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Table 1. Proportion of breast cancer due to inherited mutations in *BRCA1* or *BRCA2* among Ashkenazi Jewish patients by age at diagnosis and family history.

	Number of probands	<i>BRCA1</i> 185delAG	<i>BRCA1</i> 5382insC	<i>BRCA2</i> 6174delT	Any mutation	Relative risk	<i>P</i> value
All female probands	1008	0.042	0.025	0.037	0.103	1.0	
Age at diagnosis (years)							
<40	105	0.12	0.12	0.10	0.35		
40–44	135	0.08	0.01	0.07	0.16		
45–49	187	0.05	0.01	0.02	0.08		
50–59	305	0.02	0.03	0.02	0.07		
60+	276	0.004	0.004	0.02	0.03	(trend)	<10 ⁻⁶
Relative with breast cancer							
Mother, sister, grandmother, or aunt	570	0.06	0.03	0.04	0.13	1.9	0.01
Any male relative	21	0.10	0	0.14	0.24	2.4	0.05
Relative with ovarian cancer							
Mother or sister	50	0.20	0.08	0.04	0.32	3.5	<10 ⁻⁶
Grandmother or aunt	60	0.17	0.03	0.03	0.23	2.5	<10 ⁻⁶
Proband diagnosed age <45 years and							
any relative with breast cancer	134	0.14	0.06	0.10	0.30	4.1	<10 ⁻⁶
any relative with ovarian cancer	27	0.30	0.04	0.07	0.41	4.3	<10 ⁻⁶
No breast or ovarian cancer in 1° relatives	658	0.02	0.02	0.03	0.08		
No breast or ovarian cancer in 1° or 2° relatives	411	0.01	0.02	0.03	0.07		

Because lifetime breast cancer risks were higher than those reported from most previous studies of families of unselected patients (4–16), we undertook several tests for ascertainment bias, that is, the possibility that probands with severe family histories were more likely to be included in the project (17). First, we compared family histories of cancer among participating probands to family histories of a sample of eligible patients who declined participation and found no difference in severity (SOM Text). Second, high risks of breast cancer among women with mutations were not due to disproportionate selection of families with mothers with breast cancer, because risk estimates were not changed if mothers with mutations were excluded from the analysis (table S1B).

Risks to *BRCA1* or *BRCA2* mutation carriers with no family history of breast cancer would be lower than risks to mutation carriers with positive family history if risk modifiers (whether genetic or nongenetic) clustered in families (21). To determine whether the low-incidence families in our series were also low risk, we evaluated risk among mutation carriers from families with no cancer in the proband's nuclear family. There are two possible explanations for lack of cancer in the nuclear family of a patient with a *BRCA1* or *BRCA2* mutation. (i) The family may have truly low penetrance of the *BRCA1* or *BRCA2* mutation, with female mutation carriers remaining unaffected. (ii) Alternatively, the family may include few women with mutations because the family is small, or there is a preponderance of males, or normal alleles (rather than mutant alleles) segregated by chance to female relatives. The only means of distinguishing these alternatives is by direct testing of female relatives. Therefore, breast cancer in low-incidence families was evaluated

Table 2. Cumulative risks (standard errors) of breast cancer and ovarian cancer among relatives with *BRCA1* or *BRCA2* mutations.

Risk by age	Breast cancer			Ovarian cancer	
	<i>BRCA1</i> or 2	<i>BRCA1</i>	<i>BRCA2</i>	<i>BRCA1</i>	<i>BRCA2</i>
30	0.02 (0.01)	0.03 (0.01)	0	0	0
40	0.20 (0.03)	0.21 (0.03)	0.17 (0.05)	0.03 (0.01)	0.02 (0.02)
50	0.37 (0.04)	0.39 (0.04)	0.34 (0.07)	0.21 (0.04)	0.02 (0.02)
60	0.55 (0.04)	0.58 (0.05)	0.48 (0.08)	0.40 (0.05)	0.06 (0.05)
70	0.71 (0.04)	0.69 (0.05)	0.74 (0.08)	0.46 (0.06)	0.12 (0.07)
80	0.82 (0.05)	0.81 (0.06)	0.85 (0.08)	0.54 (0.07)	0.23 (0.12)

for second-, third-, and fourth-degree relatives (grandmothers, aunts, and cousins) with confirmed *BRCA1* or *BRCA2* mutations. Breast cancer risks to mutation carriers among these distant relatives were 20% by age 40, 51% by age 60, and 78% by age 80 (table S1C). There was no difference in risk between relatives with mutations in these families and relatives with mutations in other families.

An example of a low-incidence family is shown in Fig. 1C. The absence of cancer in this family was due to paternal transmission of mutations and chance inheritance of wild-type alleles by female relatives. Many other low-incidence families were small. In still other families, mothers and sisters carried normal *BRCA1* and *BRCA2* alleles, whereas distant relatives carried *BRCA1* or *BRCA2* mutations and proved to be at high risk of cancer. In these families, low incidence was not equivalent to low risk. Finally, older cancer-free women with *BRCA1* or *BRCA2* mutations did not cluster in a subset of families. The 11 such women in the study were from 11 different families.

To explore potential modification of risk by nongenetic factors, we evaluated risk among the relatives by birth year or

birth cohort (Fig. 1D). Age by age, breast cancer risks for relatives born after 1940 (the median birth year of our cohort) were significantly higher than risks for relatives in the same families born before 1940 (log rank $P < 0.0001$). The difference in risk was due to birth cohort and not to the genetic phenomenon of anticipation, which we also tested. Ovarian cancer risk did not vary by birth cohort ($P = 0.27$). The increase in breast cancer risk over time among mutation carriers parallels, at much higher levels, the increase in breast cancer incidence among women generally (1). The influence of birth year also introduces a risk modifier that is highly significant but not correlated within families.

To identify the factors that might explain some portion of the influence of birth year on risk, we evaluated information provided by 967 responding probands (of 1008 total) regarding menstrual and reproductive histories, exercise and body weight, contraceptive and hormone use, and environmental and occupational exposures. We reasoned that among probands with *BRCA1* or *BRCA2* mutations, factors associated with older onset of breast cancer might be protective, whereas factors associated with ear-

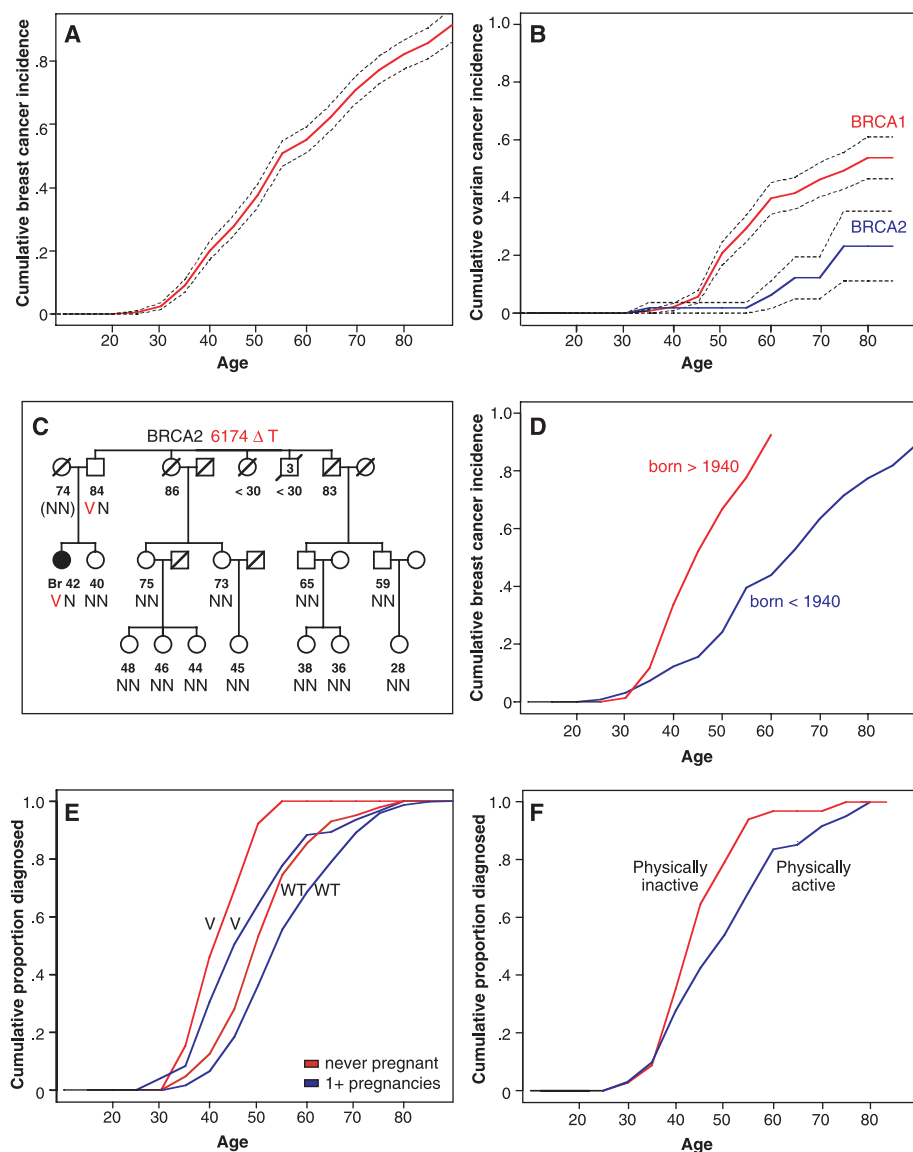


Fig. 1. Risks of breast and ovarian cancer among *BRCA1* and *BRCA2* mutation carriers. (A) Risk of breast cancer (\pm standard error) for female relatives with confirmed *BRCA1* or *BRCA2* mutations. Risks did not differ between carriers of *BRCA1* versus *BRCA2* mutations. (B) Risk of ovarian cancer (\pm standard error) among female relatives with *BRCA1* mutations and with *BRCA2* mutations. (C) Breast cancer proband with *BRCA2* mutation 6174delT (V) and no history of breast or ovarian cancer in her family. Circles represent females, and squares represent males; each relative's current age or age at death is indicated. The proband inherited the mutation from her father. All her female relatives carried wild-type alleles at *BRCA2* (NN). The family has low cancer incidence due to chance segregation of normal *BRCA2* alleles to female relatives, rather than due to low risk among mutation carriers. (D) Influence of birth cohort on risk of breast cancer among *BRCA1* and *BRCA2* mutation carriers. Age by age, breast cancer risks for mutation carriers born after 1940 were significantly higher than risks for mutation carriers in the same families born before 1940 (log rank $P < 0.0001$). (E) Age of breast cancer onset among probands by BRCA genotype and pregnancy history. Proband with *BRCA1* or *BRCA2* mutations (V) developed breast cancer at significantly younger ages than did probands with wild-type alleles (WT) at *BRCA1* and *BRCA2* ($P < 10^{-12}$). For women of all genotypes, pregnancy as opposed to nulliparity was associated with delayed breast cancer onset ($P = 0.009$). (F) Age of breast cancer onset among probands with *BRCA1* and *BRCA2* mutations by level of exercise as a teenager. Breast cancer onset was later among mutation carriers who were active in sports, dance, or casual exercise as teenagers compared with those who were not physically active. Risks in (E) and (F) were estimated by Cox regressions and adjusted for decade of birth.

adjusted for decade of birth of the proband. P values were adjusted for multiple comparisons. Analyses were carried out for the study cohort as a whole and after stratifying by *BRCA1* and *BRCA2* genotype. Relative risks associated with all risk factors are summarized in table S2. In particular, early first pregnancy has been shown to be protective against lifetime risk of breast cancer (22). Among all probands in our study, pregnancy, as opposed to nulliparity, was associated with later cancer onset ($P = 0.009$). The relative risk was approximately the same magnitude among probands with or without *BRCA1* or *BRCA2* mutations (Fig. 1E).

Two modifiable risk factors were significantly associated with delayed age at breast cancer onset among probands with *BRCA1* or *BRCA2* mutations: physical exercise as an adolescent and healthy weight (as opposed to obesity) at menarche and age 21. Proband who were physically active as teenagers developed breast cancer later than did those who were physically inactive (Fig. 1F). Physical activity as a teenager was associated with delayed breast cancer onset both among the probands generally ($P = 0.025$) and specifically among women with *BRCA1* or *BRCA2* mutations ($P = 0.034$). Normal weight (rather than overweight) at menarche ($P = 0.017$) and lighter weight at age 21 ($P = 0.021$) were also associated with older age of breast cancer onset among women with *BRCA1* or *BRCA2* mutations. These effects were consistent with the significant correlation in our cohort between physical exercise and healthy body weight ($P = 0.016$) and with previous findings that among women generally, exercise and healthy weight in early life are protective against breast cancer after menopause (23).

These results indicate that breast and ovarian cancer risks among *BRCA1* or *BRCA2* mutation carriers who are ascertained through a single affected relative are as high as risks observed in multiply affected families. This finding may have clinical implications for these women, for whom medical surveillance includes screening starting at an early age, use of new detection methods and/or chemoprevention, and often risk-reducing surgeries of the ovary and/or breast (24–28). The second finding of this study is that nongenetic factors may significantly influence the penetrance even of high-penetrance mutations. Breast cancer risk in women born before 1940 is high (~80%), but risk is even higher for women born after 1940. Identifying these nongenetic influences on penetrance suggests new directions for studies of *BRCA1*- and *BRCA2*-associated carcinogenesis.

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lier onset of breast cancer might exacerbate risk. Cox analyses were used to estimate relative hazards and hence to calculate relative risks

associated with each variable. Because prevalences of many environmental factors have changed over time, all Cox regressions were

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Supporting Online Material
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Structure of Rab GDP-Dissociation Inhibitor in Complex with Prenylated YPT1 GTPase

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Rab/Ypt guanosine triphosphatases (GTPases) represent a family of key membrane traffic regulators in eukaryotic cells whose function is governed by the guanosine diphosphate (GDP) dissociation inhibitor (RabGDI). Using a combination of chemical synthesis and protein engineering, we generated and crystallized the mono-prenylated Ypt1:RabGDI complex. The structure of the complex was solved to 1.5 angstrom resolution and provides a structural basis for the ability of RabGDI to inhibit the release of nucleotide by Rab proteins. Isoprenoid binding requires a conformational change that opens a cavity in the hydrophobic core of its domain II. Analysis of the structure provides a molecular basis for understanding a RabGDI mutant that causes mental retardation in humans.

Rab/Ypt proteins, the largest subgroup of the Ras GTPase superfamily, function as molecular switches mediating tethering, docking, fusion, and motility of intracellular membranes (1). The multitude of Rab-controlled processes is reflected in the occurrence of a large number of predominately structurally unrelated Rab-interacting proteins (2, 3). However, the Rab escort protein (REP) and the Rab GDP-dissociation inhibitor (RabGDI), which form the family of RabGDI/REP proteins, are shared by all known Rab proteins. RabGDI is a key regulator of Rab/Ypt GTPases that controls the

distribution of the active GTP and inactive GDP-bound forms between membranes and cytosol (4). RabGDI can deliver to and retrieve from the membrane only Rab/Ypt proteins that are both geranylgeranylated and GDP loaded. A RabGDI deletion is lethal in yeast, whereas the I92P mutation (5) in the α -RabGDI gene leads to X-linked nonsyndromic mental retardation in humans (6, 7).

The structure of RabGDI solved previously revealed a molecule composed of two domains tilted with respect to each other (8). Mutational analysis defined the region of the molecule involved in the association with Rab proteins (Rab-binding platform) and a putative membrane receptor-interacting region termed the mobile effector loop (MEL) (4). However, the structure of α -RabGDI reveals neither the position of the lipid-binding site nor the mechanism of GDP-dissociation inhibition or Rab membrane delivery and extraction (4). Recently, a structure of the mammalian α -RabGDI in complex with geranylgeranyl cysteine was solved, which led to the suggestion that the lipid-

binding site is located on domain I above the MEL (9).

Attempts to determine the structure of the Rab:RabGDI complex have been hampered by technical problems: First, overexpression of RabGTPases in eukaryotic expression systems results in only a minor fraction of prenylated RabGTPase bound to membranes, which precludes production of large amounts

Table 1. Statistics of diffraction data collection and refinement. The x-ray source was SLS, Villigen. The detector was a MARCCD (charge-coupled device). Completeness, R_{sym} , and $I/\sigma(I)$ are given for all data and for the highest resolution shell: 1.6 to 1.5 Å. The model was from the Protein Data Bank, PDB ID 1GND. The structure was solved by molecular replacement method using the crystallography and NMR system of ref. (26). Abbreviations: mc/sc/lig/wat, main chain, side chain, ligand (GDP, geranylgeranyl), water molecules.

Parameter	Value
<i>Data collection</i>	
Wavelength (Å)	0.9803
Resolution (Å)	19.5–1.5
R_{sym}^* (last shell)	7 (40.5)
Observations total/unique	392839/106322
Completeness (last shell)	98.4 (96.3)
$\langle I \rangle / \sigma(I)$ (last shell)	11.6 (3.1)
Molecular replacement model	Bovine α -RabGDI
<i>Refinement</i>	
Resolution (Å)	19.49–1.5
$R_{work}/R_{free}^\dagger$	19.2/21.6
Protein/GDP/Mg/geranylgeranyl/water atoms	5100/28/1/20/911
Included amino acids, RabGDI, YPT1	5–446 3–198, 206
RMSD bonds/angles (Å/degree)	0.011/1.6
B (Å ²) (mc/sc/lig/wat)	13.3/16.2/7.4, 34.4/26.4

* $R_{sym} = \sum_j |I_j - \langle I_j \rangle| / \sum_j I_j$, where $\langle I_j \rangle$ is the average intensity of reflection j for its symmetry equivalents; values in parentheses are for the highest resolution shell. $^\dagger R_{work} = \sum |F_{obs}| - k|F_{calc}| / \sum |F_{obs}|$. Five percent of randomly chosen reflections were used for the calculation of R_{free} .

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