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The Importance of a Family History of Breast Cancer in Predicting the Presence of a *BRCA* Mutation

To the Editor:

Hartge et al. (1999) describe the prevalence of the three founder Ashkenazi Jewish (AJ) mutations in *BRCA1* (MIM 113705) and *BRCA2* (MIM 600185) in 5,290 AJ volunteers from the Washington, DC, area. They report an overall mutation frequency of 2.3%, ranging from 1.2%, in those with no personal or first-degree-relative history of breast or ovarian cancer, to 50%, in women diagnosed with breast or ovarian cancer at age <40 years who had at least one first-degree relative with breast cancer diagnosed at age <50 years. The authors demonstrate, as we and others (Karp et al. 1997; Shattuck-Eidens et al. 1997; Fodor et al. 1998) have done, that, for the 297 women in their study with breast or ovarian cancer, the probability of carrying a *BRCA1* or *BRCA2* (*BRCA*) mutation decreases as age at diagnosis increases. Hartge et al. (1999, p. 965) state that, given age-at-onset information, "family history discriminated relatively little if the participant herself developed breast cancer, whereas, among other participants, family history best discriminated carriers from non-carriers." The age of the proband is clearly a powerful predictor of carrier probability, but our experience is that family history is an important determinant of the probability of a mutation, in both unaffected and affected women. Therefore, we reanalyzed Hartge et al.'s data, estimating relative risks of carrying a *BRCA* mutation for each age-at-diagnosis group (stratified by decade), in association with a first-degree-relative family history of breast cancer at any age ("positive family history") and in association with a first-degree-relative family history of at least one case of breast cancer diagnosed at age <50 years ("positive early-onset family history"). We analyzed affected and unaffected women separately. In affected women, the Mantel-Haenszel (M-H) odds ratio (OR), stratified by age at onset, for the association between a positive family history and the presence of a founder *BRCA* mutation, compared with a negative family history, was 2.6 (95% confidence interval [CI] 1.2–6.0, $P = .022$; table 1, first "OR" column). For unaffected women, the M-H OR for the presence of a mutation in women with a positive family history was 3.1 (95% CI 1.9–5.1, $P < .001$; table 1, second "OR" column). For affected women, the M-H OR for the presence of a *BRCA* mutation in association with a positive early-onset family history was 4.4 (95% CI 1.7–11.4, $P = .003$; table 2, first column). This OR is greater than that observed in

Table 1

M-H OR for the Presence of a *BRCA* Mutation in Association with a Positive Family History of Breast Cancer, Stratified by Age or Age at Onset

	Hartge et al. (1999)						Warner et al. (1999): Affected Women		
	Affected Women			Unaffected Women					
	No. of			No. of			No. of		
	Noncarriers	Carriers[b]	OR [95%CI][c]	Noncarriers	Carriers[b]	OR [95%CI][c]	Noncarriers	Carriers[b]	OR [95%CI][c]
Age[a]									
<40 years									
FH × −	21	6	1.0	557	9	1.0	14	7	1.0
FH × +	4	3	2.6 [.5–15.0]	114	10	5.4 [2.4–12.5]	3	6	4.0 [.8–20.6]
40–49 years									
FH × −	71	6	1.0	874	14	1.0	80	13	1.0
FH × +	27	5	2.2 [.6–7.6]	215	9	2.6 [1.2–5.9]	31	10	2.0 [.8–5.0]
50–59 years									
FH × −	57	2	1.0	628	8	1.0	81	4	1.0
FH × +	19	4	6.0 [1.2–30.2]	169	6	2.8 [.9–7.8]	21	5	4.8 [1.3–17.8]
≥60 years									
FH × −	46	1	1.0	611	4	1.0	95	2	1.0
FH × +	25	0	.6 [.0–15.5]	189	2	1.6 [.3–8.8]	39	1	1.2 [.1–13.9]
M-H			**2.6 [1.2–6.0]**			**3.1 [1.9–5.1]**			**2.6 [1.4–5.0]**
			P			*P*			*P*
Homogeneity			.50			.53			.63
Unity			.022			<.001			.004

[a] FH × = family history of breast cancer in any first-degree relative. The minus sign (−) indicates negative; the plus sign (+) indicates positive.
[b] Of a founder AJ *BRCA1* or *BRCA2* mutation.
[c] The logit estimate of the odds ratio was used when there was a zero cell.

Table 2

M-H OR for the Presence of a *BRCA* Mutation in Association with a Positive Family History of Early-Onset Breast Cancer, Stratified by Age or Age at Onset

	Hartge et al. (1999)						Warner et al. (1999): Affected Women		
	Affected Women			Unaffected Women					
	No. of			No. of			No. of		
	Noncarriers	Carriers[b]	OR [95%CI][c]	Noncarriers	Carriers[b]	OR [95%CI][c]	Noncarriers	Carriers[b]	OR [95%CI][c]
Age[a]									
<40 years									
FH × 50 −	23	7	1.0	614	14	1.0	17	11	1.0
FH × 50 +	2	2	3.3 [.4–26.4]	57	5	3.9 [1.4–10.3]	0	2	7.6 [.3–173]
40–49 years									
FH × 50 −	92	8	1.0	1014	17	1.0	97	17	1.0
FH × 50 +	6	3	5.8 [1.4–23.9]	75	6	4.8 [2.0–11.4]	14	6	2.5 [.8–7.1]
50–59 years									
FH × 50 −	70	4	1.0	743	12	1.0	90	4	1.0
FH × 50 +	6	2	5.8 [1.0–32.6]	54	2	2.3 [.5–10.1]	12	5	9.4 [2.7–33.1]
⩾60 years									
FH × 50 −	61	1	1.0	734	5	1.0	122	2	1.0
FH × 50 +	10	0	2.0 [.1–51.2]	66	1	2.2 [.3–18.3]	12	1	5.1 [.548.0]
M-H			**4.4 [1.7–11.4]**			**3.6 [2.0–6.4]**			**4.4 [2.1–9.2]**
			P			*P*			*P*
Homogeneity			.81			.83			.40
Unity			.003			<.001			<.001

[a] FH × 50 = family history of breast cancer at age <50 years in any first-degree relative. The minus sign (−) indicates negative; the plus sign (+) indicates positive.

[b] Of a founder AJ *BRCA1* or *BRCA2* mutation.

[c] The logit estimate of the odds ratio was used when there was a zero cell.

unaffected women with a positive early-onset family history (M-H OR 3.6, $P < .001$; table 2, second "OR" column). Thus, a family history of breast cancer is as predictive of the presence of a *BRCA* mutation in affected women as it is in unaffected women. The M-H OR for the unaffected and affected subgroups is similar and has overlapping CIs. The significance levels do differ, but this reflects the much larger size of the subgroup of unaffected women ($n = 4{,}993$; 94.4%) compared with those with breast or ovarian cancer ($n = 297$; 5.6%). In addition, a comparison of the strata-specific ORs in unaffected and affected women does not reveal a consistent pattern: none of the within-strata ORs differ statistically—the smallest *P* value is .38 (table 1, "OR" column 1 vs. column 2; table 2, "OR" column 1 vs. column 2).

To assess whether our reinterpretation of the Washington, DC, data set is valid, we performed the same analysis in 412 prevalent cases of breast cancer diagnosed in AJ women, ascertained between November 1, 1996, and May 31, 1998, in Toronto and Montreal (Warner et al. 1999). To compare exactly with the Washington, DC, study, we included only first-degree relatives with breast cancer in the analyses here. The definition of early-onset breast cancer was age at diagnosis of <50 years. The results are shown in tables 1 and 2, "OR" column 3. Notably, the M-H ORs seen in the Canadian study are identical to that observed in affected women in the Washington, DC, study: M-H OR 2.6 for the presence of a *BRCA* mutation in association with any first-degree-relative history of breast cancer and 4.4 for a positive early-onset family history. Thus, the findings from the Canadian study support our interpretation of the data published by Hartge et al. (1999) and lead us to question those authors' conclusion that the knowledge gained from knowing the family history of an affected person is "relatively small." The weight of evidence from clinical experience, from previously published work, and from their own study supports the conclusion that family history and age at diagnosis of breast cancer are both important factors in indicating the likely presence of a mutation in *BRCA1* or *BRCA2*.

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Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for *BRCA1* [MIM 113705] and for *BRCA2* [MIM 600185])

References

Fodor FH, Weston A, Bleiweiss IJ, McCurdy LD, Walsh MM, Tartter PI, Brower ST, et al (1998) Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. Am J Hum Genet 63:45–51

Hartge P, Struewing JP, Wacholder S, Brody LC, Tucker MA (1999) The prevalence of common *BRCA1* and *BRCA2* mutations among Ashkenazi Jews. Am J Hum Genet 64: 963–970

Karp SE, Tonin PN, Bégin LR, Martinez JJ, Zhang JC, Pollak MN, Foulkes WD (1997) Influence of *BRCA1* mutations on nuclear grade and estrogen receptor status on breast carcinoma in Ashkenazi Jewish women. Cancer 80:435–441

Shattuck-Eidens D, Oliphant A, McClure M, McBride C, Gupte J, Rubano T, Pruss D, et al (1997) BRCA1 sequence analysis in women at high risk for susceptibility mutations: risk factor analysis and implications for genetic testing. JAMA 278:1242–1250

Warner E, Foulkes W, Goodwin P, Meschino W, Blondal J, Patterson C, Ozcelik H, et al (1999) Prevalence and penetrance of *BRCA1* and *BRCA2* mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst 91:1241–1247

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