

More About: Multifactorial Analysis of Differences Between Sporadic Breast Cancers and Cancers Involving BRCA1 and BRCA2 Mutations

The indications for searching mutations in BRCA1 gene are based mainly on clinical data, such as significant familial background and early onset breast cancer. However, such indications are limited in the clinical practice first because large families are rare in the Western world (1) and second because the mutation detection rates in populations now under study are lower than those previously expected (2). Since breast cancers associated with BRCA1 mutations harbor specific morphologic features (3,4), it is anticipated that the use of morphologic parameters in combination or not with family history will help optimize the screening of BRCA1 germline mutations. Encouraging results

were obtained in screening medullary breast cancers for BRCA1 mutations (1).

In support of this view, Brown et al. (5) advocate for the use of steroid receptor status in the selection of case subjects for screening BRCA1 mutations. The authors consider that the absence of both estrogen receptors and progesterone receptors could be the most distinctive feature of breast cancers associated with BRCA1 mutations. We performed a multifactorial analysis incorporating steroid receptor status among several other parameters. Our results are in agreement with the proposal of Brown et al. about the importance of estrogen receptor negativity (ER(-)] in the BRCA1 germline mutation-associated phenotype (6), but progesterone receptor negativity appears to be of no further value in establishing BRCA1 status in the breast cancer we studied. Notwithstanding, other parameters associated with the estrogen receptor pathway may be used to improve the performance of genetic screening.

With this aim, we compared the expression of the estrogen-responsive gene pS2 (7) immunohistochemically by use of the P28O2 monoclonal antibody in breast cancer patients with BRCA1 mutations and in control individuals with sporadic cancers, according to the estrogen receptor status. Case patients (n = 33) with a family history (hereditary cancers) and consecutive control patients (n = 193) without a family history of breast cancer were selected from the records of the French Cooperative Network (3) and from our hospital-based registry, respectively. Since mutations in BRCA1 and BRCA2 genes do not contribute to more than 5% of all breast cancers, the control patients were

Table 1. Distribution of pS2 protein expression in estrogen receptor negative [ER(-)] breast cancers associated with mutations in BRCA1 gene and control patients with ER(-) sporadic breast cancers*

ER(-) tumors	pS2 expression status		Total	P	Odds ratio (95% confidence interval)
	Negative (%)	Positive (%)			
Sporadic breast cancers (control patients)	35 (60.3)	31 (83.8)	66		
Breast cancer patients with BRCA1 mutations	23 (39.7)	6 (16.2)	29		
Total	58	37	95	.016	3.4 (1.1-10.8)

*The pS2 expression was analyzed immunohistochemically by use of P28O2 monoclonal antibody in ER(-) tumors. A two-sided chi-squared statistical test was used to compare the differences between breast cancers associated with BRCA1 mutations and control women with sporadic cancers. The odds ratio gives the strength of the relationship between breast cancers associated with BRCA1 mutations and the pS2 expression status among the ER(-) tumors.

considered to have breast cancers predominantly of the sporadic type.

In our panel of 226 breast cancers, 95 (42.0%) were ER(-). Among those with the tumors that were both ER(-) and pS2 negative [pS2(-)], 23 (39.7%) of 58 had mutations in the BRCA1 gene (Table 1). In contrast, among those with tumors that were ER(-) and pS2 positive [pS2(+)], only six (16.2%) of 37 had mutations in the BRCA1 gene ($P = .016$; odds ratio = 3.4 [95% confidence interval = 1.1–10.8]). Consequently, among the ER(-) tumors, those that were also pS2(-) were more likely associated with a BRCA1 germline mutation than those that were pS2(+).

Our study is in agreement with that of Brown et al. with respect to the use of the estrogen receptor status of tumors to optimize identification of carriers of mutations in the BRCA1 gene. However, BRCA1 screening that uses estrogen receptor status only is not worthwhile (6) because of the low sensitivity and specificity and the large population to be tested (corresponding to about 10 000 and 50 000 case patients every year in France and in the United States, respectively). Additional parameters can be selected on the basis of pathophysiologic arguments (similar to the expression of pS2 gene used in this study), but other tumor-associated variables, such as circumscription, proliferation, or differentiation (4,6), may be considered as well in the multivariate analyses. In the clinical practice, there is a requirement for characterization of tumors with respect to these variables; this characterization will in turn guide the selection of appropriate variables for multivariate analyses. The definition of such an algorithm is often the result of the balance between the expected impact in terms of positive predictive value, the cost-effectiveness ratio, and the inter- or intra-observer reproducibility of the parameters under study. Consequently, the most operational model in discriminating tumors associated with a BRCA1 mutation could differ from those defined on a theoretical basis only.

FRANÇOIS EISINGER
JOCELYNE JACQUEMIER
EMMANUELLE CHARAFE-JAUFFRET
MARIE-CHRISTINE RIO
DANIEL BIRNBAUM
HAGAY SOBOL

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Affiliations of authors: F. Eisinger, J. Jacquemier, E. Charafe-Jauffret (Department of Genetic Oncology/INSERM E 9939), D. Birnbaum (Laboratory of Tumor Biology/INSERM U 119), H. Sobol (Department of Genetic Oncology/INSERM E 9939 and Laboratory of Tumor Biology/INSERM U 119), Paoli-Calmettes Institute, Marseille, France; M.-C. Rio, Institut de Genetique et de Biologie Moleculaire et Cellulaire, Strasbourg, Illkirch, France.

Correspondence to: Hagay Sobol, M.D., Ph.D., Department of Genetic Oncology/INSERM E 9939 and Laboratory of Tumor Biology, Paoli-Calmettes Institute, 13009 Marseille, France (e-mail: sobol@marseille.inserm.fr).

RESPONSE

The new data from Eisinger et al., indicating that approximately 80% of estrogen receptor-negative breast cancers from BRCA1 mutation carriers also lack expression of pS2, are a welcome addition to our knowledge base regarding BRCA1-associated tumors. In a recently published study, Armes et al. (1)

report a similar concordance between absence of estrogen receptor and lack of pS2 expression in breast cancers from BRCA1 mutation carriers, although they did not observe a statistically significant difference in pS2 expression between cancers from BRCA1 mutation carriers and control subjects in their series. Perhaps most importantly, given the association between pS2 expression and responsiveness to tamoxifen (2), these data underscore the concern that antiestrogen-based strategies may be ineffective for the majority of BRCA1 mutation carriers.

In our prior correspondence (3), we suggested that estrogen receptor expression of the breast cancer of affected family members could be used, via Bayesian analysis, to fine tune the *a priori* estimate of finding a pathologic mutation. Our other principal suggestion was that multifactorial prediction models be developed that incorporate discriminating elements of tumor pathology, such as hormone receptor content, that are readily available in standard pathology reports and for which there is high interobserver agreement. On this score, immunohistochemical analysis of pS2 expression would be an inappropriate component to such a model

DEBORAH L. BROWN
BERNARD F. COLE
BRADLEY A. ARRICK

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Affiliations of authors: Norris Cotton Cancer Center, Dartmouth Medical School, Hanover, NH.
Correspondence to: Bradley A. Arrick, M.D., Ph.D., Dartmouth Medical School, Kellogg Box 0128, Hanover, NH 03755 (e-mail: Bradley.Arrick@dartmouth.edu).