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Prediction of *BRCA1* Germ Line Mutation Status in Women with Ovarian Cancer using Morphology-based Criteria: Identification of a *BRCA1* Ovarian Cancer Phenotype

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Abstract

Specific morphologic features that may predict *BRCA1* germline mutation in ovarian cancer have neither been well described nor independently tested. We identified 5 morphologic features associated with *BRCA1* mutation status in a series of 20 ovarian cancers from *BRCA1* mutation carriers: 1) modified Nottingham grade 3; 2) serous/undifferentiated histology; 3) prominent intraepithelial lymphocytes; 4) marked nuclear atypia with giant/bizarre forms; and 5) abundant mitotic figures. These morphologic features were then tested on 325 ovarian tumors drawn from a population-based Greater Bay Area Cancer Registry, and classified into 3 categories independent of *BRCA1* status: “Compatible with *BRCA1*”, “Possibly compatible with *BRCA1*” and “Not compatible with *BRCA1*”. All “Compatible with *BRCA1*” tumors were additionally investigated for presence of dominant adnexal mass, fallopian tube mucosal involvement, and uterine cornu involvement. The positive and negative predictive values for “Compatible with *BRCA1*” were 11/42 (26.2%) and 267/283 (94.3%) respectively, while combining the “Compatible with *BRCA1*” and “Possibly compatible with *BRCA1*” had positive and negative predictive values of 18/85 (21.2%) and 231/240 (96.3%), respectively. Although dominant adnexal mass and uterine cornu involvement did not add further predictive value, the likelihood of *BRCA1* positivity increased to 42.9% when a tumor with “Compatible with *BRCA1*” histology was also associated with fallopian tube mucosal involvement. The combination of modified Nottingham grade 3 serous or undifferentiated histology, prominent intraepithelial lymphocytes, marked nuclear atypia with giant/bizarre nuclei and high mitotic index should help to identify women for *BRCA1* mutational analysis in the appropriate clinical setting. Ovarian tumors lacking this specific phenotype are unlikely to be associated with *BRCA1* and should not undergo mutational analysis in absence of other indications.

Keywords

BRCA1; germline mutation; serous; ovarian cancer; morphology

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Introduction

Women with *BRCA1* germline mutation are at an increased risk of developing breast and ovarian cancer. Current management of mutation carriers requires early and more frequent screening, risk-reducing mastectomy, risk-reducing salpingo-oophorectomy, and long term vigorous follow-up. Due to a relatively high penetrance, germline *BRCA1* mutations also have major implications for potentially affected family members. Given these considerations, there is significant benefit in identifying *BRCA1* mutation carriers in order to personalize care for these women. Routine testing for *BRCA1* germline mutation is not without costs. Genetic testing is expensive and the frequency of *BRCA1* mutation carriers in the general population is extremely low (0.0006)¹¹, with only 5–7% of all breast cancer and 10–12% of all ovarian cancer attributable to *BRCA1* germline mutations.^{6; 28} Although it has been suggested that testing be offered to all women with ovarian cancer, the ideal management plan would triage patients into risk levels for *BRCA* germline mutation, with those at higher risk benefiting most from genetic testing.

One way to stratify patients, other than family history, is through tumor histomorphology. It is now well established that *BRCA1*-associated breast cancer tends to be triple-negative, high grade ductal histologic type, often with prominent necrosis and this specific tumor morphology has allowed physicians to facilitate the genetic screen decision-making process in some settings.^{1; 3; 4; 8; 9; 12; 17} In contrast, other than general high grade serous histology^{4; 18; 34; 36; 38} and p53 expression^{10; 16}, characteristic histology for *BRCA1*-associated ovarian tumors has not been well described. To determine whether or not there is a characteristic and reproducibly identified ovarian tumor morphology in women with *BRCA1* mutation and if so, whether tumor histomorphology could predict *BRCA1* germline mutation in women with ovarian cancer, we investigated a series of ovarian tumors from women with known *BRCA1* mutation status drawn from a large, population-based cancer registry in the Greater Bay Area.

Materials and Methods

Case selection & study design

Two ovarian cancer data sets were accessed for this study. In order to develop a candidate set of criteria that could then be tested on a larger ovarian cancer data set with known *BRCA* mutation status, an initial “training set” of ovarian cancers was identified by computerized search of the surgical pathology files from Stanford University Hospital. The “training set” of ovarian cancers consisted of 20 ovarian, peritoneal and fallopian tube carcinomas from women with a known deleterious *BRCA1* germline mutation. The tumors were either obtained from standard ovarian cancer surgical staging procedures (n=15) or from risk-reducing salpingo-oophorectomy surgery (n=5). The larger data set of ovarian tumors (“test set”) was drawn from the Greater Bay Area Cancer Registry. This registry is operated by the Cancer Prevention Institute of California as part of the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. The patients were participants in a case-control study of ovarian cancer.²⁰ Briefly, patients were eligible to participate in the study if they were diagnosed between March 1, 1997-July 31 2001 with invasive or low malignant potential epithelial ovarian tumors, were age 20–64 years and resided in one of the six San Francisco Bay Area counties (Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara). Of the 915 eligible patients, 24 (2.6%) were not contacted because their physician refused permission, 209 (22.8%) refused to participate, had died, or could not be located, and 682 (74.6%) were interviewed. Of the patients that were interviewed, 608 (66.4%) provided a blood or mouthwash sample for DNA extraction. Patients were screened for *BRCA1* germline mutations by single-strand conformation polymorphism analysis or by the protein truncation test.^{23; 35} We obtained tissue blocks on 325 (53.5%) of the cases.

Sections of the paraffin-embedded tissue were cut and H&E slides were prepared for review by the study pathologist (T.A.L.).

Selection of specific morphologic criteria (the “training set”)

The set of cases obtained from the surgical pathology files at Stanford University Hospital were evaluated by one of the pathologists (T.A.L.) for tumor histology (serous, endometrioid, mucinous, clear cell, etc.), growth pattern (papillary versus glandular; solid and papillary or glandular versus solid and sheet-like), tumor grade, necrosis, nuclear anaplasia, mitotic index, and presence of tumor infiltrating lymphocytes. Tumor grade was based on a 3-tier scheme using the modified Nottingham scheme for grading breast cancer as detailed by Shimizu et al.³¹ Mitotic index was scored as low, intermediate and high based on the modified Nottingham grading scheme. Atypical mitotic figures were noted, but were not otherwise quantified. Nuclear anaplasia was scored positive when tumor cell nuclei exhibited significant deviation from the surrounding tumor cell nuclei in any given tumor; nuclear anaplasia, so defined could be focal or multifocal. Tumor infiltrating lymphocytes were arbitrarily scored as positive if >40 intraepithelial lymphocytes were present in a single high power field, but in most cases they were so prominent that formal counts were not required. The presence of any tumor cell necrosis was scored as positive.

Following review of this “training set” of ovarian cancer cases, the following primary criteria were formulated: serous or undifferentiated subtype, high grade (grade 3) histology, prominent tumor infiltrating lymphocytes, marked nuclear atypia with giant/bizarre nuclei, and high mitotic index. Serous subtype included tumor histology with papillary, micropapillary, and so-called “pseudoendometrioid” and “transitional” patterns.³² Undifferentiated tumor histology included solid sheets of cells without glandular, microglandular, papillary, micropapillary or so-called “transitional” patterns. The constituent cells were non-uniform and highly pleomorphic.

Evaluation of specific morphologic criteria for predicting *BRCA1* mutation (the “test set”)

Based on the specific morphologic criteria identified in the “training set”, tumors from the ovarian cancer patients who participated in the case-control study were evaluated blinded to *BRCA1* mutational status by two separate pathologists (M.F. and T.A.L.) and classified into 3 categories: “Compatible with *BRCA1*”, “Possibly compatible with *BRCA1*” and “Not compatible with *BRCA1*”. Tumors placed into the “Compatible” category showed high grade (grade 3) serous/undifferentiated histology, prominent intraepithelial lymphocytes, marked nuclear atypia with giant/bizarre nuclei, and abundant mitoses. In addition to the basic tumor histologic subtype (serous and/or undifferentiated), all tumors classified as “Compatible” were required to demonstrate high-grade histology based on the Shimizu grading scheme.³¹

Cases that showed more than two but not all of the “Compatible” features were placed into the “Possibly compatible with *BRCA1*” category. All other tumors, including those with histology other than high grade serous/undifferentiated, few to no intraepithelial lymphocytes, minimal to moderate atypia with monomorphic nuclei, and few or scattered mitoses were categorized as “Not compatible with *BRCA1*” (Table 1).

Evaluation of additional predictive criteria

Since necrosis is considered one of the histologic features of *BRCA1* breast carcinoma, each of the tumors in the test set was separately evaluated for the presence of tumor cell necrosis even though necrosis was not identified as a key histologic feature for *BRCA1* germline mutation in the initial training set,.

Given the prevailing theory that *BRCA1* ovarian carcinomas are likely to be tubal in origin all tumors that demonstrated “Compatible with *BRCA1*” histology were additionally investigated for presence or absence of fallopian tube mucosal involvement, a dominant mass (defined as follows: the bulk of the tumor must be within ovarian parenchyma and limited to 1 ovary, or 1 involved ovary must exceed the other in greatest dimension by more than 2-fold²⁹), and uterine cornu involvement. Histopathological classifications were compared with germline *BRCA1* mutation status.

Results

Test set demographics

We tested 608 ovarian cancer cases in the case-control study for *BRCA1* germline mutations.^{23; 35} Of these, 325 patients (53.5%) also had tumor blocks and H&E slides available for retrospective review, with 27 patients (8.3%) *BRCA1* positive and 298 (91.7%) *BRCA1* negative (Table 2). Only 2 patients, who carried a *BRCA1* mutation (7.4%; 1 “Compatible” and 1 “Maybe compatible”), had a prior history of breast cancer

Performance of specific histologic criteria in predicting *BRCA1* status

We reviewed 325 ovarian tumors, which included 199 serous (high grade, low grade, and low malignant potential), 43 mucinous (predominantly low malignant potential), 34 endometrioid (high grade, low grade, and low malignant potential), 30 clear cell (all carcinoma), 5 undifferentiated, and 14 miscellaneous (adenosarcoma, etc) cases (Figure 1). They were categorized (Table 2) as follows: 42/325 (12.9%) “Compatible with *BRCA1*” (Figure 2A–C); 43/325 (13.2%) “Possibly compatible with *BRCA1*” (Figure 3A–C) and 240/325 (73.8%) “Not compatible with *BRCA1*” (Figure 4A–C).

Germline *BRCA1* mutations were present in 11/42 (26.2%) “Compatible with *BRCA1*”, 7/43 (16.3%) “Possibly compatible with *BRCA1*” and 9/240 (3.8%) “Not compatible with *BRCA1*” (Table 2). Of the 11 “Compatible” cases, 8 were high grade serous and 3 had undifferentiated histology. All 7 of the “Possibly compatible” cases also showed high grade serous histology, while the 9 “Not compatible” cases included 6 high grade serous, 1 serous low malignant potential, 1 endometrioid, and 1 clear cell histology (Figure 5).

The sensitivity and specificity of “Compatible with *BRCA1*” morphology predicting for *BRCA1* positive status were 40.7% (11/27) and 89.6% (267/298), respectively; while the sensitivity and specificity of combining “Compatible” and “Possibly compatible” were 66.7% (18/27) and 77.5% (231/298), respectively. The positive and negative predictive value for “Compatible” was 26.2% (11/42) and 94.3% (267/283), respectively (Table 3).

Comparing the sensitivity and specificity of “Compatible” alone (40.7%, 89.6% respectively) versus combined “Compatible” and “Possibly compatible” (66.7%, 77.5% respectively), shows that the more lax set of criteria increased the sensitivity and decreased the specificity. Hence, although six high grade serous cases were placed into the “Not compatible” category that were *BRCA1* positive, the specificity of our criteria would have diminished greatly if we had included all high grade serous cases into the “Compatible” category without the other criteria.

Performance of additional criteria

Tumors were also evaluated for presence of prominent necrosis, defined as sheets or aggregates of necrotic tumor cells in absence of contiguous hyaline or infarction-type necrosis. Based on this definition, prominent necrosis trended toward tumors classified as “Compatible with *BRCA1*”, but this did not reach statistical significance ($p=0.06$).

To determine whether additional locational criteria would improve on the specific histologic criteria, all tumors classified as “Compatible with *BRCA1*” were further evaluated for the presence of a dominant mass, fallopian tube mucosal involvement and uterine cornu involvement. Of the forty-two “Compatible with *BRCA1*” cases, 14/42 (33.3%) had presence of a dominant mass, 7/42 (16.7%) had fallopian tube mucosal involvement, of which only two did not have a concurrent dominant mass and 2/42 (4.7%), in addition to presence of a dominant mass and fallopian tube mucosal involvement had uterine cornu involvement. Of the 14 cases with a dominant mass, 4 were *BRCA1* positive (28.6%); of the 7 cases with fallopian tube mucosal involvement, 3 were *BRCA1* positive (42.9%); none of the cases with uterine cornu involvement were *BRCA1* positive (Figure 6).

Discussion

The lifetime risk of ovarian and breast cancer for women in the general U.S. population is 1.4% and 12%, respectively, whereas women who carry *BRCA1* germline mutations have significantly greater risks of 15–40% for ovarian cancer and 60–80% for breast cancer.^{21; 24} Knowledge of such increased risks can empower women to make informed medical decisions to reduce their cancer risk, including whether to undergo prophylactic surgical procedures. Germline *BRCA1* mutation not only impacts individual health care delivery, but also has important implications for potentially affected family members.^{2; 7; 26; 27; 33}

Despite the obvious benefits of *BRCA1* germline mutation testing, it is equally important to note that ovarian and breast cancers associated with *BRCA1* mutation represent only a small fraction of all ovarian and breast carcinoma. Our results are in keeping with current population-based prevalence estimates of <10% *BRCA1* germline mutation among ovarian cancer patients.²⁸ The relatively low prevalence of being a *BRCA1* mutation carrier in the general population is an important consideration in developing genetic screening guidelines given the expense of genetic testing and the harm to patients and their families due to the possibility of false positive results. Consequently, optimal utilization of the mutation test requires careful patient selection and triage of patients depending on stratified risk factors. One potential criterion for patient selection for *BRCA1* testing, besides age at onset and family history, is tumor histology. This can be effective for breast cancer, where *BRCA1*-associated breast cancers tend to show high grade, invasive ductal histology with triple-negative, basal phenotype.^{12; 39} In this study, we show that a combination of high grade (modified Nottingham grade 3) serous/undifferentiated histology, prominent intraepithelial lymphocytes, marked nuclear atypia with giant, bizarre nuclei and abundant mitoses is strongly associated with germline *BRCA1* mutation positive ovarian cancer. More importantly, absence of this phenotype has a negative predictive value >95%.

Currently, women are selected for *BRCA1* mutation testing on the basis of a family history, but only a minority of women with ovarian cancer report a positive family history in a first degree relative and <10% of these women harbor a *BRCA1* mutation.²⁵ In addition, family history may be under-reported or uninformative due to paucity of female first degree relatives. In general, the threshold for genetic testing is a mutation probability of 20%, and this is currently reached only for cases with a strong family history.⁶ Based on our data, this threshold would also be reached by the presence of the specific ovarian cancer *BRCA1* histology that we have described. In fact, the positive predictive value of histomorphology alone performs as well as the Society of Gynecologic Oncologists clinical screening criteria.¹⁵ The addition of *BRCA1* histomorphology to age of diagnosis and family history could conceivably enhance our ability to identify patients with *BRCA1* mutations by defining more precisely those subgroups of patients with a high probability of harboring a mutation. Similar testing algorithms have been proposed for women with early onset triple-negative breast cancer.³⁹ Finally, and perhaps more importantly, given the negative

predictive value, women harboring ovarian tumors that do not conform to the specific *BRCA1* phenotype should not undergo mutational analysis in absence of other strong indications.

Prior studies of *BRCA1* ovarian cancers have emphasized serous histology.^{22; 26; 30} However, the specific histomorphologic features of these tumors were not otherwise specified and the predictive value of including tumor morphology to identify *BRCA1* mutations had not been evaluated. One of the strengths of our study is the inclusion of ovarian cancer patients recruited from a large population-based cancer registry; prior studies were based entirely on *BRCA1* mutation carriers ascertained through high-risk families selected for genetic testing, which may have selectively enriched for certain tumor types.^{16; 34} This study is also the first to test the predictive value of a set of potential *BRCA1* tumor histologic characteristics generated from a separate training set of known *BRCA1* ovarian cancers. Soslow et al reviewed a series of ovarian cancers for possible *BRCA*-specific tumor morphology, but that study included tumors with *BRCA1* and *BRCA2* abnormalities (which have dissimilar breast cancer morphology); as well as cases with somatic *BRCA1* mutation and *BRCA1* promoter hypermethylation.³² Unlike their study, we did not find tumor necrosis to be a specific feature of *BRCA1* germline mutation. The “SET (Solid, pseudoEndometrioid, and Transitional cell carcinoma-like) morphology” described by these authors³² is similar to the tumor morphology identified in our study, but is not sufficiently predictive of *BRCA1* germline status in absence of high grade histology (modified Nottingham grade 3), tumor infiltrating lymphocytes, cellular anaplasia, and mitotic index,. Many of the tumors in the “Possibly compatible with *BRCA1*” category in our study exhibited “SET” morphology, but lacked one or more of these additional histologic features; most were not associated with *BRCA1* germline mutation.

In recent years there has been widespread adoption of a 2-tiered grading scheme for non-uterine serous carcinoma.¹⁹ The scheme is based on fundamental differences between low grade and high grade serous carcinoma with respect to molecular biology, natural history, and response to standard treatment.¹³ While we fully endorse this scheme in routine diagnostic practice, we believe the application of the modified 3-tier Nottingham scheme for grading ovarian cancer³¹ is superior to the 2-tier scheme in predicting *BRCA1* status. We found serous tumors with grade 3 histology are far more likely to be associated with *BRCA1* mutation than those with grade 2 histology using the 3-tier scheme; inclusion of grade 2 tumors (“Possibly compatible with *BRCA1*”) in the algorithm identified a few additional *BRCA1*- associated tumors, but at a cost of decreased specificity.

One limitation to this study is the incomplete evaluation of fallopian tube in archival material. Although the number of “Compatible with *BRCA1*” cases also demonstrating fallopian tube mucosal involvement was comparatively small (7/42; 16.7%), the likelihood of *BRCA1* positivity increased to 42.9% when a tumor with “Compatible with *BRCA1*” histology was also associated with fallopian tube mucosal involvement. Tubal mucosal involvement may prove to be an additional predictive feature for *BRCA1* testing on further analyses that include full evaluation of the fallopian tube. Another potential limitation is the variation in number of sections taken for individual tumors in archival material obtained from a wide catchment area; however, this does not appear to have had a significant effect, given the high negative predictive value.

In addition to the specific serous/undifferentiated phenotype, three other histologic subtypes of ovarian tumor (serous LMP, endometrioid, and clear cell) occurred in our *BRCA1* mutation carriers. However, each subtype represented <5% of the *BRCA1* positive cases. Endometrioid and clear cell histology have been reported as being rarely associated with *BRCA1* mutation in other studies^{5; 14; 28; 37} and it is possible that these 2 subtypes represent

a minor, but true association with the *BRCA1* mutation; however, given the small numbers of cases, it is equally likely that they represent a chance occurrence since these tumor types also tend to occur more commonly in younger women. Serous tumors of low malignant potential on the other hand, have not been reported in other studies and are highly unlikely to be related to *BRCA1* mutation. Nevertheless, these cases illustrate the hazards in strict reliance on histologic criteria. The criteria proposed here are meant as a general guideline and should be considered as one of the factors when considering a patient for possible genetic testing. Personal and family history and other clinical factors are always essential.

In summary, age at diagnosis, family history of breast and/or ovarian cancer, and ethnicity are all essential parameters to consider when assessing risk, but there are limitations as to how well such factors accurately predict *BRCA1* status. Integrating information about specific ovarian cancer histology, especially when fallopian tube mucosal involvement is also present may help refine these estimates. The combination of high grade (modified Nottingham grade 3) serous/undifferentiated histology, prominent intraepithelial lymphocytes, marked nuclear atypia with giant/bizarre nuclei and high mitotic index should help to identify women for *BRCA1* mutational analysis in the appropriate clinical setting as well as, in absence of this phenotype, to exclude women from mutational analysis.

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Figure 1.
Histologic subtypes of the 325 total cases. Undiff: Undifferentiated; Misc: Miscellaneous

Figure 2. Histologic categorization of cases. “Compatible with *BRCA1*” showing high grade serous histology (A), abundant mitotic figures, severe atypia with giant bizarre nuclei (B), and prominent intraepithelial lymphocytes (C).

Figure 3. Histologic categorization of cases. “Possibly compatible with *BRCA1*” showing high grade serous histology (A) without prominent intraepithelial lymphocytes (B), but with severe atypia with bizarre nuclei and only scattered mitotic figures (C).

Figure 4. “Not compatible with *BRCA1*” showing high grade histology with transitional features (A), few to no intraepithelial lymphocytes (B), monomorphous nuclei with minimal atypia, no giant/bizarre nuclei and no mitotic figures (C).

Figure 5.

Histologic subtypes of the 27 *BRCA1* positive cases. HG: High grade; C: Compatible with *BRCA1*; PC: Possibly compatible with *BRCA1*; NC: Not compatible with *BRCA1*. Undiff: Undifferentiated; LMP: low malignant potential

Figure 6.

Relationship between cases with “Compatible with *BRCA1*” histology, presence of dominant mass, fallopian tube mucosal involvement and uterine cornu involvement and *BRCA1* positive status; C: Compatible with *BRCA1*; DM: Dominant mass; FTM: Fallopian tube mucosal involvement; UC: Uterine cornu involvement

Table 1

Histologic criteria for categorization

	Compatible with <i>BRCA1</i> *	Not compatible with <i>BRCA1</i>
Histologic subtype	Serous or undifferentiated	Other
Modified Nottingham grade	3	1–2
Intraepithelial lymphocytes	Prominent	Few to none
Cytologic atypia	Marked with giant/bizarre forms	Minimal/moderate with monomorphic nuclei
Mitoses	Abundant	Few to scattered

* : Those with more than 2 but not all of the “Compatible with *BRCA1*” features were placed into the “Possibly compatible with *BRCA1*”

Table 2*BRCA* classification of ovarian cancer patients by genotype and histology

	Genotyping			
		<i>BRCAI</i> +	<i>BRCAI</i> –	Total
Histology	Compatible	11	31	42
	Possibly Compatible	7	36	43
	Not compatible	9	231	240
	Total	27	298	325

Table 3

Predictive value of histopathologic *BRCA* classification in a population-based ovarian cancer case series.

	Positive predictive value	Negative predictive value
Compatible	11/42 (26.2%)	267/283 (94.3%)
Compatible and Possibly Compatible	18/85 (21.2%)	231/240 (96.3%)