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Research Article

Cancer Epidemiology, Biomarkers & Prevention

A *BRCA1/2* Mutational Signature and Survival in Ovarian High-Grade Serous Carcinoma

Fei Dong[1], Phani K. Davineni[1], Brooke E. Howitt[1], and Andrew H. Beck[2]

Abstract

Background: Mutational signatures have been identified by the broad sequencing of cancer genomes and reflect underlying processes of mutagenesis. The clinical application of mutational signatures is not well defined. Here we aim to assess the prognostic utility of mutational signatures in ovarian high-grade serous carcinoma.

Methods: Open access data of 15,439 somatic mutations of 310 ovarian high-grade serous carcinomas from The Cancer Genome Atlas (TCGA) are used to construct a Bayesian model to classify each cancer as either having or lacking a *BRCA1/2* mutational signature. We evaluate the association of the *BRCA1/2* signature with overall survival on the TCGA dataset and on an independent cohort of 92 ovarian high-grade serous carcinomas from the Australian Ovarian Cancer Study (AOCS).

Results: Patients from TCGA with tumors harboring the *BRCA1/2* mutational signature have improved survival (55.2 months vs. 38.0 months), which is independent of *BRCA1/2* gene mutation status, age, stage, and grade (HR = 0.64; $P = 0.02$). In the AOCS dataset, the *BRCA1/2* mutational signature is also associated with improved overall survival (46.3 months vs. 23.6 months) independent of age and stage (HR = 0.52; $P = 0.007$).

Conclusions: A *BRCA1/2* mutational signature is a prognostic marker in ovarian high-grade serous carcinoma. Mutational signature analysis of ovarian cancer genomes may be useful in addition to testing for *BRCA1/2* mutations.

Impact: This study identifies the use of mutational signatures as a biomarker for survival outcome in ovarian high-grade serous carcinoma. *Cancer Epidemiol Biomarkers Prev; 25(11); 1511–6. ©2016 AACR.*

Introduction

Advances in sequencing technology and informatics have led to the identification of mutational signatures in human cancer (1). These signatures are defined by the type and frequency of somatic events and represent a molecular phenotype of the underlying etiologic factors involved in cancer development.

Patterns of somatic sequence alterations have been associated with specific tumor types and mutational processes. The most common mutational signature in human cancer shows an enrichment of C>T transitions at CpG sites, which reflect spontaneous deamination of methylated cytosine to thymine and has been associated with age. Analysis of breast and ovarian carcinomas has identified a distinct mutational signature associated with loss of function mutations in *BRCA1* or *BRCA2* (1, 2). Genomes of cancers with *BRCA1/2* mutations have a relatively even distribution of types of nucleotide substitutions and lack of enrichment of C>T transitions compared to *BRCA1/2* wild-type cancers.

The identification of *BRCA1/2* mutations in breast and ovarian cancer has been increasingly recognized to have clinical significance beyond implications for hereditary cancer risk. *BRCA1/2* mutations are associated with response to platinum-based chemotherapy and favorable outcome in ovarian cancer (3–6). Tumor cells with *BRCA1/2* defect show *in vitro* sensitivity to PARP inhibitors (7, 8), and the use of PARP inhibitors to treat cancers with *BRCA1/2* mutation is a subject of clinical trials (9, 10).

No prior studies have evaluated the prognostic significance of mutational signatures in ovarian cancer. In this article, we develop a Bayesian statistical model to identify ovarian cancers that possess a *BRCA1/2* mutational signature, and we evaluate the prognostic significance of this classification in two independent cohorts of high-grade ovarian serous carcinoma.

Materials and Methods

Tumor samples

The Cancer Genome Atlas (TCGA) open access whole exome sequencing and clinical data from 310 ovarian serous carcinomas was obtained from the TCGA data portal (https://tcga-data.nci.nih.gov/tcga/). Sixteen tumors with less than 10 somatic mutations were excluded from the Bayesian analysis. Germline and somatic *BRCA1* and *BRCA2* mutations and somatic copy number alterations were obtained via the TCGA ovarian cancer publication and cBioPortal for Cancer Genomics (http://www.cbioportal.org/; refs. 3, 11). All samples with *BRCA1* or *BRCA2* variants were classified as *BRCA1/2* mutated, with the exception of samples with only *BRCA2* K3326*, a known benign variant. Clinical follow up was available for 292 of 294 patients.

The Australian Ovarian Cancer Study (AOCS) open access whole genome sequencing and clinical data from 92 donors was obtained from the International Cancer Genome Consortium data repository (https://dcc.icgc.org/; ref. 12). For donors with

[1]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. [2]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Fei Dong, Brigham and Women's Hospital, 75 Francis Street, Amory 3, Boston, MA 02115. Phone: 617-525-7813; fdong1@partners.org

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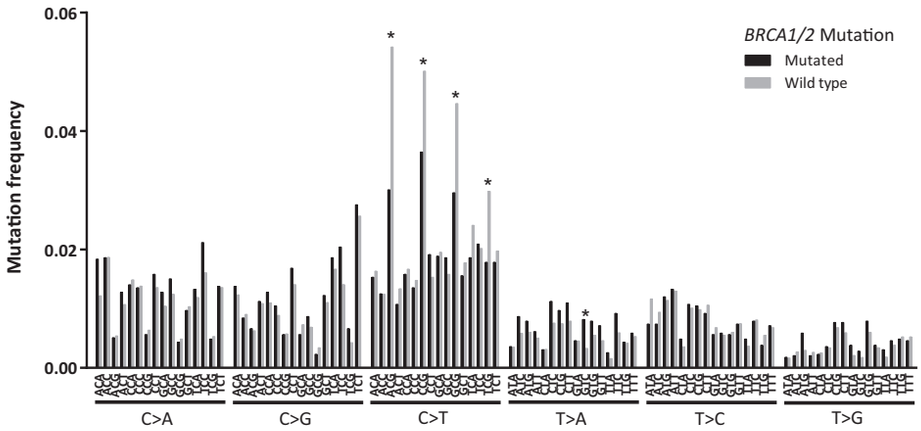

Figure 1.
Mutational signatures of *BRCA1/2* mutated and wild-type ovarian serous carcinomas. Asterisks designate mutation frequencies that are statistically significant at a Bonferroni-adjusted *P* value of < 0.0005.

multiple samples, only one sample with the lowest sample identification code was used for analysis.

Processing of sequencing data

Single nucleotide substitutions were mapped to human genome version 37 via Galaxy (https://usegalaxy.org/), and the 5′ and 3′ nucleotides adjacent to the substitution event were extracted. Consideration of six substitution classes (C>A, C>G, C>T, T>A, T>C, T>G) and the adjacent bases accounted for 96 possible substitution types. For each tumor, we computed the proportion of total substitutions from each of the 96 substitution types, and we used these proportions as the 96 input features for the Naïve Bayes analysis.

Bayesian classifier

We used Naïve Bayes to build a classifier to compute the conditional posterior probability of *BRCA1/2* mutational status given the observed proportions of mutational substitution types. To implement the analysis, we used the *NaiveBayes* function in the klaR package in R with default parameters. On the TCGA dataset, we built the model using mutational status, including germline and somatic *BRCA1/2* mutations (classification label), and the mutational substitution proportions (input features), and we predicted for each tumor the presence or absence of a *BRCA1/2* mutation, which we defined as a probabilistic representation of the tumor's mutational signature. The probabilistic prediction was then converted into a binary variable by thresholding at a posterior probability cut-off of 0.5, and tumors with probability greater than 0.5 were defined as having a *BRCA1/2* mutational signature. The binary *BRCA1/2* mutational signatures were then used in survival analyses. On the AOCS dataset, we applied the Bayesian model learned on the TCGA dataset to the mutational substitution proportions from the AOCS tumors to predict the presence or absence of a *BRCA1/2* mutational signature. The binary *BRCA1/2* signature predictions were then used in survival analyses.

Statistical methods for significance testing

Chi-square test was used to test for differences in frequencies of mutational substitution types. Mann–Whitney test was used to compare distributions of continuous variables. The log-rank test was used for the comparison of survival distributions. Univariate and multivariate survival analyses were performed using Cox proportional hazard models. All tests were two-sided with statistical significance set at $P < 0.05$. Bonferroni correction was applied to adjust for multiple comparisons, where appropriate.

Results

Distribution of substitution mutations in *BRCA1/2* mutated and wild-type cancers

A total of 15,439 somatic substitution mutations from 310 ovarian serous carcinomas were classified into 96 subtypes based on six substitution classes (C>A, C>G, C>T, T>A, T>C, T>G) and the flanking 5′ and 3′ nucleotides. A total of 69 of 310 carcinomas (22.3%) exhibited germline or somatic mutations in *BRCA1/2*. *BRCA1/2* mutated serous carcinomas demonstrated distinct mutational signatures compared to *BRCA1/2* wild-type carcinomas (Fig. 1 and Supplementary Table S1).

In ovarian high-grade serous carcinomas, the most common mutation types involved C>T transitions at CpG sites, which accounted for 16.2% of all mutations. *BRCA1/2* mutated carcinomas exhibited a decreased enrichment of C>T transitions at CpG sites compared to *BRCA1/2* wild-type carcinomas (11.4% vs. 17.9%, $P \leq 0.0005$). In addition, *BRCA1/2* mutated carcinomas showed a significant relative increase of T>A transversions at GpTpC sites (0.82% vs. 0.33%, $P = 0.0002$).

BRCA1/2 mutational signature and *BRCA1/2* mutation

A Bayesian model was constructed and applied to each tumor to derive a posterior probability of *BRCA1/2* mutation status based on the tumor's overall mutational substitution profile. To gain insight into the mutational patterns driving the model's predictions, we evaluated the mutational profiles of tumors with high confidence associations with posterior probability less than 0.1 (least *BRCA1/2*-like) or greater than 0.9 (most *BRCA1/2*-like). These tumors were shown to be particularly enriched for differentiating mutational subtypes. As expected, the mutational profiles of tumors predicted to have a low probability of a *BRCA1/2*-associated mutational signature were found to have increased prevalence of C>T transitions at CpG sites (Fig. 2). These findings supported that the Bayesian predictor classified cancers based on mutational signatures.

Although the predicted *BRCA1/2* mutational signature was highly correlated with the presence of *BRCA1/2* mutation, this association was imperfect, showing an area under the receiver operating characteristic curve of 0.86 ± 0.02 (Fig. 3A–C). The Bayesian prediction and *BRCA1/2* mutational status were

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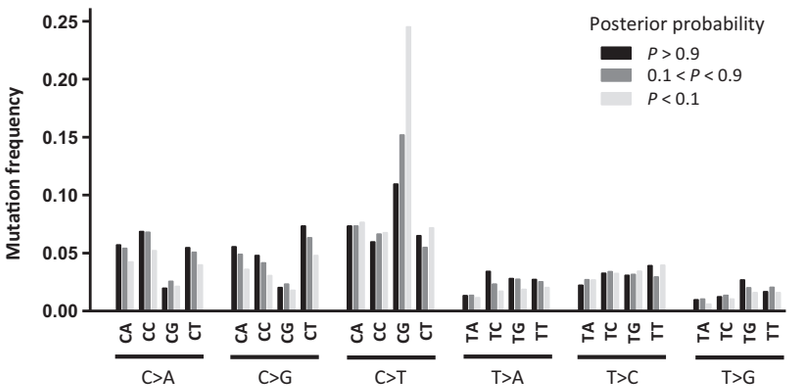

Figure 2.
Mutational profiles, subcategorized based on Bayesian posterior probability, in which $P > 0.9$ is most highly associated with *BRCA1/2* mutation, and $P < 0.1$ is most highly associated with wild-type *BRCA1/2*.

discordant in 74 of 294 tumors (25%) with sensitivity of 80.0% and specificity of 73.4% (Supplementary Table S2). This analysis suggested that a subclass of ovarian serous carcinomas with *BRCA1/2* mutations had mutational signatures similar to *BRCA1/2* wild-type carcinomas, and a subclass of ovarian serous carcinomas without *BRCA1/2* mutations had signatures similar to *BRCA1/2*-mutated carcinomas.

We postulated that the presence of a *BRCA1/2* mutational signature may provide additional information to *BRCA1/2* mutational status alone to more precisely subtype ovarian high-grade

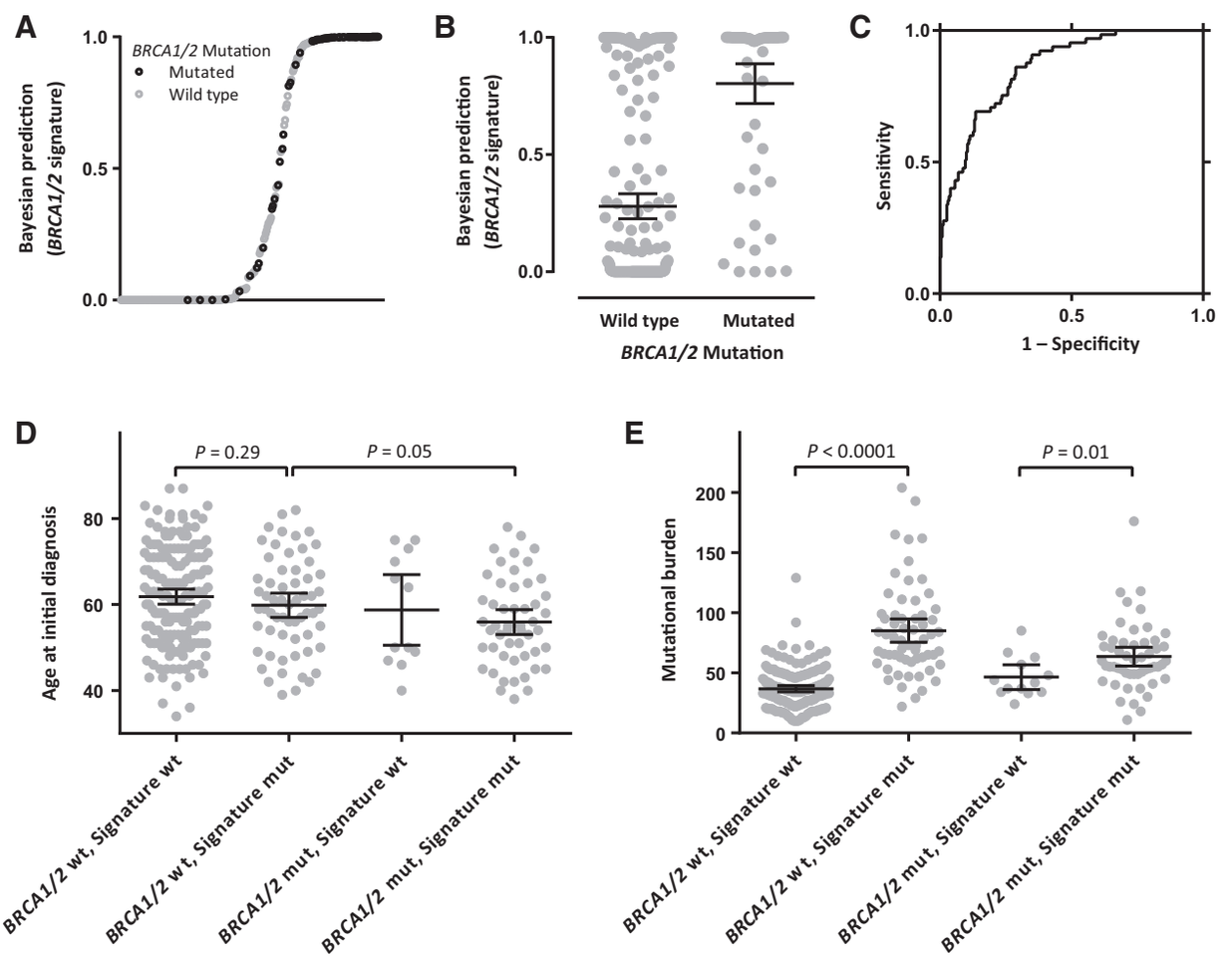

Figure 3.
Abbreviations: wt, wild type; mut, mutated. **A** and **B,** association of the Bayesian model's *BRCA1/2* mutational signature prediction with the presence of *BRCA1/2* mutations. **C,** receiver operating characteristics curve of mutational signature to predict *BRCA1/2* mutations (area under the curve, 0.86 ± 0.02). **D** and **E,** association of *BRCA1/2* mutations and *BRCA1/2* mutational signature with age and mutational burden, the total number of somatic mutations identified in each tumor. Error bars demonstrate 95% confidence interval.

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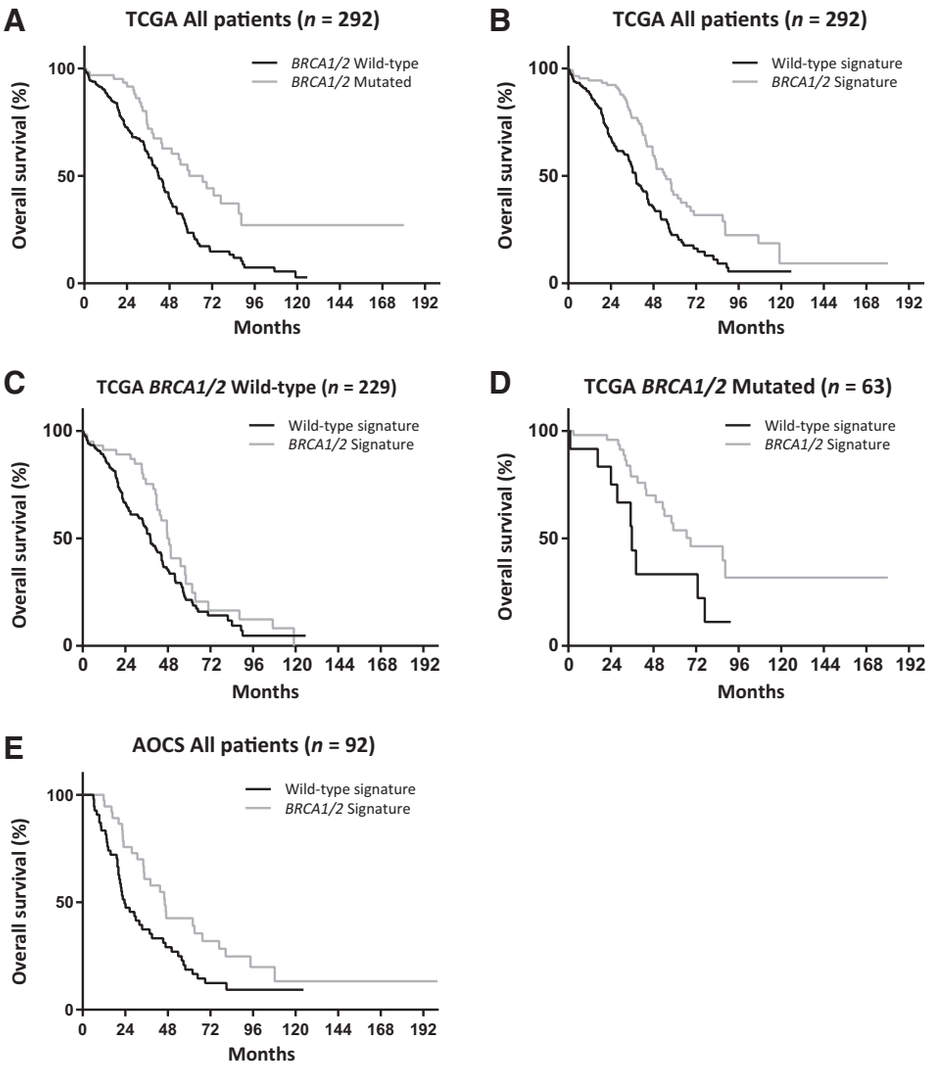

Figure 4.
A–D, TCGA overall survival stratified by *BRCA1/2* mutation ($P = 0.0002$, **A**) and *BRCA1/2* mutational signature ($P < 0.0001$, **B**). The *BRCA1/2* mutational signature was significantly associated with survival in patients without *BRCA1/2* mutation ($P = 0.01$, **C**) and with *BRCA1/2* mutation ($P = 0.01$, **D**). **E,** the *BRCA1/2* mutational signature is associated with overall survival in the AOCS cohort ($P = 0.003$).

serous carcinoma. To begin to evaluate this hypothesis, we studied the association between *BRCA1/2* mutation, *BRCA1/2* mutational signature, age, and mutational rate.

Patients with *BRCA1/2* mutation were diagnosed at a younger age (median 55 years compared to 61 years for patients without *BRCA1/2* mutation, $P = 0.003$). Among *BRCA1/2* wild-type patients, the median age at presentation of patients with a *BRCA1/2* mutational signature was similar to patients with wild-type signature ($P = 0.29$; Fig. 3D). Total mutational burden was positively associated with the *BRCA1/2* mutational signature overall ($P < 0.0001$) and in analyses stratified by *BRCA1/2* mutational status (both $P \leq 0.01$; Fig. 3E). These findings suggested that the *BRCA1/2* mutational signature was not significantly associated with age but was associated with biological features of cancer development such as mutational burden.

In a subset of 62 *BRCA1/2* mutated carcinomas with copy number information, copy number loss of the gene with sequence alteration (*BRCA1* or *BRCA2*) was compared to mutational signature. The majority of neoplasms (50 of 62, 81%) displayed copy number loss in *BRCA1* or *BRCA2* together with a mutation. A total of 44 of 50 carcinomas (88%) with *BRCA1/2* mutational signature showed copy loss of *BRCA1/2*, whereas 6 of 12 carcinomas (50%) with wild-type signature showed *BRCA1/2* copy loss ($P = 0.01$).

Association of *BRCA1/2* mutations and *BRCA1/2* mutational signature with clinical outcome

We then evaluated the association of *BRCA1/2* mutations and mutational signatures with clinical outcome. Most patients in the TCGA cohort had clinical stage III–IV and pathologic grade 3 cancers and were treated with adjuvant chemotherapy without radiotherapy (Supplementary Table S3).

Both *BRCA1/2* mutation and the *BRCA1/2* mutational signature were associated with improved overall survival in univariate analyses (Fig. 4A and B, both $P \leq 0.0002$). Median survival was 55.2 months for patients with a *BRCA1/2* signature compared to 38.0 months for patients with a wild-type signature. The *BRCA1/2* signature remained significant in analyses stratified by *BRCA1/2* mutation status (Fig. 4C and D). These findings showed that the *BRCA1/2* mutational signature had independent prognostic value

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Table 1. Multivariate survival analysis by Cox regression, including *BRCA1/2* signature, *BRCA1/2* mutation, age, stage, and grade in the TCGA dataset

	HR	95% Confidence interval	*P* value
BRCA1/2 signature	0.64	0.44–0.92	0.02
BRCA1/2 mutation	0.58	0.37–0.92	0.02
Age	1.01	1.00–1.03	0.07
Stage II	1.00		
Stage III	1.44	0.58–3.57	0.43
Stage IV	1.59	0.60–4.22	0.35
Grade 2	1.00		
Grade 3	1.69	0.92–3.08	0.09

in ovarian cancer beyond that achieved by *BRCA1/2* mutational status alone.

We evaluated the prognostic value of the *BRCA1/2* signature in multivariate survival analysis by a Cox proportional hazards model, which also considered *BRCA1/2* mutation, age, stage, and grade. In this model, *BRCA1/2* mutation status (HR = 0.58; $P = 0.02$) and *BRCA1/2* mutational signature (HR = 0.64; $P = 0.02$) were statistically significant and independent predictors of improved overall survival (Table 1).

Finally, we validated the prognostic value of the *BRCA1/2* mutational signature in an independent cohort from the Australian Ovarian Cancer Study. Here we considered an additional 5,757 mutations from 92 ovarian high-grade serous carcinomas. The mutational frequencies from *BRCA1/2*-mutated and wild-type carcinomas in TCGA were used to calculate Bayesian posterior probabilities of each cancer in AOCS.

The *BRCA1/2* mutational signature was associated with improved survival in the AOCS cohort in univariate analyses (Fig. 4E; $P = 0.003$). Median survival was 46.3 months for patients with a *BRCA1/2* signature compared to 23.6 months for patients with a wild-type signature in the AOCS cohort. The *BRCA1/2* signature remained significant in multivariate models adjusted for stage and age (HR = 0.52; $P = 0.007$; Table 2).

Discussion

In this study, we develop a Bayesian statistical model using somatic substitution mutation frequencies and identify a subset of ovarian high-grade serous carcinomas with a distinctive mutational signature associated with *BRCA1/2* mutation. The *BRCA1/2* mutational signature is present in some patients without demonstrable *BRCA1/2* mutation and is an independent predictor of outcome along with *BRCA1/2* mutational status in multivariate analysis.

Breast and ovarian cancers with *BRCA1/2* mutation have been well characterized to have unique biological and clinical features, collectively termed "BRCAness" (13). Features of BRCAness include DNA repair deficiency, distinctive gene expression patterns, response to platinum-based chemotherapy, and sensitivity to PARP inhibition. The field has dedicated significant effort to identifying *BRCA1/2*-associated features in sporadic cancers with the hope of expanding therapeutic options for a greater number of patients. Prior work has evaluated BRCAness in sporadic ovarian cancer by gene expression profiling and by analysis of somatic genomic alterations, including genomic instability, loss of heterozygosity, and mutational burden (14–17). These studies measure a variety of biological outputs and consistently identify BRCAness in a subset of sporadic cancers with implications in drug response and prognosis. The mechanism of BRCAness in ovarian cancers without *BRCA1/2* mutation is not well understood, but studies have implicated mutations in other homologous recombination genes in pathogenesis (18).

Table 2. Multivariate survival analysis by Cox regression, including *BRCA1/2* mutational signature, age, and stage in the AOCS dataset

	HR	95% Confidence interval	*P* value
BRCA1/2 signature	0.52	0.32–0.84	0.007
Age	1.01	0.98–1.04	0.46
Stage III	1.00		
Stage IV	0.53	0.25–1.11	0.09

More recently, the broad sequencing of cancer genomes have revealed mutational signatures in human cancer (1). Signatures of somatic alterations reflect mutational processes during tumor development, including a *BRCA1/2*-associated signature in breast and ovarian cancer. In that study, non-negative matrix factorization is used to approximate the contribution of a discrete number of signatures to the overall mutational profile of a cancer (19). Compared to non-negative matrix factorization, our Bayesian model also considers the overall mutational profile and uses the presence or absence of a known driver mutagenic exposure (e.g., *BRCA1/2* mutational status) to supervise model construction. This method may be readily applied to large sequencing datasets for hypothesis testing to derive and evaluate mutational signatures of a variety of known genetic and environmental exposures implicated in carcinogenesis.

We utilize open access data from two large cohorts to make observations about prognosis, and our analysis has limitations. The observed mutational signatures are associated with *BRCA1/2* mutations, but the rationale for the presence of a *BRCA1/2* mutational signature in the absence of mutation in some tumors is not explained in this analysis. These cases may reflect alternative mechanisms of *BRCA1/2* inactivation, defects of other genes in the homologous repair pathway, or limitations of whole exome sequencing in the TCGA dataset to identify *BRCA1/2* mutations. Similarly, a subset of patients with *BRCA1/2* mutation may have nonpathogenic mutations or have developed sporadic ovarian cancer via non-*BRCA1/2*-associated pathways. These hypotheses are not fully explored in this study. Although mutational signatures appear to be a prognostic indicator that is independent of *BRCA1/2* mutations, the overlap and redundancy between mutational signatures and other genomic features associated with *BRCA1/2* mutation, such as genomic instability and loss of heterozygosity, are not characterized.

Despite these limitations, our findings support the concept of BRCAness in a subset of ovarian high-grade serous carcinomas without *BRCA1/2* mutation, as defined by a signature of somatic events in the cancer genome. We liken the analysis of mutational signatures to that of gene expression profiles, a set of data rooted in biology with a potential to affect clinical decision making. We hypothesize that the improved survival of patients with a *BRCA1/2* mutational signature is driven by enhanced sensitivity to platinum-based chemotherapy, and these patients may be candidates for PARP inhibitor therapy. These hypotheses would need to be tested in controlled trials.

This analysis demonstrates the utility of mutational signatures to connect tumorigenic processes, molecular phenotype, and outcome and shows that whole exome sequencing can provide useful prognostic information derived from mutational patterns beyond what can be obtained from more targeted

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sequencing panels or single gene analysis. In ovarian high-grade serous carcinoma, a *BRCA1/2* mutational signature predicts improved overall survival independent of *BRCA1/2* mutational status alone. These findings suggest a potential indication for the broad sequencing of ovarian cancer genomes to inform prognosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: F. Dong
Development of methodology: F. Dong, A.H. Beck
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F. Dong, P.K. Davineni, B.E. Howitt, A.H. Beck
Writing, review, and/or revision of the manuscript: F. Dong, B.E. Howitt, A.H. Beck
Study supervision: F. Dong

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