

DNA Repair Mutations and Outcomes in Ovarian Cancer—Response

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We appreciate the thoughtful comments from Dr. Soslow (1) and agree with many of his points. As he pointed out, many institutions reserve genetic testing for ovarian cancers with high-grade serous histology (2). We believe such a restriction in current practice is a mistake and will miss identifying carriers of mutations in *BRCA1* and *BRCA2* as well as other more recently identified ovarian cancer susceptibility genes, a point we were attempting to highlight by dividing our cases into serous and nonserous carcinomas. We agree that carcinosarcomas and some high-grade endometrioid carcinomas are likely to be closely related to high-grade serous carcinoma. The Cancer Genome Atlas (TCGA) only characterized pure high-grade serous ovarian carcinomas, however. Therefore, we do not have equally detailed molecular annotation on other histologic types, and it may be premature to lump all of these carcinomas into one bin.

In a careful pathologic review, Gilks and colleagues (3) reclassified one third of endometrioid ovarian cancers as either serous or clear-cell carcinoma but two thirds were not reclassified, and those remaining endometrioid carcinomas did exhibit real differences from serous carcinomas, including a lack of WT-1 expression and a difference in outcome. Therefore, it seems unlikely that all high-grade endometrioid ovarian carcinomas are variants of serous carcinomas, though they may

indeed demonstrate similarly high rates of mutation in homologous recombination (HR) genes. For example, we have previously identified a germline *BRCA1* mutation in a patient with a stage IA, grade 3 endometrioid ovarian carcinoma with squamous differentiation, a feature considered characteristic of endometrioid (not serous) carcinoma.

Until we move to a molecularly driven classification scheme, we must continue to understand mutation patterns in patients with ovarian cancer using current pathology schemes. In referring patients for genetic testing, both the Society of Gynecologic Oncology and the National Comprehensive Cancer Network recommend offering testing to all women with invasive ovarian carcinoma. Before we make those guidelines more restrictive, we should remember that clinicians rely on real-world pathology that represents greater variability than the carefully reviewed cases presented in our series and other research studies. Furthermore, even the largest population series of *BRCA1* and *BRCA2* testing have included only small numbers of nonserous cases (4), and data about the histologic predilection of inherited mutations in other ovarian cancer genes are even more limited (5). Therefore, until we understand mutational patterns in a much larger number of ovarian cancers than presented here, it would be unwise to alter genetic testing guidelines.

Our data influenced several recently opened and upcoming PARP inhibitor trials to include endometrioid as well as serous ovarian carcinomas. Like Dr. Soslow, we argued during trial design that undifferentiated carcinomas and carcinosarcomas were likely serous variants and should also be included, but to no avail. Clearly, more data are needed to come to a consensus on the role of HR deficiency in various subtypes of ovarian carcinoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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