Letter to the Editor

Clinical Cancer Research

DNA Repair Mutations and Outcomes in Ovarian Cancer—Letter

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It was with great interest that I read the article by Pennington and colleagues (1) in the recent issue of *Clinical Cancer Research*. Pennington and colleagues sought to determine the therapeutic implications (particularly, the effect on platinum sensitivity) of somatic *BRCA1/2* mutations and mutations in other homologous recombination DNA repair genes. They found that germline or somatic mutations in homologous recombination genes were present in almost one third of the 390 ovarian carcinomas studied, stratified into serous and "nonserous" types. The authors concluded that "somatic *BRCA1/2* mutations and mutations in other homologous recombination genes have a similar positive impact on overall survival and platinum responsiveness as germline *BRCA1/2* mutations."

Separating ovarian carcinomas into serous and "nonserous" types has its merits, but the drawbacks obscure important, clinically relevant details. Some of the tumors assigned to the "nonserous" category are, in fact, intrinsically related to high-grade serous carcinoma. It is possible that the authors have overlooked recent advances in our understanding of the pathogenesis of carcinosarcoma and relationships between tumors historically considered "high-grade endometrioid carcinoma" and high-grade serous carcinoma of ovary. The gynecologic pathology community increasingly considers carcinosarcoma to represent a tumor-progression phenomenon, usually from a high-grade serous carcinoma substrate (2). As such, it is debatable whether to classify carcinosarcoma as a "nonserous carcinoma." Multiple studies have by now shown that most examples of tumors historically considered "high-grade endometrioid carcinoma" of the ovary are in reality variants of high-grade serous carcinoma (3, 4). The evidence here is the clinical, immunophenotypic, and genotypic similarity between these two entities; furthermore, most examples of "high-grade endometrioid carcinoma" fail to show morphologic features on microscopy that are specific for endometrioid differentiation. I would therefore argue that most or all of the "high-grade endometrioid carcinomas" studied in this report are more likely high-grade serous carcinomas than "high-grade endometrioid carcinomas." Even if one were to disagree with these assertions, it would not be possible to overlook the work by Shih and Kurman (5) positing that ovarian carcinomas can be broadly categorized into two groups: Type I tumors that frequently have identifiable precursor lesions and indolent-to-moderately aggressive clinical courses; and type II tumors that lack macroscopic precursors and behave in a highly aggressive fashion. High-grade serous and "high-grade endometrioid" carcinomas as well as carcinosarcomas are considered type II tumors.

It would be easy to assume that these types of distinctions are philosophical or only academic in nature. Instead, they have important practical implications. In many centers, genetic counseling and germline genetic testing for hereditary breast and ovarian cancer syndromes are restricted to patients with high-grade serous carcinoma. Classifying a high-grade serous carcinoma as "high-grade endometrioid carcinoma" or failing to note that a carcinosarcoma arose in the context of a high-grade serous carcinoma would deprive at-risk patients from being tested. Interestingly enough, the *BRCA1* and *BRCA2* mutations reported by Pennington and colleagues were restricted to serous carcinomas, "high-grade endometrioid carcinomas" and carcinosarcomas. They were not found in clear-cell carcinoma, low-grade endometrioid carcinoma, or the one malignant Brenner tumor tested (all type I ovarian carcinomas). The take-home message should therefore be that, based on the results reported in this article and others, deleterious *BRCA* mutations are restricted essentially to high-grade serous carcinomas and variants thereof.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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