Letter to the Editor

Cancer Prevention Research

PARP Inhibitors for Chemoprevention—Letter

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We read with great optimism To and colleagues' (1) article about PARP inhibitors as effective chemopreventive strategy for treating homologous repair (HR)–deficient tumors. Their overarching conclusion stated in the *discussion* is that "...synthetic lethality (i.e., PARP inhibitor therapy for high risk individuals) may be a useful strategy for developing chemopreventive regimens for a variety of cancers." More explicitly, the authors suggest that this chemopreventive approach "may eventually provide an alternative to watchful waiting (or prophylactic mastectomy)" in high-risk individuals. Although a very intriguing and promising study, we wish to extend the discussion and open a dialogue in regard to the potential clinical impact of this work.

We applaud the investigators for "thinking out of the box" for a subset of individuals who have an increased likelihood of being diagnosed with either breast, pancreatic, or ovarian cancers (2). This study certainly addresses an issue of how to manage high-risk individuals (e.g., *BRCA1*-mutant carriers) without intrusive medical procedures before patients present with a tumor. Yet, a number of considerations should be addressed:

1. The authors claim that the PARP inhibitors veliparib and olaparib can delay the development or detection of tumors in mice (by multiple weeks depending on the experiment). The key control missing from these experiments are other therapies. Could a tolerable, low dose of gemcitabine or a platinum have the same or better effect? As a corollary, the authors also claim that veliparib and olaparib were well tolerated, but there was a dose-dependent effect. Although some reports claim PARP inhibitors show mild toxic events, and in fact, in some instances could reduce the side effects of other drugs, it has still been reported that these inhibitors can induce fatigue, nausea, and myelosuppression (3). In sum, the possible long-term effect of PARP inhibitor treatment on normal tissues in a patient without any cancer or even a high-risk individual needs further clinical evaluation (4).
2. The investigators used a well-characterized mouse model that harbors BRCA1 deficiency combined with a *p53* null allele (5). It is necessary to include a control wherein mice harbor one mutant copy of *BRCA1*, because this mirrors the high-risk individuals the study is trying to target. This is important because giving high-risk individuals (i.e., those who carry an inherited mutant *BRCA1* gene) a PARP inhibitor may actually facilitate tumorigenesis, not delay it. Thus, giving PARP inhibitors to HR-heterozygous genetic carriers may increase the chances of a "second hit," and thus provide a "synthetic opportunistic" setting for chromosomal instability. Moreover, restoration of HR proficiency in *BRCA*-mutant carriers has been demonstrated after exposure to PARP inhibitors (6), likely due to reversion mutations as a resistance mechanism. Along these lines, "preventative" targeting may have adverse implications since PARP1 has been demonstrated to have diverse functions beyond DNA repair, which can be protumorigenic or antitumorigenic (7).
3. The authors do not address that even though their chemopreventive strategy delays tumor onset, it still does not prevent cancer. This is important because even if we take the leap that this strategy could delay onset of tumors in high-risk individuals by years, these patients still will eventually develop tumors and will need to be treated. Thus, it is likely that these late onset tumors will thus develop as PARP resistant and no longer be sensitive to PARP inhibitor or platinum-based therapies?

Our hope is that an approach that includes better imaging, early detection assays, and innovative chemopreventive approaches (such as the one proposed by this study) will lay the groundwork for preventing and treating cancer in high-risk individuals who carry a *BRCA1* mutation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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