Reviewer's report

Title: A Polymorphism in the Base Excision Repair Gene PARP2 is Associated With Differential Prognosis by Chemotherapy among Breast Cancer Patients

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Reviewer: Alicia Beeghly-Fadiel

Summary: Multiplicative interactions for 127 genetic variants in the base excision repair (BER) pathway were evaluated for interactions with three treatments (any chemotherapy, anthracycline chemotherapy, and radiotherapy) in regard to breast cancer survival among 1,408 postmenopausal women. An undisclosed number were selected to be tested for replication among 6,392 breast cancer cases from nine BCAC studies. One variant in the PARP2 gene had a replicated interaction with any chemotherapy (P=0.036) and anthracycline chemotherapy (P=0.009). Two variants in XRCC1 had replicated interactions with anthracycline chemotherapy. Three variants in POLB had suggestive interactions with any chemotherapy, but not anthracycline. No interactions with radiotherapy were replicated. The study and results are certainly interesting; the presentation of results and manuscript could be a little bit improved. These are Minor, but Essential Revisions.

1. Is the question well defined? Yes.

2. Are the methods appropriate and well described? Yes, with a few minor issues. First, the abstract describes a multiplicative interaction term, and implies that the P-value is from the Wald test, but the methods section says that the likelihood ratio test was used. This discrepancy should be clarified. The meta-analysis of the MARIE results and BCAC results is appropriate, however, the BCAC results seem to have been pooled, and adjusted for study site, rather than a meta-analysis across available BCAC sites, which would make more sense. Also, I will note that the selection of confounders would be better if a 10% change in estimate was evaluated, rather than an automated procedure, such as backward selection, but I recognize that this preference may differ.

3. Are the data sound? Yes.

4. Are the tables and figures appropriate/acceptable? Yes, with a few minor issues. Table 1: the additional information about neoadjuvant therapy under tumor size is unclear. I prefer P-values in Table 1, but recognize that this is also personal preference. Figure 1 is okay, but what would be more interesting is the
equivalent for the variants. If 127 were evaluated, and 14, 13, and 14 were tested for replication, how many total were tested, and then how many total replicated. By my count 4 total replicated, of which 2 are the same variant, so 3, but the paper focuses only one 1 in PARP2, and the abstract doesn't even mention the 2 in XRCC1. Figure 2 is not very informative. Since the paper is focused on testing interactions with variants, why not show the difference in variant effects by treatment? And again, how about the effects by BCAC site, then the meta across, so readers can decide if the results are robust or not?

5. Acceptable for reporting standards and data deposition? Yes.

6. Is the discussion and conclusion adequately supported? Mostly. As mentioned above, there seem to be 3 total replicated findings, but only PARP2 is discussed, not XRCC1. Plus three variants in POLB are suggestive, and since the association didn’t differ by anthracyclines or radiotherapy, what other treatments were there? Any other ideas for this potential difference? The discussion is overly focused on PARP2, and should be expanded.

7. Are the limitations clearly stated? Yes.

8. Appropriate acknowledgement of prior work (theirs and others)? Mostly. Additional information on prior studies that evaluated interactions between genetic variants and breast cancer treatment would be beneficial.

9. Accurate title and abstract? Not quite. Again, the focus is on PARP2, and XRCC1 is not included or discussed. Also, results are specific to post-menopausal women, not all breast cancer cases, so this should be clarified.

10. Acceptable writing? Yes, although at the end of the introduction, the clarification is needed that variants were tested for replication, and were not all replicated variants.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.