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Unwrapping the Implications of *BRCA1* and *BRCA2* Mutations in Ovarian Cancer

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Three large studies have demonstrated improved survival in *BRCA*-associated ovarian cancers compared to sporadic ovarian cancers.[1–3] These trials have combined *BRCA1* and *BRCA2* mutation carriers because of the relative rarity of *BRCA1* and *BRCA2* mutations, which only account for approximately 10% and 5% of unselected cases of serous ovarian cancer, respectively.[4] However, although both mutations are associated with hereditary breast and ovarian cancers, it has been suggested that these cancer predisposition syndromes represent related but clinically distinct entities.[5] The lifetime risk of ovarian cancer is higher in *BRCA1* than *BRCA2* mutation carriers, estimated at 36–60% and 16–27%, respectively.[6,7] *BRCA1* mutation carriers tend to develop ovarian cancer on average about eight years earlier than *BRCA2* mutation carriers.[1,4] Microarrays of *BRCA1* and *BRCA2*-associated ovarian cancers also show significant differences in gene expression.[8] Moreover, the protection conferred by risk-reducing salpingo-oophorectomy against breast and gynecologic cancers may differ between carriers of *BRCA1* and *BRCA2* mutations.[9]

In light of these observations, two recent reports have examined survival separately in *BRCA1* and *BRCA2*-associated ovarian cancers in small cohorts.[10,11] Both studies found significantly improved survival in *BRCA2*-associated ovarian cancers and smaller statistically non-significant improvement in survival in *BRCA1*-associated ovarian cancers.

In this issue of *JAMA*, Bolton et al[12] report their analysis of patients with *BRCA1* and *BRCA2* ovarian cancer who were included in a large international dataset. Incident cases of ovarian cancer were pooled from 26 international prospective clinical genetics protocols, the majority of which were affiliated with either the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) or the Ovarian Cancer Association Consortium (OCAC). Baseline clinical characteristics such as year of diagnosis, age, stage, grade, and histology were controlled for, when available, with respect to overall survival.

In their analysis of 3879 patients with ovarian cancer (2666 non-carriers, 909 *BRCA1* mutation carriers, and 304 *BRCA2* mutation carriers), the authors report fully adjusted hazard ratios for overall mortality at five years of 0.73 and 0.49 for *BRCA1* and *BRCA2* mutation carriers, respectively, compared to non-carriers. The differences in overall survival observed in *BRCA1* and *BRCA2* mutation carriers was statistically (and clinically) significant compared to both the sporadic cohort and each other. In a secondary analysis, the authors also found that the survival advantage conferred by *BRCA1* mutations may be partially mitigated as the mutation site moved from the 5’ to 3’ end, suggesting that the site of *BRCA1* mutation may have individual prognostic significance.

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This article has several important strengths. It is, by far, the largest study of *BRCA*-associated ovarian cancer outcomes reported to date. With 1,213 carriers it is several times larger then the two previous largest series by Chetrit et al[2] (213 *BRCA1/2* mutation carriers) and by Paroah et al[13] (151 *BRCA1/2* mutation carriers). The study by Bolton et al also examined an ethnically diverse group of patients from multiple continents and is therefore more generally applicable than prior reports that drew from more homogenous populations. For these reasons, this study is the most definitive report thus far describing outcomes of *BRCA1* and *BRCA2*-associated ovarian cancers.

This study has several important limitations, as acknowledged by the investigators. Most importantly, 30% of patients have missing data – including stage (19%), grade (22%), and histology (5%). The lack of information on chemotherapy type and route (64%) and debulking status (71%) is particularly noteworthy because these are also established predictors of survival.[14] This amount of missing data is not unexpected given that cases were collected primarily from clinical genetics databases and not prospective treatment protocols with this degree of missing data, it is possible that unmeasured confounders may account for some of the observed differences. However, the size of the overall cohort, the statistical adjustment techniques used, and the magnitude of differences observed make it unlikely that the reported survival advantages- are artifactual. This study decisively establishes that *BRCA1* and *BRCA2*-associated ovarian cancers each have a distinctly separate and better prognosis compared to sporadic ovarian cancers.

These data have important implications for the future of ovarian cancer research and treatment. Phase III studies that do not stratify by *BRCA* mutation status or account for this factor in a preplanned statistical analysis risk possible confounding because about 15% of unselected patients with serous ovarian cancer will carry germline *BRCA1/2* mutations.[15] Moreover, other studies have found differences in chemotherapy responsiveness[10] and progression-free survival[16] between sporadic, *BRCA1* and *BRCA2*-associated ovarian cancers. Germline *BRCA* testing needs be consistently incorporated into both the routine management and future Phase III trials of ovarian cancer.[17]

Perhaps equally important, the results reported by Bolton et al provide impetus for rethinking the current approach to the development of targeted agents in molecularly defined subsets of ovarian cancer. To date, large-scale genomic analyses of serous ovarian cancers have not identified high-frequency somatic oncogenic driver mutations amenable to targeted intervention.[3] The principal exception may be the so-called “BRCAness” phenotype that can be targeted by poly(ADP-ribose) polymerase (PARP) inhibitors.[18] Members of the PARP inhibitor family block base excision repair, a low fidelity DNA repair pathway that appears necessary to maintain genomic stability in tumors with deficient homologous recombination mechanisms that depend on intact *BRCA1* and *BRCA2* genes. Early clinical trials of PARP inhibitors have shown promise in *BRCA*-associated[19–21] and even sporadic ovarian cancers.[22] An important consideration is whether the unknown mechanisms underpinning the differences in survival of *BRCA1* and *BRCA2*-associated ovarian cancers observed in the study by Bolton et al may also result in differential sensitivity to agents that target the resultant homologous recombination defects. To date, trials of PARP inhibitors have not been large enough to detect differences in efficacy among the *BRCA* gene mutations. Upcoming trials of PARP inhibitors in ovarian cancer that specifically enrich for *BRCA1* and *BRCA2* carriers may be at particular risk for confounding if differences in these two biologically distinct groups are not considered.

In the future, even germline *BRCA* status may not be sufficient to fully sub-classify ovarian cancers and select the best treatment. Data from The Cancer Genome Atlas Research Network (TCGA) suggest that beyond germline mutations, high-grade serous cancers have

functional alterations in the homologous recombination pathway by somatic *BRCA1/2* mutation, epigenetic silencing, or other putative homologous recombination defects.[3] Thus, while only a small proportion (10–15%) of patients carry germline *BRCA1/2* changes, nearly half of all serous ovarian cancers have function defects in homologous DNA repair.[3] The prognostic importance of these non-germline homologous recombination defects remains unclear: in The Cancer Genome Atlas series, patients with epigenetically silenced BRCA1 had significantly worse outcomes than patients with germline or somatically-acquired *BRCA1/2* mutations. Further complicating matters, secondary mutations may restore *BRCA1/2* function in germline mutant tumors and lead to treatment resistance later in the clinical course.[23]

The biology of sporadic and *BRCA*-associated ovarian cancers also may be influenced by other cancer susceptibility alleles. Recent data from the CIMBA investigators found that several single nucleotide polymorphisms (SNP's) were associated with ER and PR status, and therefore underlying tumor biology, in *BRCA1* and *BRCA2*-associated breast cancers.[24] These early results suggest that germline *BRCA1/2* status most likely will also be found to interact with other genetic regions in ovarian cancer patients. As understanding of these mechanisms, increases, it is virtually certain that both modifying alleles and epigenetic regulation will be found to alter the influence of *BRCA* germline mutations in complex ways.

The findings of Bolton et al are the latest evidence that ovarian cancer is a much more genetically and biologically heterogeneous disease than previously appreciated. Further studies in similarly large datasets are needed to better understand the effects of somatic and epigenetic alterations in *BRCA* gene function as well as complex interactions with other inherited alleles. The accelerating availability of detailed somatic and germline genetic information will challenge all physicians who stand at the bedside of patients with cancer and struggle to deliver compassionate, individualized care.

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