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Editorial

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Comments on: Peripheral blood *BRCA1* methylation profiling to predict familial ovarian cancer

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> ▸ See the article "Peripheral blood *BRCA1* methylation profiling to predict familial ovarian cancer" in volume 32, e23.

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It is well recognized that approximately 20% of ovarian cancer cases can be attributed to pathogenic variants in *BRCA1/2* [1,2]. Therefore, the majority of ovarian cancer cases must be associated with other genetic or epidemiologic risk factors. Silencing of tumor suppressor genes including *BRCA1/2* by promoter methylation has been shown to be associated with early onset ovarian cancer [3] and breast cancer [4]. Testing for *BRCA1* methylation in the blood may be a feasible strategy to identify those who are at risk for developing ovarian cancer, even in the absence of a mutation in *BRCA1/2*. Since there is still no effective screening test for ovarian cancer, there is a need for novel strategies to identify those at increased risk for this malignancy, in addition to those with a hereditary predisposition attributed to a germline mutation in *BRCA1/2*.

In this issue, Jung et al. [5] evaluated *BRCA1* methylation in a total of 107 women, comprised of 55 women without cancer, including 44 without a *BRCA1/2* mutation (BRCAwt) and 11 with a *BRCA1/2* mutation (BRCAm), and another 52 women with ovarian cancer, including 33 BRCAwt and 19 BRCAm, from the Korean Gynecologic Cancer Bank. The authors used cumulative methylation index (CMI) to calculate the overall BRCA1 promoter methylation level. *BRCA1* methylation was more common in BRCAm compared to BRCAwt, both in cancer and non-cancer patients. *BRCA1* methylation in ovarian cancer patients was high, and no different between BRCAwt and BRCAm. However, in women without a diagnosis of ovarian cancer, there was a significantly higher CMI in those who were BRCAwt with a family history of cancer (breast, ovarian, pancreatic), compared to those who did not have a family history. The implication is that the presence of *BRCA1* methylation in unaffected individuals who have a family history of cancer may signal the disruption of normal functioning of the *BRCA1* gene, which could predispose those individuals to ovarian cancer.

Identification of *BRCA1* methylation may have important therapeutic and prognostic implications as well. *BRCA1* methylation is associated with defective homologous recombination repair, therefore these patients could benefit from treatment with a poly (ADP-ribose) polymerase inhibitor [6,7]. However, the association between *BRCA1* methylation and survival remains uncertain. One study reported that women with methylated epithelial ovarian cancers had a higher overall survival (OS) compared to those with unmethylated cancers (72% vs. 22% at 200 months, respectively) [8]. On the other hand, another study found no survival difference between those with methylated and unmethylated

ovarian cancers (median OS, 46.6 vs. 48.0 months; hazard ratio=1.02; 95% confidence interval=0.87–1.18) [9].

It remains to be elucidated how *BRCA1* methylation could contribute to familial ovarian cancer development. There will likely never be a trial to compare risk-reducing interventions such as surgery in those with and without *BRCA1* methylation. However longitudinal evaluation through a population-based or prospective cohort study could provide a better estimate of the lifetime risk of ovarian cancer in these individuals. There are clearly different testing methods across institutions, and ideally there should be agreement on a validated process for determining methylation status. This will lend to more consistent reporting and resolve some of the discrepancies that could arise when comparing results across studies. This study highlights the need to further evaluate *BRCA1* methylation not just for ovarian cancer patients, but also for unaffected individuals in the general population who remain at risk for this potentially lethal malignancy.

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