Letter to the Editor

Clinical Cancer Research

KRAS rs61764370 in Epithelial Ovarian Cancer–Response

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Ratner and colleagues reported an association between rs61764370 and risk of epithelial ovarian cancer (EOC) in 2 small case–control studies ($n < 1{,}000$ in total; ref. 1). They also reported increased risk in *BRCA1* mutation carriers ($n = 23$) and in women not carrying *BRCA1/2* mutations but with family histories of the disease ($n = 31$), and an association with poorer survival. We attempted to replicate these findings in 8,669 EOC cases (249 with family histories) and 10,012 controls from 19 studies and examined prognosis in 5 studies with progression-free survival data and 18 with all-cause mortality data (2). We also analyzed 683 cases and 2,044 controls carrying *BRCA1* mutations (2). These analyses completely failed to validate the original findings. This result was not surprising considering the high potential for false discovery in genetic association studies (3).

Weidhaas and Slack assert that fundamental differences between our studies explain the discrepant results. First they claim differences between the "high-risk" populations. However, all *BRCA1* carriers in our study were from "fully annotated" hereditary breast and ovarian cancer families. Differences between the 2 studies with regard to non*BRCA1/2*-associated familial EOC are far more likely due to random error, given the few familial subjects in the Ratner study, than any of the trivial differences they describe. They also provide a multitude of theoretical differences that might account for discrepancies in risks of nonfamilial EOC. These are unlikely to be important and they provide no empirical evidence justifying their claims. Their only potentially salient point concerns possible bias that might occur in case–control studies that include prevalent cases and where the single-nucleotide polymorphism (SNP) is also associated with survival. We directly examined EOC survival without finding a significant association, nor did our results change when we restricted analyses to cases recruited within 18 months of diagnosis. The positive results in the original study by Ratner and colleagues (1) most likely arose by chance or from genotyping errors. In this regard, their data show evidence of significant deviation from Hardy–Weinberg equilibrium, but this was not reported in their study (1).

rs61764370 testing, as currently marketed for risk assessment in *BRCA1/2*-negative familial subjects, is based on analysis of only 31 cases. The assertion of theoretical deficiencies in our analysis without empirical evidence for such claims does not refute the lack of adequate evidence in support of this clinical use. The existing data do not support the use of this *KRAS* SNP for ovarian cancer risk assessment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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