Letter to the Editor

Clinical Cancer Research

KRAS rs61764370 in Epithelial Ovarian Cancer–Letter

Joanne B. Weidhaas and Frank J. Slack

Pharoah and colleagues, in their report on the Ovarian Cancer Association Consortium study (henceforth referred to as the Pharoah study; ref. 1), state that they failed to validate the association of rs61764370, a functional *KRAS* DNA variant, and ovarian cancer risk as previously reported by Ratner and colleagues (henceforth referred to as the Ratner study; ref. 2). However, the groups studied in these articles have fundamental differences. Most importantly, the high-risk population to which Ratner and colleagues refer—women from *BRCA*-negative hereditary breast and ovarian cancer families (the only women for whom clinical testing for rs61764370 is offered)—was not discussed by Pharoah and colleagues. These differences need to be highlighted.

High-risk Populations

The "high-risk" populations in the Ratner study were probands from fully annotated hereditary breast and ovarian cancer families with known *BRCA* status, whereas the patients in the Pharoah study self-reported as having a first-degree relative with ovarian cancer. These 2 cohorts are not directly comparable because of the exclusion of breast, as well as the lack of accuracy in self-reported family history versus pathologic documentation as required in the Ratner study. Therefore, one simply cannot draw appropriate conclusions about the utility of clinical testing of the rs61764370 single-nucleotide polymorphisms (SNP) in *BRCA*-negative hereditary breast and ovarian cancer families on the basis of the Pharoah study, as the inclusion criteria for this study were much less stringent. A recent publication showing the clinical and biologic association of the rs61764370 SNP with triple-negative breast cancer further validates the importance of this marker in hereditary breast and ovarian cancer families (3), and numerous additional appropriate validation studies are completed and will soon be in press.

Studies of Sporadic Ovarian Cancer

Subject inclusion criteria for cases and controls differed between the 2 studies, as evidenced in these reports. With respect to criteria for cases, pathologic confirmation of ovarian cancer was required in the Ratner study but not in the Pharoah study, with up to 10% unknown; recruitment took place within 2.5 years of diagnosis in the Ratner study, but there was no limit between diagnosis and enrollment in the Pharoah study; and fallopian cancer was included in the Ratner study but excluded in the Pharoah study. With respect to criteria for controls, only women were allowed in the Ratner study, whereas men were allowed in the Pharoah study; and controls were required to have no prior history of cancer in the Ratner study, but cancer history was allowed or often unknown in the Pharoah study. Because the rs61764370 has been associated with poor survival (4) and with risk of other cancers (3, 5), inclusion of prevalent cases and controls with a prior history of cancer would provide significant bias. In comparing studies using such diverse criteria, discussing differences in inclusion criteria is necessary. We also believe that using imputed data on a different SNP, with greater than reported discordance from the rs61764370 SNP, is an inappropriate surrogate of the rs61764370 SNP and can lead to erroneous conclusions in the study of rs61764370. However, the differences in inclusion criteria for these studies likely remain the major issue.

Disclosure of Potential Conflicts of Interest

J.B. Weidhaas and F.J. Slack have patented IP with regard to the KRAS-variant through Yale University, and have founded a company, Mira Dx, which has subsequently licensed IP from Yale University. Information on Mira Dx is available on their website. Neither J.B. Weidhaas nor F.J. Slack has a sponsored research agreement from Mira Dx.

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