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From Medscape Genomic Medicine > Viewpoints in Genomic Medicine Exploring the Clinical Value of *KRAS* Mutation Testing in Ovarian Cancer

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A *KRAS*-Variant in Ovarian Cancer Acts as a Genetic Marker of Cancer Risk

Ratner E, Lu L, Boeke M, et al
Cancer Res. 2010;70:6509-6515

Clinical Implications of the Cancer Genome

MacConaill LE, Garraway LA
J Clin Oncol. 2010;28:5219-5228

Summary

Previous research identified an uncommon variant of the *KRAS* oncogene (rs61764370) that increases levels of *KRAS* in in vitro assays, suggesting that it may be associated with a biologically relevant increased risk for cancer development.^[1] Indeed, 2 case-control studies revealed a greater risk for the development of non-small cell lung cancer in individuals with this mutation vs those without the mutation. Although the variant is seen in fewer than 20% of patients with all solid tumors, it is present in more than 25% of patients with epithelial ovarian cancer.^[1]

In the analysis by Ratner and colleagues, investigators exploring an association between the presence of rs61764370 and the risk of developing ovarian cancer found the mutation in 25% of patients examined vs only 15% of individuals in a non-cancer "control" population. Of greatest interest, however, the *KRAS* mutation was found in 19 (61%) of 31 patients who appeared to have a familial history of ovarian cancer but no evidence of a *BRCA1* or *BRCA2* mutation. When compared with families with a *BRCA* association, patients in this group were less likely to have Jewish Ashkenazi ethnicity, and were more likely to be older and to have a history of lung cancer within the family.

In their review article, MacConaill and Garraway identify *KRAS* and *BRCA* as classic examples of synthetic lethality, in which cancer cell growth driven by expression of an oncogene is, in turn, dependent on expression of a second gene for survival. Whether a druggable target will be found for *KRAS*-mutated ovarian cancer similar to poly ADP ribose polymerase (PARP) inhibitors in *BRCA*-mutated breast cancer^[2] remains to be seen, but the identification of the *KRAS* mutation in this patient population certainly points to new possible avenues for therapeutic intervention.

Viewpoint

The association between *BRCA1* and *BRCA2* and the risk of developing breast and ovarian cancers is well established. However, it is also known that a not insignificant percentage of individuals with a recognized strong familial risk of developing ovarian cancer have no known abnormality in *BRCA*. While it is possible that the *BRCA* mutations in these patients have yet to be discovered, it has been suggested that other genetic abnormalities unrelated to *BRCA* may be responsible for the observed familial risk.^[3]

The data from Ratner and colleagues provide strong support for the conclusion that the *KRAS* mutation rs61764370 may be responsible for a substantial proportion of familial ovarian cancer not accounted for by *BRCA* genetic abnormalities. Certainly, before making a definitive statement regarding the relevance of this mutation in this specific setting, it will be important for other groups with sizable populations of women with familial ovarian cancer to examine for the presence of rs61764370 in patients without a documented *BRCA* mutation. Assuming this observation is confirmed, routine testing for this *KRAS* variant may be indicated in patients with ovarian cancer and a family history of the malignancy in the absence of *BRCA1* or *BRCA2* abnormalities.

Yet, even if further research bears out the association with the *KRAS* variant in this population, can one justify the cost of this type of exploration when the abnormality will be present in fewer than 1 in 50 or 1 in 100 ovarian cancer patients? Do cost considerations outweigh the predictive utility associated with documenting rare genetic abnormalities outside of a pure research setting? MacConaill and Garraway note that the cost of sequencing an individual cancer genome has been steadily and rapidly decreasing; as this trend continues over the next several years, it is likely that the cost-effectiveness of these types of investigations will increase, allowing them to be more widely available for routine clinical purposes, and thus enabling patients to benefit from therapeutic advances targeting driver mutations.

[Abstract](#)

[Abstract](#)

References

1. Chin L, Ratner E, Leng S, et al. A SNP in a let-7 microRNA complementary site in the *KRAS* 3'UTR increases non-small cell cancer risk. *Cancer Res.* 2008;68:8535-8540. [Abstract](#)
2. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med.* 2009;361:123-134. [Abstract](#)
3. Pharoah P, Antoniou A, Bobrow M, Zimmern R, Easton D, Ponder B. Polygenic susceptibility to breast cancer and implications for prevention. *Nat Genet.* 2002;31:33-36. [Abstract](#)