

PIK3CA Mutations in Ovarian Cancer

To the Editor: In the April 15 issue of Clinical Cancer Research, Levine et al. (1) reported the frequent occurrence of somatic mutations in the phosphatidylinositol 3-kinase p110α catalytic subunit gene PIK3CA in breast and ovarian cancer. While their study broadly supports the conclusions of our previous report in these cancer types (2), there are some important differences.

We observed a highly significant overrepresentation of PIK3CA mutations among the endometrioid and clear cell histological subtypes compared to the serous subtype (P = 0.001; ref. 2). Such a bias was not unexpected given that the major histological subtypes of ovarian cancer arise through different developmental pathways (3, 4), and that we have also shown that PTEN mutations were also predominantly clustered among the endometrioid and clear cell type cancers (5). It was therefore surprising to us that Levine et al. did not observe any correlation between the presence of a PIK3CA mutation and histological subtype among their large cohort (n = 198) of ovarian tumors. We also noted that nearly all the mutations (21 of 24) among their ovarian cancers were an A1634C change in exon 9. In most PIK3CA mutation studies, including our own, the mutations identified in exon 9 have almost exclusively been G1624A and G1633A changes, and to date, only one study has reported the A1634C mutation (6).

In the course of our investigations, we did identify an apparent A1634C change in some tumors, but in most instances, this same variant was detected in the DNA from matching normal tissue. On further investigation, it became clear that the A1634C variant was in fact derived from a pseudogene on chromosome 22 with an almost exact match with the PIK3CA exons 9 to 13. Therefore, we redesigned the primers to exploit the few sequence differences that exist for these exons and optimized the PCR conditions to use the highest annealing temperature possible. Under these conditions, clean sequence traces were obtained and none of the ovarian tumors were shown to harbor the A1634C variation. Others have also noted the need to redesign the exon 9 primers to avoid confusion with the pseudogene (7, 8). Levine et al. used the sequencing primers reported by Samuels et al. (9), which closely match the pseudogene sequence and thus are very likely to be prone to mispriming.

Consequently, although some of the A1634C changes reported by Levine et al. may represent bona fide PIK3CA mutations, it is possible that many are not, and therefore their conclusion that mutations are not associated with ovarian cancer histological subtype may need to be reevaluated.

References


In Response: We appreciate the attention given by Drs. Campbell, Russel, and Phillips to our recent publication “Frequent Mutation of the PIK3CA Gene in Ovarian and Breast Cancers” (1). In this article, we report a 12% mutational frequency among 198 ovarian carcinomas and 18% among 72 breast carcinomas. We also modeled the identified mutations to gain further insight into their structural and functional implications.

Campbell et al. (2) highlight the differences between our study and their own article in which they recognized an association between PIK3CA mutations and histologic subtype. In their report, 20% (8 of 40) of the endometrioid and clear cell ovarian carcinomas contained mutations. In our study, we also identified mutations in 15% (6 of 41) of the endometrioid and clear cell carcinomas. In contrast to Campbell et al., we identified mutations in 18 of 148 (12%) serous ovarian carcinomas, which is not significantly different than the aforementioned 15%. All of the tumors in our study

© 2005 American Association for Cancer Research. doi:10.1158/1078-0432.CCR-05-1024

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Clin Cancer Res 2005;11(19) October 1, 2005 7042
were from moderate- to high-grade advanced stage ovarian carcinomas; however, the stage and grade of the ovarian carcinomas in the Campell study are not delineated in their publication.

Interestingly, Campell claims that the primers used in the landmark study by Samuels et al. (3) failed to account for a highly homologous sequence on chromosome 22. They cite two related publications in which alternate primers were used to avoid potential mispriming. On close examination of the two sequences, it becomes apparent that the primers used by Samuels et al. and those cited in the present letter both contain the same number of sequence differences between the PIK3CA sequence and the sequence on chromosome 22 (4, 5). Unfortunately, the primers used in the Campell publication and alluded to in the letter are not publicly available for review.

Although we cannot refute with certainty the fact that some mispriming may have occurred, it is interesting to note that our study and the studies of Hartmann et al. (6) and Lee et al. (7) all identified A1634C mutations in ovarian, hepatocellular, and glioblastoma multiforme tumors, respectively. However, in these studies and others that used the primers from Samuels et al., none of over 1,000 independent samples from large tumor sets identified the A1634C mutation, despite using the same PCR primers and conditions (1, 3, 7–9). Included in these studies were 229 lung cancers, 185 gastric cancers, 125 breast carcinomas, 109 separate ovarian carcinomas, and 234 colon cancers. If mispriming were indeed occurring to the extent suggested by Campell et al., one would expect to find the same mutation among other tumor types when analyzed using the same reagents. This implies that either the A1634C mutation is present to the degree and specificity reported or the proposed pseudogene may be amplified in a large proportion of unique tumors.

We thank Dr. Campell and colleagues for their recognition of our work.

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References
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