Letters to the Editor

Cyclin E Overexpression Relates to Ovarian Cancer Histology but not to Risk Factors

To the Editors: Schildkraut et al. (1) report that the relationship between calculated lifetime number of ovulatory cycles (LOC) and risk of epithelial ovarian cancer is significantly stronger among cancer cases overexpressing cyclin E than those not overexpressing it. They conclude that this difference provides evidence for the involvement of repeated ovulation in the etiology of ovarian cancer, at least for the subgroup of cases overexpressing cyclin E. This conclusion is not warranted from their analysis, for two reasons.

First, the authors tabulate odds ratios for ovarian cancer risk according to LOC and to the various factors from which LOC is calculated, first for cyclin E-positive cases versus controls, then for cyclin E-negative cases versus controls. Although there are some differences in the point estimates for the cyclin E-positive versus E-negative cases, most of these differences do not reach customary statistical significance. The most pronounced difference is in oral contraceptive use, where 1 year of use has an odds ratio of 0.91 (95% confidence interval, 0.87-0.95) for cyclin E-positive ovarian cancer, but 0.99 (95% confidence interval, 0.96-1.02) for cyclin E-negative cancer. However, a rough calculation of the statistical difference between these two points estimates gives a \( P \) value of 0.11. Similarly, the \( P \) value for the difference in odds ratios for the variable LOC is \( \sim 0.056 \). The authors do calculate a case-case difference in LOC risk by tertiles of that variable and find nominal statistical significance for only the highest tertile. It is not clear whether the correct 2 degree-of-freedom test for this case-case difference is statistically significant; it is not stated.

Furthermore, the basic case-case comparison is problematic. The authors show major differences between cyclin E positivity and case histologic type. Serous, endometrioid, clear-cell and other cancer types, invasive and borderline, show cyclin E positivity in 44% of cases, whereas mucinous tumors show cyclin E positivity in 12%. The authors discuss the fact that mucinous ovarian cancers seem to have different etiologic factors than serous and other histologic types. Their discussion is limited to the fact that mucinous tumors may be associated with cigarette smoking. The authors miss the crucial point that mucinous ovarian tumors are not associated with parity or oral contraceptive use (2, 3). These two factors are the major contributors to the calculated LOC variable. The authors’ group of cyclin E-negative cases is 5-fold enriched for mucinous tumors (53 of 319, versus 7 mucinous of 217 cyclin E-positive cases). Thus, the authors’ claim of different risk associations between cyclin E-positive and E-negative tumors is confounded by the histologic groups that they have not properly controlled. With adequate control, there would be no statistical differences in risk for cyclin E positivity according to LOC or the other reproductive risk factors, and thus, little evidence for the authors’ conclusions from their data about evidence for the involvement of repeated ovulation in the etiology of ovarian cancer.

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References
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