Re: Relationship Between Lifetime Ovulatory Cycles and Overexpression of Mutant p53 in Epithelial Ovarian Cancer

Schildkraut et al. (1) recently reported an association between number of lifetime ovulatory cycles and the risk of p53-overexpressed invasive epithelial ovarian cancer, but not of p53-negative ovarian cancer. From the data they presented, I conclude exactly the opposite: p53-positive and p53-negative cancers are equally associated with ovulation-related risk factors, the sole exception being age at diagnosis, which was on average some 3 years greater for the p53-positive case subjects. The study participants were all less than 55 years of age at diagnosis/interview; the majority were premenopausal or perimenopausal. Schildkraut et al. estimated the number of lifetime ovulatory cycles from a linear combination of five factors: age at most recent menstrual period ("index age"'), age at menarche, and total durations of pregnancies, breastfeeding, and oral contraceptive use. None of the last four mentioned factors differed significantly between the p53-positive and p53-negative case subjects [P = .71, .14, .06, and 0.23, respectively (1)].

Comparing p53-positive and p53-negative cancers, the decreasing odds ratio trends with increasing months pregnant were very close (1), consistent in magnitude with the protective trends seen for parity in many other studies (2,3). Similarly, p53-positive and p53-negative cancers had virtually identical odds ratio trends with duration of oral contraceptive use (1), again of the same magnitude as seen elsewhere (2,3). Age at menarche and duration of breastfeeding contributed very little to the variation in number of ovulatory cycles (1). Thus, only index age is responsible for the purported difference in risk according to lifetime ovulatory cycles.

Furthermore, the authors’ adjustment for continuous age terms need not remove the age effect present in the categories of lifetime ovulatory cycles. It is straightforward to show that, even with adjustment for age as a continuous term, age at diagnosis can completely account for the pattern of odds ratios in lifetime ovulatory cycles seen by Schildkraut et al.

While the suggested biologic rationale—that p53 overexpression indicates ovulatory proliferation-induced, neoplastic DNA damage (4)—is attractive, the data of Schildkraut et al. provide evidence to the contrary, that p53 overexpression more likely results from damage occurring during neoplastic proliferation of the tumors. They show that, in addition to older age at diagnosis, p53-positive tumors are more likely to be of poorer differentiation than p53-negative tumors (P < 10⁻⁵) and of distant rather than local–regional stage at diagnosis (P = .0002) (1). These well-known features (4–6) thus indicate that p53-positive cancers are those diagnosed later in the neoplastic process, when more genetic errors have accumulated. Therefore, the results do not provide evidence for p53-specific causal mechanisms in the pathogenesis of ovarian cancer.

Finally, Schildkraut et al. (1) state that pregnancy, oral contraceptive use, and lactation all convey their protective effects only through anovulation. However, the number of analyzed case subjects (n = 197) provided insufficient study power to make this conclusion. Ovulation may be involved in the disease process, but it cannot be the entire mechanism (7). Simply put, the reduction in risk with parity [odds ratio = 0.83 for each successive pregnancy (2)] is just too strong compared with the fraction of ovulatory years prevented, at most 5% per pregnancy (i.e., odds ratio = 0.95); these odds ratios are statistically incompatible [two-sided Wald test, P < 10⁻⁵, using the data summarized by Whittemore et al. (2)] and remain so even accounting for latency (8,9). How “incessant” ovulation is actually involved in ovarian cancer pathogenesis remains a very interesting question, certainly beyond the idea of ovulatory wound repair and accompanying cellular proliferation.

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References

(1) Schildkraut JM, Bastos E, Berchuk A. Relationship between lifetime ovulatory cycles and overexpression of mutant p53 in epithelial ovarian cancer.


Note

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Response

In our recent article (1), we concluded that exposure to a high number of ovulatory cycles was associated with an increased risk of developing ovarian cancers that overexpress p53. Although the data that we presented were adjusted for various potential confounders, including age, Dr. Risch suggests that all the variation in ovulatory exposure may be explained by age. Dr. Risch also suggests that the relationship between age and p53-positive ovarian cancer is explained by the association between late stage ovarian cancer and p53 overexpression and is a result of tumor progression.

Because of the issues raised by Dr. Risch, we conducted a paired-matched, case–control analysis applying a conditional logistic regression model. Control subjects were matched to the p53-positive ovarian cancer patients on the basis of “exact” age and Surveillance, Epidemiology, and End Results (SEER) registry^1 in a ratio of 4:1 to achieve a sufficient statistical power. Because of the excess number of available control subjects, we were able to achieve exact age matches for all 105 p53-positive ovarian cancer patients. Odds ratios for medium (versus low) ovulatory cycle exposure and high (versus low) ovulatory cycle exposure were 4.9 (95% confidence interval [CI] = 1.4–17.6) and 15.8 (95% CI = 3.8–66.0), respectively. Thus, these results, matched by age and controlling for menopausal status and nulliparity, are consistent with those of our original article and strengthen our conclusion concerning the relationship between ovulatory cycle exposure and ovarian cancer.

We also compared the p53-positive ovarian cancer patients with control subjects, according to stage, and found a relationship between ovulation and case-control status, regardless of stage. For women diagnosed with local or regional disease, controlling for age, menopausal status, and nulliparity, adjusted odds ratios for medium (versus low) and high (versus low) ovulatory cycle exposure were 3.2 (95% CI = 0.4–27.2) and 6.5 (95% CI = 0.6–71.0), respectively. For women with advanced disease, adjusted odds ratios were 6.7 (95% CI = 1.1–42.2) and 13.8 (95% CI = 2.0–95.5) for medium (versus low) and high (versus low) ovulatory exposure, respectively. Another plausible interpretation of the association between p53 mutations and advanced stage is that ovarian cancers have a more aggressive behavior because of their p53 status and are therefore more likely to be detected at an advanced stage. However, the biologic basis for the association between p53 and advanced stage ovarian cancer has not been established, and caution must be taken when interpreting this relationship, since precursor lesions for ovarian cancer remain undefined.

Although these additional analyses strengthen our original conclusion concerning ovulation and the risk of developing ovarian cancer, a larger study that optimizing ovarian cycles and overexpression of mutant p53 in epithelial ovarian cancer. J Natl Cancer Inst 1997;89:932–8.

Notes

^1Editor’s note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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Re: Carcinogenicity of the Drinking Water Mutagen 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(SH)-furanone in the Rat

Komulainen et al. (1) recently reported dose-dependent tumor incidence in seven distinct tissues of male and female Wistar rats that had consumed drinking water containing 3-chloro-4-(dichloromethyl)-5-hydroxy-2(SH)-furanone (MX). They suggested cautiously that MX should be studied as a candidate risk factor to explain a ‘‘possible association between consumption of chlorinated drinking water and cancer in humans,’’ but they noted specifically that their findings ‘‘cannot be extrapolated to humans.’’ However, in their accompanying editorial, Melnick et al. (2) proceeded with just such an extrapolation. They estimated potential cancer risks to humans from MX in drinking water and compared these risks with those from two other disinfect-