


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 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 is also representative of older, postmenopausal women with ovarian cancer is needed to confirm our current findings and to achieve a better understanding of the pathogenic processes leading to this disease.

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Reference


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(5H)-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(5H)-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 disinfectant.
tion products (i.e., bromodichloromethane and chloroform). They acknowledged that their estimates were dependent on a number of assumptions about the validity of extrapolating from laboratory animals to humans, but although they state that “there is no information that would indicate that these assumptions are inappropriate,” there is little evidence that they are appropriate. Multisite carcinogenicity of putative carcinogens is not exceptional (3,4), and we note that that there is no generally accepted explanation as to why the tumors in rats occur at different sites. Perhaps MX affects p53 or converts different proto-oncogenes to activated oncogenes. At present, however, these speculations are unverified.

In any case, it would have been helpful if Melnick et al. had reported not just the upper bounds (presumably 95% confidence limits) for the MX and other disinfection products’ unit cancer risks but also the corresponding point estimates and their standard errors. Such reporting would have enabled the readers to derive point estimates of MX potencies (i.e., the ratios of the estimated exposure-specific risks) and their 95% confidence limits. Those limits, and any upper bound potency estimates based on them, are certainly of interest, but they are not the same as the ratios of the upper-bound unit cancer risks that were quoted in the editorial (2). The latter could be seriously misleading.

To date, MX has been detected in drinking water in Finland (5), the U.K. (6), The Netherlands (7), the United States (8), Canada (9), Japan (10), China (11), and Russia (12). It seems likely that MX may be found in any country where raw water rich in humic material is chlorinated. Prospective epidemiologic studies could, in principle, determine whether associations exist between measured MX concentrations in drinking water and cancer incidence in humans. But such studies are likely to require decades of research before interpretable results would become available. If it were possible to make realistic estimates of past MX levels, then retrospective epidemiologic studies might provide a shortcut. Alternatively, historical reconstruction of the net mutagenicity of drinking water, as pioneered by the Finnish researchers (13–15), may be a promising approach. In the meantime, we suggest that comments on the public health implications of the challenging results reported by Komulainen et al. (1) should be tempered by caveats that reflect the considerable gaps in current knowledge.

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References


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Editor’s note: Drs. Komulainen (2) and Melnick (1) declined to comment.

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Re: Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China

A recent study (1) of workers in Chinese factories clearly demonstrated that exposure to benzene at even low concentrations was associated with an appreciable hazard of blood dyscrasias. Because gasoline in some countries contains benzene in concentrations ranging from trace amounts to as high as 30%, we have investigated the hematologic consequences of exposure to benzene in unofficial vendors of gasoline and motor mechanics in the north of Nigeria (2).