Re: Sex, Smoking, and Cancer: a Reappraisal

In a recent issue of the Journal (1), Perneger criticizes us (2), as well as a number of other authors, for stating that case–control study results dealing with relative risks of cancer also apply to absolute risks of cancer. The studies in question concerned male–female differences in risks of lung and bladder cancer according to cigarette smoking history. Our results did indeed show that female smokers had a higher relative risk of lung cancer compared with male smokers, at the same level of smoking (2), and we further concluded that female smokers had higher absolute risk of lung cancer than male smokers. Zang and Wynder (3) concluded similarly. Perneger is theoretically correct that the latter conclusion concerning absolute risks does not follow from the former one on relative risks. However, his criticism is wrong because its validity depends upon the male and female absolute risks for never smokers, i.e., the baseline category for the relative risks. That is, a high enough baseline lung-cancer risk among male never smokers compared with female never smokers could, in theory, account for our findings of twofold to threefold higher smoking-related relative risks for females (2). As we pointed out 7 years ago (4,5), data on these baseline absolute risks had been available for some time. At that time, nine studies had demonstrated that the difference in baseline risk between male and female never smokers is small and, therefore, cannot explain the twofold to threefold higher relative risks seen for females. This result has been confirmed by the Nurses Health Study/Health Professionals’ Follow-up Study, with incidence rates among male and female nonsmokers of 10.1 and 12.2 per 100,000 per year, respectively (ratio 1.21) (6). In total, these 10 studies identified 1022 cases of lung cancer among male never smokers and 1832 among nonsmoking females. A combined precision-weighted estimate of the common female/male ratio of absolute age-adjusted rates from these 10 studies is 0.80 (95% confidence interval = 0.73 to 0.87). Even if we use a conservative value for this ratio equal to the lower 95% limit, the highest relative risk solely attributable to differing baseline risks is 0.73\(^{-1} = 1.37\). Thus, twofold to threefold higher relative risks for female smokers compared with male smokers require that female smokers be at higher absolute risk than male smokers at the levels of cigarette smoking where these twofold to threefold relative risks occur. These levels are not very great, beginning at less than 5 pack-years (2) or 5 kg of tar (7).

The above evidence strongly suggests that women who have been regular smokers since young adulthood are at greater absolute risk of lung cancer than are men with the same smoking history, and they certainly are at greater risk than men relative to the risk levels they could achieve by not smoking. Contrary to Perneger’s discussion (1), this conclusion does not depend on whether multiplicative, additive, or other regression models are used for analysis.

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In his commentary (1), Perneger claims that our reports (2,3) and those of other investigators (4,5) of a sex difference in smoking-related lung cancer risk are incorrect, because they were based on “misunderstandings about the meanings of relative risk versus absolute risk...
and the meanings of statistical interaction versus biologic interaction.” In response to this statement, it is important to point out that, unlike other risk factors, cigarette smoking is the major cause of lung cancer and only a relatively small percentage of never smokers develop this disease. Therefore, the greater susceptibility to tobacco carcinogens for women implied by our relative risk estimates, coupled with their recent increase in smoking rates compared with those of men, indicate that the incidence of lung cancer in women may equal, or even surpass, that in men in future decades. To dismiss, on minor semantic grounds, findings that were confirmed by several recent studies, is to ignore a potential public health issue that merits further investigation.

More specifically, Perneger’s critique seems to reflect a misinterpretation of our methods. Because all odds ratios were separately calculated for males and females in both of our studies (2,3), “relative risks of cancer for women versus men” were never directly estimated. In addition, as males and females were never combined in the same analysis, we could not have estimated the “statistically significant interaction” between smoking and sex that Perneger cites as one of the major reasons behind the “misinterpretation” of our results. In fact, we computed only sex-specific odds ratios and showed that they were consistently higher in women than in men at every level of lifelong exposure to cigarette smoking. In general, Perneger’s assertion that our conclusions are incorrect because the data came from a sex-matched case–control study has no methodological basis. In our study, the relative risk of males versus females was never directly estimated, and the risk factor in the odds ratios was exposure to tobacco smoke rather than sex.

As a final point, Perneger disputes the conclusion by Castelao et al. (5) that women are at greater risk of bladder cancer than are men, by citing “contradictory” estimates of an equal or higher incidence in male versus female “ever smokers” and “never smokers.” Rather than contradicting Castelao’s findings, these incidence rates represent a classic example of why sex differences in susceptibility to tobacco carcinogens have so long been overlooked and misinterpreted; namely, whenever exposure to cigarette smoking is merely recorded as “ever smokers” versus “never smokers” without considering dose, the exposure of men will consistently be underestimated compared with that of women, and the risk of men will be consistently overestimated compared with that of women.

The reason for this result is that, in past decades, men on average have smoked more cigarettes and have chosen brands with higher yields of tar than have women. Thus, Perneger’s reasoning overlooks the fact that the equal or higher incidence of bladder cancer in male ever smokers is probably a result of their greater exposure to cigarette smoking and, possibly, to other bladder cancer risk factors, such as alcohol use. On the other hand, women’s higher susceptibility to tobacco carcinogens than that of men is bound to be camouflaged when the exposure measure fails to incorporate dose.

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RESPONSE

I thank Drs. Risch and Miller, and Dr. Zang, for their comments. Both letters defend the substance of the published findings, i.e., that women smokers are in fact at higher risk of lung cancer than are male smokers. This may be true, but it is beside the point. My commentary was about rigor in interpreting data from epidemiologic studies, not about risk factors for lung cancer. The cited studies (1–4) observed that the relative risk of cancer associated with smoking is greater in women than in men but concluded that the risk of cancer is higher in women who smoke than in men who smoke. I questioned the logic of this argument. That the conclusion may be true in the case of lung cancer, as shown by other data such as incidence rates of lung cancer in non-smokers of either sex, does not validate the flawed reasoning shown above.

Furthermore, the numerical example worked out in the commentary concerned bladder cancer, not lung cancer. At times, it appears as though the authors of these correspondences have applied statements that I made about bladder cancer also to lung cancer. This assumption is incorrect. Only the principles of adequate interpretation of risk statements have general applicability.

Dr. Zang attributes sex differences in the risk of bladder cancer to misclassification of smoking status. I do not believe that this may be true. The original analysis by Castelao et al. (4), which was based on relative risks, suggests that women are at higher risk of bladder cancer associated with smoking than are men (negative interaction between male sex and smoking), whereas examination of incidence rates indicates that the absolute risk of bladder cancer attributable to smoking is greater in men than in women (positive interaction between male sex and smoking). This seeming contradiction stems from different risk scales being used (multiplicative or additive)—hence, my recommendation that the risk scale be explicitly stated when describing statistical interactions. It has nothing to do with misclassification of exposure to smoking in men and women. In fact, as shown in Table 1 of the commentary, the incidence of bladder cancer is more than 3 times higher in men than in women, regardless of smoking status. A finer stratification by amount smoked would not change this.

I am reassured that all writers agree that risks of disease in men and women cannot be compared in a sex-matched case–control study. Nevertheless, their original interpretation of the findings from their studies (1–3), quoted in my commentary, implies otherwise, and as much can be said about the study by Castelao et al. (4). Perhaps, as a profession, we epidemiologists should pay attention not only to rigorous methodol-
ogy but also to clear and careful communication of our results.

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