

## Sex, Smoking, and Cancer: a Reappraisal

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Several studies (1–4) have reported that the relative risk of cancer in smokers, compared with nonsmokers, is greater in women than in men. These results have led to speculations about the biologic mechanisms underlying this difference, such as a molecular interaction between sex hormones and tobacco carcinogens. The news media have echoed widely such results, perhaps because anything suggesting that women and men are inherently different strikes a chord among the public.

In this commentary, I suggest that the evidence from these studies is interpreted incorrectly, because of misunderstandings about the meanings of relative risk versus absolute risk and the meanings of statistical interaction versus biologic interaction.

### RELATIVE RISK VERSUS ABSOLUTE RISK

To present my argument, I will use data from the study by Castelao et al. (4) that compared smoking habits of case patients diagnosed with bladder cancer with smoking habits of sex-matched community control subjects. In this well-conducted study, both case patients and control subjects were identified from the same underlying population, validated instruments were used to assess exposure, and sound statistical methods were used to analyze results. Odds ratios (ORs) of cancer associated with smoking were higher in women than in men, whether for ever smoking (OR = 2.8 [95% confidence interval = 2.0 to 4.0] for women and OR = 2.4 [95% confidence interval = 2.0 to 2.9] for men) or current smoking (OR = 4.6 [95% confidence interval = 3.0 to 7.0] for women and OR = 3.6 [95% confidence interval = 2.8 to 4.6] for men). In a regression model predicting the risk of bladder cancer, the interaction between sex and lifetime number of cigarettes smoked was statistically significant.

From these results, Castelao et al. (4) concluded, “when comparable numbers of cigarettes are smoked, the risk of bladder cancer may be higher in women than in men.” This message was reproduced in the Journal’s Memo to the Media and was highlighted by the Associated Press (“Women smokers may face a higher risk of bladder cancer than men who smoke the same amount”) (5). These summary statements are wrong, because of the unfortunate substitution of “risk” for “relative risk, as compared with nonsmokers of the same sex.” When case patients and control subjects are matched on sex, as they were in this and previous studies (1–4), relative risks of cancer for women versus men cannot be estimated. The statistically significant interaction term only means that the *relative* risk of cancer associated with smoking differs between men and women.

To demonstrate why this distinction is important, let us reconstruct the disease incidence patterns in the underlying population (Table 1). This data reconstruction can be done for the study by Castelao et al. (4) because both case patients and control subjects were representative of the underlying general population. To define the populations at risk, we start by assuming that there were equal numbers of men and women in the popu-

lation (say, 0.5 million men and 0.5 million women followed for 10 years; however, any large number would lead to the same conclusion), and then we apply the prevalence rates of “ever smoking” reported among control subjects by Castelao et al. (4), i.e., 66.8% (788 male control subjects who ever smoked/1180 total male control subjects) among men and 55.1% (184 female control subjects who ever smoked/334 total female control subjects) among women (Table 1, A). Dividing the numbers of cancer patients in each sex-smoking category (Table 1, B) by the corresponding numbers of person-years produces estimates of incidence rates of bladder cancer (Table 1, C). Reassuringly, these rough estimates are comparable to population-based incidence rates reported elsewhere (6). These estimates contradict the authors’ conclusions that women are at greater risk of bladder cancer than men—in fact, the incidence of bladder cancer is more than three times higher in men than in women, whether in ever smokers or in never smokers (Table 1, D).

The substitution of “risk” for “relative risk” may have been an oversight as a result of overzealous manuscript editing.<sup>1</sup> However, numerous previous reports, all published in authoritative journals, have committed the same mistake. For example, Risch et al. (1), having observed that relative odds of lung cancer associated with smoking were higher in women than in men, concluded: “In summary, our data suggest that female smokers, dose-for-dose, are at higher risk of lung cancer than male smokers.” Zang and Wynder, also commenting on studies of lung cancer, stated, “given the same level of cigarette smoking exposure, the risk of . . . lung cancer . . . is consistently higher for women than for men” (2) and “dose for dose, females are more susceptible to the effects of tobacco carcinogens than males” (3). Coming as they do from sex-matched case-control studies, all of these conclusions are similarly incorrect.

Relative risks tell only part of the story. Relative risks are obtained by dividing each absolute risk (or incidence rate) by that of the reference category: for a global analysis, women who never smoked (Table 1, D) and, for a sex-stratified analysis, never smokers of either sex (Table 1, E). Only the latter can be estimated from a sex-matched case-control study. However, in the reconstructed population experience, we can also compute the absolute risks of bladder cancer that are attributable to male sex, ever smoking, or both (Table 1, F). A new notion emerges: The increase in the risk of bladder cancer associated with male sex is more than twice as large among smokers as that among

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See “Notes” following “References.”

**Table 1.** Reconstructed cohort study of bladder cancer in men and women, ever smokers and never smokers, from the study by Castela et al. (4)

	Women	Men	
<b>A) Person-years of follow-up*</b>			
Never smokers	2 245 000	1 660 000	
Ever smokers	2 755 000	3 340 000	
<b>B) Total cases of bladder cancer [from (4)]</b>			
Never smokers	75	199	
Ever smokers	259	981	
<b>C) Incidence rate of bladder cancer (cases per person-years), or absolute risk†</b>			
Never smokers	3.34 per 10 <sup>5</sup>	11.99 per 10 <sup>5</sup>	
Ever smokers	9.40 per 10 <sup>5</sup>	29.37 per 10 <sup>5</sup>	
<b>D) Relative risks of bladder cancer in all subgroups compared with women who never smoked</b>			
			Relative risk of bladder cancer in men
Never smokers	1.00	3.59	3.59
Ever smokers	2.81	8.79	3.12
<b>E) Relative risks of bladder cancer in ever smokers, stratified by sex</b>			
Never smokers	1.00	1.00	
Ever smokers	2.81	2.45	
<b>F) Attributable risks of bladder cancer in all subgroups compared with women who never smoked</b>			
			Risk of bladder cancer attributable to male sex
Never smokers	0	8.65 per 10 <sup>5</sup>	8.65 per 10 <sup>5</sup>
Ever smokers	6.06 per 10 <sup>5</sup>	26.03 per 10 <sup>5</sup>	19.97 per 10 <sup>5</sup>
<b>G) Risk of bladder cancer attributable to ever smoking, stratified by sex</b>			
Never smokers	0	0	
Ever smokers	6.06 per 10 <sup>5</sup>	17.38 per 10 <sup>5</sup>	

\*Assume 500 000 men and 500 000 women, followed for 10 years, and apply the prevalence of ever smoking as described previously (4).

†The “incidence rate” is given by the number of new cases of disease divided by the number of person-years at risk, and the “absolute risk” is given by the proportion of persons initially free of disease who develop the disease over a given period. The two notions are equivalent as long as risk is low, as in this example, where the cumulative 10-year risk of bladder cancer ranges from 0.035% in a female nonsmoker to 0.3% in a male smoker.

nonsmokers, or, adopting the perspective of sex-matched studies, the risk attributable to smoking is almost three times larger in men than in women (Table 1, G). These results are impressive, particularly if one is a male smoker.

Both the relative risk approach and the absolute risk approach constitute legitimate viewpoints on a complex reality; neither is right or wrong. Each serves a different purpose. For instance, evidence exists that results presented in relative risk format are more likely to induce behavior change in individuals (7). On the other hand, absolute risk data may be more relevant for public health decisions (8).

## STATISTICAL INTERACTIONS

The relative risk and absolute risk analyses agree on one thing: The effect of smoking on bladder cancer risk differs between men and women. This defines a statistical interaction

between smoking and sex. Paradoxically, however, the relative risk approach finds that smoking is more harmful in women, whereas the absolute risk analysis finds that it is more harmful in men. How is this possible? The short answer is that both the existence and the direction of an interaction depend on the underlying statistical model; if different models are used, interactions will differ too. A statistical interaction exists when cancer risk data collected for two or more risk factors do not fit the model (9). The relative risk model used by Castela et al. (4) is multiplicative: It requires that the relative risk associated with the joint presence of two risk factors (here, smoking and male sex) be the product of the two relative risks taken in isolation. If  $I$  denotes cancer incidence and  $N$ ,  $S$ ,  $W$ , and  $M$  designate nonsmokers, smokers, women, and men, respectively, this multiplicative model can be written as:

$$\frac{I_{MS}}{I_{WN}} = \frac{I_{MN}}{I_{WN}} \times \frac{I_{WS}}{I_{WN}} \quad [1]$$

If the equality holds, the multiplicative model is correct, and there is no interaction. If the equality does not hold, an interaction exists. In our example (Table 1, D), multiplying the relative risk of male sex among nonsmokers (relative risk = 3.59) by the relative risk of smoking in women (relative risk = 2.81) predicts a relative risk of 10.09 in men who smoke. Because the observed value (relative risk = 8.79) is lower, the required equality does not hold, and a negative interaction is said to exist between male sex and smoking on a multiplicative scale. This finding was given much emphasis in the professional and lay media.

Now if the additive risk model is used, the reasoning is similar, but “product” is replaced by “sum,” and “relative risk” is replaced by “attributable risk.” The additive model is written as:

$$I_{MS} - I_{WN} = (I_{MN} - I_{WN}) + (I_{WS} - I_{WN}) \quad [2]$$

In our example (Table 1, F), the absolute risk attributable to smoking among women (6.06 cases of bladder cancer per 10<sup>5</sup> person-years) is added to the risk attributable to male sex among nonsmokers (8.65 cases of bladder cancer per 10<sup>5</sup> person-years), to yield an expected 14.71 additional cases per 10<sup>5</sup> person-years in men who smoke, compared with women who do not. Because the observed risk difference (26.03 cases per 10<sup>5</sup> person-years) is much greater, there is a positive interaction between smoking and the male sex on an additive scale.

The fact that statistical interactions can be contradictory, depending on the risk scale used, is not unique to the problem being examined in this commentary. It is arithmetically impossible to make up a situation where there is neither a multiplicative nor an additive interaction between two risk factors, except for the trivial case where one of the presumed “risk factors” does not influence the risk of disease. Whether the interaction is statistically significant or not is only a question of statistical power.

So far we have considered only two risk scales, the additive and the multiplicative. The multiplicative scale is equivalent to an additive scale after a logarithm transformation. The additive model described in equation 2 simplifies to

$$I_{MS} = I_{MN} + I_{WS} - I_{WN}, \quad [3]$$

and the multiplicative model described in equation 1 simplifies to

$$I_{MS} = \frac{I_{MN} \times I_{WS}}{I_{WN}} \quad [4]$$

which becomes, after logarithm transformation,

$$\log(I_{MS}) = \log(I_{MN}) + \log(I_{WS}) - \log(I_{WN}). \quad [5]$$

Logarithms aside, equations 3 and 5 are identical. It turns out that the logarithm is a special case of a family of power transformations (10), of the general form:

$$T_p(x) = \frac{(x^p - 1)}{p}, \text{ for } p \neq 0,$$

and

$$T_p(x) = \log_e(x) \text{ for } p = 0.$$

The simple additive scale also is a special case, where  $p = 1$ . Under certain conditions (each risk factor must increase the incidence of disease, whether the other risk factor is present or absent), a value for  $p$  can be found that will eliminate interaction altogether. By trial and error, for the bladder cancer data (Table 1, C), interaction disappears for  $p = 0.12$ . Indeed,  $T_{0.12}(29.37) = T_{0.12}(11.99) + T_{0.12}(9.40) - T_{0.12}(3.34)$ . Thus, the same risk data are compatible with a positive interaction (on an additive scale), a negative interaction (after logarithm transformation), and no interaction (after transformation of power = 0.12).

The message is loud and clear: If an “interaction” can be reversed or eliminated by statistical manipulation, it must be of a statistical nature, not of a biologic nature. To recount: A statistical interaction exists when the observed risk patterns of disease in populations do not fit predictions from a particular statistical model. In contrast, biologic interaction refers to causal pathways of disease in individuals. The two notions, despite the unfortunate shared name, operate on different conceptual planes.

## CAUSAL DISEASE PATHWAYS

If biologic and statistical interactions address different aspects of reality, can the observed statistical risk patterns tell us anything about the pathogenesis of bladder cancer? According to epidemiologists Rothman and Greenland (11), the answer is a qualified “yes.” Their model of disease causation states that disease occurs when a “sufficient cause” is formed in an individual. Smoking is not a sufficient cause of bladder cancer. If it were, all smokers would have this disease. For bladder cancer to occur in a smoker (male or female), additional conditions must be met. These conditions may include, among others, genetic predisposition, previous DNA damage, exposure to other environmental carcinogens, and immune reaction. The conjunction of conditions (including smoking) that triggers necessarily the occurrence of bladder cancer is called a sufficient cause, and the components of the sufficient cause are said to “interact” on a biologic level.

Several sufficient causes may exist for the same disease, and each usually requires several components. Let us imagine that smoking and male sex (or rather specific carcinogens linked with these labels) belong only to separate sufficient causes of bladder cancer: Smoking requires one set of conditions to produce bladder cancer, and male sex requires a fully independent set of conditions. In this case, smoking-related bladder cancer and male-sex-related bladder cancer develop independently, even in male smokers, and the risks of bladder cancer attributable to each risk factor should be additive (11). Since the additive model is obviously wrong (Table 1, C), it is possible that both smoking and male sex may contribute to at least one suf-

ficient cause of bladder cancer—in other words, that they interact in a biologic sense. Note that it is not the negative multiplicative interaction, but the positive additive interaction, that leads to this possibility. But there is at least one alternative explanation: Smoking may be merely associated with one of the unmeasured components of the sufficient cause involving male sex (or *vice versa*). For instance, if alcohol consumption was a component cause of bladder cancer associated with male sex and if smokers tended to drink more than nonsmokers, a positive additive interaction would appear between smoking and male sex.

## A WAY OUT?

Correcting the first issue addressed in this commentary (i.e., misinterpretation of relative risk estimates) requires epidemiologic training, cautious interpretation of results, and careful proofreading of manuscripts before submission and after editing. The misunderstanding of interaction, statistical or biologic, will be more difficult to eradicate. The underlying concepts are fairly abstract and require familiarity with mathematical expressions. Greenland and Rothman (9) suggest removing “interaction” from the statistical vocabulary and replacing this term by more precise phrases, such as “heterogeneity of effect on a multiplicative scale.” Whether this proposal gains acceptance remains to be seen, but a little jargon may be an acceptable price to pay for better communication. Other proposals to distinguish statistical and biologic interactions are most welcome.

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## NOTES

<sup>1</sup>*Editor's note:* The omission of the concept of relative risk was not the result of overzealous editing, but rather, underzealous editing or a “sub-additive interaction” between author, senior editor, and editorial board.

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