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RE: "LONG-TERM HORMONE REPLACEMENT THERAPY AND RISK OF BREAST CANCER IN POSTMENOPAUSAL WOMEN"

In their paper on long-term hormone replacement therapy and risk of breast cancer, Newcomb et al. (1) adjusted for multiple risk factors by applying the frequently used logistic regression model implying multiplicative odds.

Endogenous gonadal hormones have an important role in causing breast cancer (2). At present, the dominant multistage theory of carcinogenesis assumes that cancer arises from one single normal cell turning malignant over the course of a certain number of transitions. An exposure can affect the first transition rates (early-stage carcinogens) or one of the later transition rates (late-stage carcinogens). Hormones are regarded as late-stage carcinogens (promoters) for breast cancer (3). Kinetics of late-stage carcinogens may best be described by additive relative risk models (3, 4). Moreover, when at least two causal agents act on the same stage of the transition process, multiplicative models are not truly appropriate because they do not correspond with the biologic process.

Current practice in epidemiologic research on hormone-dependent cancer which relies on multiplicative relative risk models (logistic regression in their standard form) could represent an incongruity between the mathematical and the biologic models (4). There is some empirical evidence that the use of additive models in addition to multiplicative models to assess the effect of hormonal risk factors in postmenopausal cancer should be considered. Walker and Rothman (5) and later Breslow and Storer (6) examined the relation of replacement estrogen therapy and endometrial cancer in postmenopausal women. They concluded that the data better corroborates the additive model than the multiplicative model and that the additive model may also lead to quite different relative risk and odds ratio estimates. These results on the effect of hormonal risk factors are further empirically supported by a recent study (4) on reproductive risk factors for postmenopausal breast cancer, where again evidence was found of a better fit of the additive model compared with the multiplicative model.

Newcomb et al. (1) tested for effect modification; however, we do not see inclusion of a number of significant interaction terms to be an appropriate modification of the multiplicative model to account for the additive effect of numerous predictors. To account for the additive structure of the data, a vast number of interaction terms would have to be included.

Therefore, theoretical models and the empirical data suggest that additive relative risk regressions are a more appropriate method to analyze data on hormonal risk factors for breast cancer. The use of additive models instead of the ones applied may thus lead to different conclusions than the ones the authors published.

References

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THE FIRST THREE AUTHORS REPLY

We thank Stronegger and Rásky for their letter to the editor (1), in which they suggest that an additive relative risk model may be more appropriate for the evaluation of breast cancer risk factors, and, in particular, for modeling the effects of hormone replacement therapy, as in our recent paper (2).

The choice of multiplicative, additive, or any other model structure depends on many factors: interpretability, parsimony, descriptiveness, mathematical tractability, and biologic plausibility (3, 4). Although we agree that, in some, simple circumstances, an additive relative risk model may be the most efficient description, in general we believe that,

TABLE 1. Comparison of the fit and effect on relative risks associated with any hormone replacement therapy use for the additive model with those of the multiplicative model for some of the results presented in table 2 of Newcomb et al. (2)

Use	Multiplier of RR*,† (95% CI*)	Addition to RR† (95% CI)
Never	1.00	0.00
Ever	1.05 (0.93, 1.18)	0.04 (−0.11, 0.19)
Deviance	8,002.897	8,010.300
Never	1.00	0.00
Former	1.12 (0.98, 1.29)	0.14 (−0.07, 0.34)
Recent	0.92 (0.77, 1.09)	−0.12 (−0.33, 0.09)
Deviance	7,998.855	8,005.861

* RR, relative risk; CI, confidence interval.
† Adjusted for type of menopause, time since menopause, age at menopause, age at first full-term pregnancy, history of benign breast disease, body mass index, family history of breast cancer, alcohol consumption, and education.