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Smoking and Estrogen-Related Cancer – Reply

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We thank Dr. Olsen and colleagues for their comments on our recent paper (1). We also have been intrigued by the association of smoking with melanoma and basal cell keratinocyte carcinoma, but wonder if he associations of smoking with these cancers differs by sex. This possibility has not been assessed in detail, but some studies of both cutaneous melanoma (2,3) and basal cell keratinocyte carcinoma (3,4) report inverse associations in men but absent or substantially weaker associations in women. In this context, it is relevant that in marked contrast to melanoma and basal cell carcinoma, cigarette smoking is associated with an *increased* risk of squamous cell keratinocyte carcinoma (3,5), probably with no sex difference (3). Given these findings, it is difficult to assign a mechanism for smoking's impact on UV-related carcinogenesis.

Olsen et al are concerned about the absence of clear dose-response patterns with regard to smoking duration and amount. For the hormonal, metabolic, and anti-inflammatory mechanisms that might underlay any inverse association with cancer incidence, it is not clear what patterns should be expected. The effects of these mechanisms are likely to dissipate once smoking stops. If their impact is simply to suppress on-going carcinogenesis, then cancer risk might well not depend on smoking duration, only current or recent status. In addition, these biological mechanisms might require only a modest amount of exposure to achieve a close-to-maximal effect. All this would contrast with what would be expected with the carcinogenic impact of smoking, for which cumulative doses and long latency are likely to pertain. These considerations also complicate the interpretation of Mendelian randomization analyses.

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The authors declare no conflicts of interest.

We agree with Dr. Olsen and colleagues that causality is often difficult to establish using epidemiological data alone. For that reason, preclinical data bearing on the associations of interest as well as related human data will remain important in understanding the true effects of most carcinogenic and anti-carcinogenic exposures.

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