Cigarette Smoking and Estrogen-Related Cancer—Letter

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In their recent publication, Baron and colleagues (1) reviewed the epidemiologic and biological evidence for the protective association between tobacco smoking and four "estrogen-related" malignancies (endometrial cancer, endometrioid and clear-cell ovarian cancers, and thyroid cancer). Notably, the review included thyroid cancer, for which the inverse association with smoking is observed in both women and men (2), and thus likely to be mediated through pathways that are not estrogen-related.

While Baron and colleagues focused on smoking and estrogen-related cancers, we note that a protective effect of smoking has been consistently observed for other cancers that occur more frequently in men than women, including melanoma and basal-cell carcinoma (BCC). The inverse association between smoking and these two cancers does not differ by sex, and is robust to careful adjustment for important potential confounding factors, including surveillance bias (3). Of the potential mechanisms described by Baron and colleagues that may be relevant in skin carcinogenesis is the effect of various constituents of cigarette smoke as exogenous ligands for the aryl hydrocarbon receptor (AhR). The AhR is a key regulator of UV-induced inflammation and apoptosis, and of keratinocyte proliferation and differentiation (4). It has also been implicated in regulating the efficacy of BRAF inhibitors and checkpoint inhibitors in advanced melanoma (4).

Finally, it remains unclear whether the inverse association between smoking and various estrogen- and nonestrogen-related cancers reported in epidemiologic studies reflect true causal effects, or the effects of reverse causality or latent confounding. For melanoma and BCC, the inverse association is observed for current but not past smokers, and dose-response relationships are not consistent across studies. It may be that a small amount of smoking is sufficient to induce the protective effect, and that that effect diminishes soon after smoking cessation; however, the lack of clear association with duration and intensity of smoking casts doubt on the argument of causation. With the advent of new genetic instruments for smoking initiation and lifetime smoking derived from large genome-wide association studies (5), Mendelian randomization studies may be able to overcome these challenges and assist in understanding the etiological relevance of the observed inverse association between smoking and different cancer types.

Authors' Disclosures

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