

Epidemiology of Diet and Melanoma—Letter

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In a recent review, Yang and colleagues summarized epidemiologic studies on diet and melanoma (1). We thank the authors for drawing attention to this topic given the rising incidence of melanoma worldwide. We would like to add several observations regarding the relationship between folate/folic acid and melanoma.

The authors described a meta-analysis of 13 randomized controlled trials, which found no association between folic acid supplementation and melanoma risk (2). However, the results should be interpreted with caution, because few melanoma cases ($n = 126$) were included and follow-up was relatively short (mean trial duration was 5.2 years). The authors described another meta-analysis of 3 trials, which found an inverse association between folic acid supplementation and melanoma risk (3). However, even fewer melanoma cases ($n = 38$) were included, and all three studies were included in the former meta-analysis (2). Therefore, although these two meta-analyses were published in the same year with different results, the larger meta-analysis may be more appropriate for interpretation (2).

The authors also mentioned a prospective cohort study from France that reported a positive association between dietary folate intake and overall skin cancer risk (HR for top vs. bottom tertile,

1.79; 95% confidence interval, 1.07–2.99; ref. 4). However, of the 144 skin cancer cases included, only 20 were melanoma. Thus, it is difficult to extrapolate the findings to melanoma specifically, because other types of skin cancers may have driven the association. In addition, the study could have been strengthened if the analysis had further accounted for citrus consumption, a potential confounder. Citrus fruits are major sources of dietary folate, and we found that citrus consumption was positively associated with melanoma and nonmelanoma skin cancer risk in two prospective studies (5, 6). As the direction of confounding is likely positive and biased away from the null, adjustment may attenuate or even nullify any association.

In fact, we recently found a positive association between dietary folate intake and melanoma risk, and the magnitude of effect was attenuated after adjusting for citrus consumption (7). We, however, discovered that total folate intake (which includes dietary and supplemental intake) was not associated with melanoma risk. Thus, findings regarding dietary folate intake may be because of other components found in folate-rich foods rather than folate per se. Furocoumarins in citrus fruits may in part be responsible for the positive association because of their potential photocarcinogenic properties.

The association between folate intake and melanoma risk remains unclear. Because new randomized trials are unfeasible given the potential adverse effects of folate on melanoma, further observational studies are warranted.

Disclosure of Potential Conflicts of Interest

A.A. Qureshi reports receiving a commercial research grant from Sanofi and Regeneron, has ownership interest (including stock, patents, etc.) in Nix-Tix, and is a consultant/advisory board member for Eli Lilly, Amgen, AbbVie, CDC, Janssen, Merck, Novartis, and Pfizer. No potential conflicts of interest were disclosed by other authors.

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