

## Aspirin use and the risk of malignant melanoma



*To the Editor:* “Daily aspirin dose ‘doubles risk of skin cancer in men,’” reported the *Daily Telegraph*.<sup>1</sup> A Google search for “aspirin and melanoma” in June 2018 yielded several similar links from news outlets and medical trade publications, all pointing to an article in press by Orrell et al<sup>2</sup> that was recently published in the *Journal*. Are these alarming headlines justified by the study?

Orrell et al<sup>2</sup> found an adjusted relative risk of malignant melanoma of 1.83 in aspirin-exposed men; the adjusted risk was 0.53 for women but was not statistically significant. This study’s methodology has substantial weaknesses. The exposed population was selected based on a documented aspirin prescription, while the unexposed population included other adults in the system without a history of melanoma. This method avoids self-reported exposure but causes confounding by indication. Aspirin prophylaxis is indicated for older patients with increased cardiovascular disease risk. Indeed, the exposed group was 15 years older, on average, than the unexposed group. Although the researchers controlled for age, regression alone does not adequately account for additional comorbidities implied by a prescription, especially when the groups differ greatly at baseline. In addition, an aging, high-risk subpopulation is likely to interact with the health system more often, leading to surveillance bias.

Despite the large cohort (66,134 men), relatively few aspirin users were identified (664, or 1% of men). Only 26 melanoma cases (23 men) were reported among aspirin users, compared with 1675 cases (670 men) in the unexposed group. Attributing this extreme gender skew entirely to aspirin strains credulity, particularly considering the small sample size. Even more concerning, many patients were almost certainly misclassified: <1% of the sample was counted as aspirin-exposed, but over half of US adults 45 to 75 years of age report taking aspirin regularly.<sup>3</sup> The prescription rate in this study is also far lower than clinical guidelines predict, but this is unsurprising because verbal recommendations often go undocumented. Prescriptions for over-the-counter medications may be needed for payment by Medicaid and other insurers, or at hospitals and long-term care facilities. Therefore, the selection criteria may well have captured the sickest and poorest subset of aspirin users.

As the authors note, this finding disagrees with previous results. Three studies, including 1

randomized trial, showed no effect of aspirin on melanoma risk, while 5 studies showed a statistically significant preventive benefit of aspirin; 1 study found increased melanoma risk in women, but no dose–response relationship.<sup>4</sup> In our review of the literature, there is compelling evidence from metaanalyses of numerous large randomized trials showing reduced cancer incidence among aspirin users. The effect held for as many as 12 types of cancer, suggesting a common mechanism of action.<sup>5</sup> The US Preventive Services Task Force now recommends aspirin for colorectal cancer prevention in most patients over 55 years of age.

In light of this study’s limitations, the best evidence does not support aspirin as a risk factor for any cancer, including melanoma. Most clinicians would likely agree. Will laypeople, seeing the current spate of news articles, reach the same conclusion?

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