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Aspirin and endometrial cancer risk

Beth Y. Karlan, MD, Editor-in-Chief
Gynecologic Oncology Reports

Dear Dr. Karlan,

We enjoyed reading the recent meta-analysis by Verdoodt et al. (2016), which summarized the associations between non-steroidal anti-inflammatory drugs (NSAIDs) and endometrial cancer risk in epidemiologic studies. We applaud the authors for a comprehensive analysis and for examining associations stratified by NSAID type and study design, and for additionally examining the potential for differences between population- and hospital-based case–control studies. We outline below a few minor concerns with an otherwise excellent article.

We have contributed two studies to the Verdoodt et al. analysis. In the Vitamins And Lifestyle (VITAL) cohort (Brasky et al., 2013), regular NSAID use was defined as use of individual medications (i.e., aspirin, ibuprofen, naproxen, and COX-2 inhibitors) ≥1 day/week for ≥1 year. The results from our work in the VITAL cohort (n = 262 cases) were suggestive of an inverse association between aspirin and endometrial cancer incidence: low use (<4 days/week or <4 years) was associated with a 23% reduction in risk (HR 0.77, 95% CI: 0.54–1.09), and high use (≥4 days/week and ≥4 years) was associated with 36% reductions in risk (HR 0.64, 95% CI: 0.41–1.01). The trend across categories was $P < 0.03$. We believe that Verdoodt et al. chose the incorrect point estimate to reflect associations in this cohort in a manner comparable to others in the analysis. The authors chose to include the HR corresponding to low use (i.e., HR 0.77, referenced above) in their analytic Table 3 and forest plot in Figure 1. Their reasoning for this choice was not specified. The association between *any* aspirin use (i.e., low and high use) relative to non-use and endometrial cancer risk, as reported in the manuscript text was in fact both inverse and statistically significant (HR 0.72, 95% CI: 0.53–0.98). Using a random effects model in STATA, we performed a meta-analysis of aspirin use and endometrial cancer risk among the prospective studies included in the Verdoodt et al. paper. We substituted for the VITAL cohort the HR and 95% CI for any aspirin use. The result of our meta-analysis was a pooled RR of 0.91 (95% CI: 0.83–0.99). The *P* value was 0.03. Although the difference between these results is indeed very small, we note – for better or for worse – the strong reliance of *Gynecologic Oncology*'s readership upon statistical significance, and thus the slight difference in interpretation of Verdoodt et al.'s primary finding may be meaningful in this context.

In a subsequent analysis among postmenopausal women participating in the Women's Health Initiative (WHI), we did not observe an association between consistent intakes of NSAIDs (overall or by medication type) with endometrial cancer risk (Brasky et al., 2014). Given that intakes recorded in the WHI reflected use over the prior two weeks (and despite our efforts to mitigate the error by combining NSAID data from baseline with that from a follow-up questionnaire), it would not be surprising to anticipate that any but the strongest associations might be masked by measurement error. This error is easily demonstrated in colorectal cancer, where an inverse association is well established: we reported no association between inconsistent NSAID use (defined as NSAID use at baseline or the year 3 follow-up) and colorectal cancer risk relative to no NSAID use at either time point (HR 1.00, 95% CI: 0.86–1.17), but observed inverse associations with colorectal cancer risk for consistent NSAID use (i.e., use of NSAIDs at both baseline *and* year 3) (HR 0.78, 95% CI: 0.64–0.95), and significant duration-dependent trends among these users ($P < 0.02$). The discrepancy between these findings emphasizes the challenge in examining NSAIDs in relation to cancer occurrence in most studies, regardless of design, and highlights the continued and predominantly unmet need for strong measurement of medication use that includes recency of use, frequency, intensity (i.e., number of pills taken per pill-taking day), duration, and dose.

Lastly, we would like to call the editor's attention to this and indeed any meta-analysis that includes all papers examining associations between a given exposure and outcome without an a priori assessment and analytic plan for studies of potentially poorer quality. The authors included in the meta-analysis their recent assessment of low-dose aspirin and non-aspirin NSAIDs, in an enormous case–control study using a Danish prescription registry (Brøns et al., 2015). Unlike other studies in the meta-analysis, regular-strength aspirin, sold primarily over the counter in Denmark, was not assessed. Indeed, low-dose aspirin is not thought to hold significant anti-inflammatory properties (Vaucher et al., 2014). Consistent with this hypothesis, in the VITAL cohort the reduction in endometrial cancer risk from aspirin use was restricted to regular-strength formulations. Unfortunately, only our studies in VITAL and the WHI have separately examined low-dose and regular-strength aspirin. The authors were also insufficiently able to assess potential confounding by body mass or several other endometrial cancer risk factors. Given this context, and the study's significant weight in the meta-analysis, it would have been worthwhile to report summary point estimates with and without its exclusion. Similarly, the study by Schreinemachers et al. (Schreinemachers and Everson, 1994), also lacked the capacity to assess or statistically adjust for potential confounders aside from age.

Although we agree in principal that meta-analyses are useful for summarizing associations across epidemiologic studies, the issues we outline here highlight the challenge in performing such analyses, the relative ease with which results from such analyses are beholden to choices that investigators make in selecting results to summarize, and the need to establish a strong degree of epidemiologic rigor to ensure meaningful interpretation and dissemination of findings.

Best Regards,
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