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ORIGINAL ARTICLE

Use of aspirin, other nonsteroidal anti-inflammatory drugs and acetaminophen and risk of endometrial cancer: the Epidemiology of Endometrial Cancer Consortium

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Background: Regular use of aspirin has been associated with a reduced risk of cancer at several sites but the data for endometrial cancer are conflicting. Evidence regarding use of other analgesics is limited.

Patients and methods: We pooled individual-level data from seven cohort and five case–control studies participating in the Epidemiology of Endometrial Cancer Consortium including 7120 women with endometrial cancer and 16 069 controls. For overall analyses, study-specific odds ratios (ORs) and 95% confidence intervals (CI) were estimated using logistic regression and combined using random-effects meta-analysis; for stratified analyses, we used mixed-effects logistic regression with study as a random effect.

Results: At least weekly use of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with an approximately 15% reduced risk of endometrial cancer among both overweight and obese women (OR = 0.86 [95% CI 0.76–0.98] and 0.86 [95% CI 0.76–0.97], respectively, for aspirin; 0.87 [95% CI 0.76–1.00] and 0.84 [0.74–0.96], respectively, for non-aspirin NSAIDs). There was no association among women of normal weight (body mass index < 25 kg/m^2, $P_{heterogeneity} = 0.04$ for aspirin, $P_{heterogeneity} = 0.003$ for NSAIDs). Among overweight and obese women, the inverse association with aspirin was stronger for use 2–6 times/week (OR = 0.81, 95% CI 0.68–0.96) than for daily use (0.91, 0.80–1.03), possibly because a high proportion of daily users use low-dose formulations. There was no clear association with use of acetaminophen.

Conclusion: Our pooled analysis provides further evidence that use of standard-dose aspirin or other NSAIDs may reduce risk of endometrial cancer among overweight and obese women.

Key words: endometrial cancer, aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen

Introduction

Endometrial cancer, the fourth most common cancer among women in high-income countries, affects more than 380 000 women worldwide each year [1], including 63 000 in the United States [2], and age-standardized incidence rates are increasing. A major risk factor is exposure to estrogen in the absence of a progestogen [3]; the main source of estrogen in post-menopausal women is adipose tissue, where aromatase converts androgens to estrogens. Estimates suggest one in three endometrial cancers are attributable to overweight and obesity [4].

While regular use of aspirin reduces risk of colorectal and possibly other cancers [5], data for endometrial cancer are less clear. Meta-analyses suggest an inverse association that is stronger among obese women [6–9], but they are susceptible to publication bias and the included studies varied in their categorization of medication use and adjustment for confounders. They were also unable to separate standard from low-dose aspirin, yet individual studies have reported weaker associations for low-dose aspirin [6, 10]. It is plausible that anti-inflammatory medications might be more protective among obese women because obesity is associated with chronic low-grade inflammation [11]. Furthermore, aromatase-mediated conversion of androgens in fat cells is the primary source of estrogen in post-menopausal women and non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to down-regulate aromatase activity in cell lines [12]. By suppressing inflammation and aromatase, NSAIDs may mitigate some of the excess endometrial cancer risk associated with obesity.

A recent review called for studies pooling data from multiple sources to clarify the relation between aspirin and endometrial cancer [13]. To this end, we pooled individual-level data from 12 studies in the Epidemiology of Endometrial Cancer Consortium (E2C2) to evaluate associations between analgesic use and endometrial cancer risk. Our *a priori* hypothesis was that use of aspirin (standard-dose) and other NSAIDs, but not low-dose aspirin or acetaminophen, would be associated with reduced risk, particularly among obese women.

Methods

We included five case–control and seven cohort studies that provided data regarding use of aspirin, non-aspirin (NA-) NSAIDs and/or acetaminophen (supplementary Table S1, available at *Annals of Oncology* online). All studies were approved by the relevant institutional review board(s) and participants provided informed consent.

The E2C2 data harmonization process has been described [14]. In brief, cohort studies are analyzed as nested case–control studies with up to four controls per case, matched on year-of-birth, cohort entry date and other study-specific criteria as appropriate, randomly selected from cohort members who had not had a hysterectomy or endometrial cancer by the case diagnosis date. Studies provided information on demographic, anthropometric, reproductive, medical and lifestyle factors (e.g. height, weight [see supplementary Table S2, available at *Annals of Oncology* online], parity, oral contraceptive (OC) and menopausal hormone therapy (MHT) use, diabetes, smoking) according to specified definitions. We excluded cases (and their matched controls) with non-epithelial tumors or tumors of unknown histology (196 cases/754 controls) and women missing data for aspirin, NA-NSAIDs and acetaminophen (814 cases/4977 controls, including controls individually-matched to cases without data). With the exception of the Breast Cancer Detection Demonstration Project (BCDDP) where women reported past and current medication use, cases (and matched controls) diagnosed before collection of medication data in the cohort studies were also excluded (344 cases/502 controls). The final study group comprised 7120 cases and 16 069 controls.

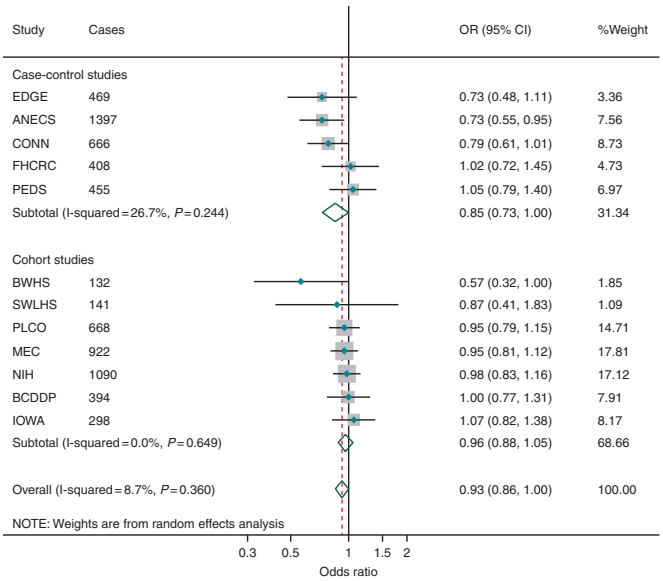
Supplementary Table S1, available at *Annals of Oncology* online shows the questions used to ascertain medication use in each study. The Australian National Endometrial Cancer Study (ANECS) asked about use in the five years before enrolment while the other case–control studies asked about ever use. For the Iowa Women's Health Study (IOWA), Multiethnic Cohort Study (MEC), NIH-AARP Diet and Health Study (NIH) and Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), data were collected at baseline and not updated during follow-up. For the Black Women's Health Study (BWHS), data were updated from the most recent questionnaire before a participant became a case/was selected as a control. Data for the Swedish Women's Lifestyle and Health Study (SWLHS) came from the national pharmacy prescription database. 'Regular' medication use was defined as use at least once/week, but this definition differed slightly depending on the questions used to ascertain medication use, for example, BWHS only asked women to report use of at least 3 days/week. In studies with information about frequency of use, we further classified women as using the medications less than once/week, once/week, 2–6 times/week or daily. These cut points were selected for pragmatic reasons based on categories used in the original studies and in order to look separately at women who reported daily aspirin use as this was considered more likely to be low dose.

Statistical analyses

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 13 (StataCorp LP, College Station, TX, USA). For the overall models, pooled odds ratios (pORs) were calculated using a two-stage method. First, study-specific ORs and 95% confidence intervals (CI) were estimated for the associations between regular use of medications (yes/no) and risk of endometrial cancer using multivariable logistic regression (conditional regression for the matched studies). Models were adjusted for age (continuous), parity, body mass index (BMI) (kg/m^2, continuous) and OC use (ever/never; further adjustment for OC duration in studies with this information made little difference), highest level of education (high-school/college/university) and smoking (never/former/current). See supplementary Methods, available at *Annals of Oncology* online, for further details regarding models and handling of missing data. Study-specific estimates were pooled using random-effects models and heterogeneity was assessed using I^2 and Q statistics.

To address our primary hypothesis that any inverse association with medication use would be more pronounced among obese women, we stratified by BMI (normal <25, overweight 25–29.9, obese ≥30 kg/m^2). We also assessed whether associations differed by study design, race, parity, OC use and, among post-menopausal women, use of MHT, or between type 1 and type 2 cancers (see supplementary Methods, available at *Annals of Oncology* online). For stratified analyses, we used generalized mixed regression models allowing the exposure effect to vary across studies [15]. Models were constructed to allow for the individual-level case–control matching in cohort studies with each unmatched case–control study treated as a single set (this gave identical estimates to standard unconditional models for these studies).

To estimate the potential impact of changing aspirin use if observed associations were causal, we used the age-standardized incidence rate for endometrial cancer in the United States [16], the BMI distribution in the USA female population (33% normal weight, 27% overweight, 40% obese) [17], and relative risks for overweight and obesity in the study population (overweight = 1.5; obese = 3.5) to estimate incidence rates by BMI. We then used the relative risks for overweight and obese women who used aspirin (versus all normal weight women, assuming no aspirin effect in this group) to estimate the potential reduction in incidence and thus the proportion and number of cancers potentially preventable if all overweight/obese women took aspirin at least once a week.



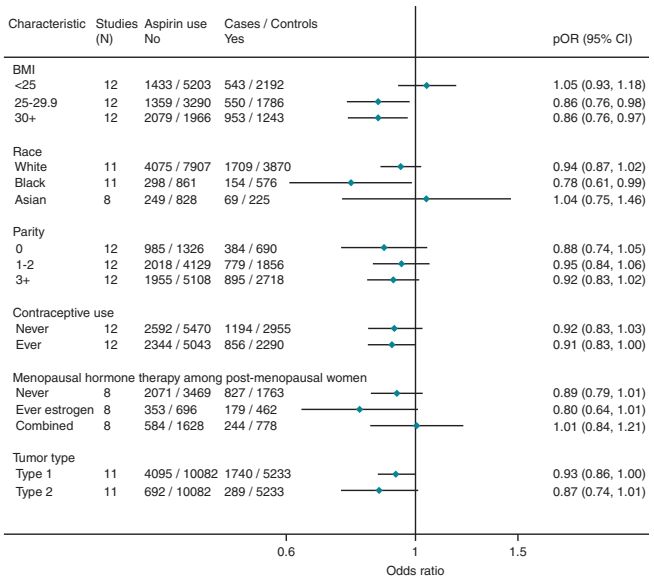


Figure 1. Forest plots showing adjusted estimates and 95% confidence intervals (CIs) for the association between regular use of aspirin and risk of endometrial cancer (A) overall, by study design with estimates ordered from smallest to largest and (B) stratified by participant characteristics and tumor type. The size of the box indicates the weight of the study, the line represents the 95% CI and the diamonds represent the pooled estimates. OR, odds ratio; EDGE, Estrogen, Diet, Genetics and Endometrial Cancer Study; ANECS, The Australian National Endometrial Cancer Study; FHCRC, Fred Hutchinson Cancer Research Center Study; CONN, Connecticut Endometrial Cancer Study; PEDS, Patient Epidemiologic Data System; BWHS, Black Women's Health Study; NIH, NIH AARP Diet and Health Study; IOWA, Iowa Women's Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; MEC, Multiethnic Cohort Study; SWLHS, Swedish Women's Lifestyle and Health Study; BCDDP, Breast Cancer Detection Demonstration Project.

Results

The proportion of controls classified as regular users of aspirin ranged from 9% to 43% across the studies, NA-NSAIDs from 9% to 36% and acetaminophen from 15% to 36% (supplementary Table S1, available at *Annals of Oncology* online). The prevalence was lowest in Estrogen, Diet and Genetics of Endometrial Cancer Study (EDGE) where women were asked to report medications used continuously for at least 6 months and, for aspirin, the Swedish study, which only recorded prescription medications.

Aspirin

Overall, there was a borderline significant inverse association between regular use of aspirin and endometrial cancer risk (Figure 1A; pOR = 0.93, 95% CI 0.86–1.00). There was no significant heterogeneity between the studies, but the inverse association was stronger for case–control (pOR = 0.85, 95% CI 0.72–1.01) than for cohort studies (pOR = 0.96, 95% CI 0.88–1.05). Figure 1B shows no association among women of normal weight, but regular use of aspirin was associated with a 14% risk reduction among both overweight (OR = 0.86, 95% CI 0.76–0.98) and obese (OR = 0.86, 95% CI 0.76–0.97) women ($P_{heterogenity} = 0.04$). This pattern was also seen when we excluded studies that had previously published results stratified by BMI (OR [95% CI] for BMI < 25 and ≥25: 1.09 [0.93–1.26] and 0.87 [0.78–0.97]) and when we stratified by study design (case–control studies 0.95 [0.76–1.19] and 0.81 [0.68–0.95]; cohort studies 1.10 [0.95–1.26] and 0.89 [0.81–0.99]. Figure 1B also shows that the association was strongest for black women, likely because of a higher prevalence of overweight/obesity (77% among controls), than for white (51%) and Asian (29%) women. The association did not differ significantly by parity, OC or MHT use, or between type 1 and type 2 cancers.

Table 1 shows that in studies with information about frequency of use, there was no association between endometrial cancer and use of aspirin once/week (OR = 0.98, 95% CI 0.80–1.20) or daily (OR = 0.96, 95% CI 0.86–1.07), and only a suggestive inverse association with use two to six times/week (OR = 0.89, 95% CI 0.78–1.02). However, among overweight and obese women there was a significant 19% reduction in risk of endometrial cancer for use 2–6 times/week and a non-significant 9% reduction for daily use. Only two studies [ANECS and Fred Hutchinson Cancer Research Center Study (FHCRC)] provided data regarding aspirin dose; both showed an inverse association with use of standard aspirin two or more times/week and, combined, the estimates were 0.62 (0.47–0.82) for standard and 1.14 (0.82–1.58) for low-dose aspirin.

Compared with all normal-weight women (assuming no association with aspirin use in this group), obese women who did not use aspirin were 3.6 times as likely to develop endometrial cancer (pOR = 3.63, 95% CI 3.32–3.96), but this was reduced to 3.2 times for obese women who used aspirin (pOR = 3.20, 95% CI 2.88–3.57). For overweight women the risks were 1.54 (1.41–1.68) for non-users *versus* 1.35 (1.20–1.51) for users of aspirin. If the association between aspirin use and endometrial cancer is causal, and all overweight and obese women took aspirin at least once a week, we estimate that this could translate to a reduction in incidence of up to 7.5% equivalent to 4600 fewer cases/year in the United States.

Non-aspirin NSAIDs

There was no overall association between regular use of non-aspirin NSAIDs and risk of endometrial cancer and little

Table 1. Odds ratios (OR) and 95% confidence intervals (CIs) for the association between frequency of aspirin and nonsteroidal anti-inflammatory drugs (NSAID) use and endometrial cancer risk, overall and by body mass index (BMI)

Frequency of use	Aspirin[a]			Non-aspirin NSAIDs[a]		
	Cases *N* (%)	Controls *N* (%)	OR[b] (95% CI)	Cases *N* (%)	Controls *N* (%)	OR[b] (95% CI)
Overall						
<1/week	3472 (70)	6130 (65)	1.00 (Ref)	3443 (76)	6878 (77)	1.00 (Ref)
1/week	179 (4)	428 (4)	0.98 (0.80–1.20)	124 (3)	319 (3)	0.80 (0.62–1.02)
2–6/week	450 (9)	1114 (12)	0.89 (0.78–1.02)	446 (10)	771 (9)	0.93 (0.81–1.08)
Daily	877 (17)	1790 (19)	0.96 (0.86–1.07)	492 (11)	989 (11)	0.94 (0.82–1.08)
BMI < 25.0 kg/m^2						
<1/week	919 (71)	2925 (68)	1.00 (Ref)	954 (81)	3277 (80)	1.00 (Ref)
1/week	52 (4)	196 (5)	1.04 (0.74–1.46)	28 (2)	159 (4)	0.65 (0.42–1.01)
2–6/week	128 (10)	495 (11)	1.05 (0.84–1.32)	90 (8)	284 (7)	1.10 (0.84–1.44)
Daily	199 (15)	710 (16)	1.09 (0.90–1.31)	100 (9)	359 (9)	1.19 (0.93–1.53)
BMI ≥ 25.0 kg/m^2						
<1/week	2466 (69)	3108 (62)	1.00 (Ref)	2421 (75)	3493 (74)	1.00 (Ref)
1/week	126 (3)	224 (4)	0.93 (0.72–1.20)	92 (3)	153 (3)	0.88 (0.65–1.19)
2–6/week	312 (9)	600 (12)	0.81 (0.68–0.96)	342 (11)	477 (10)	0.87 (0.73–1.04)
Daily	672 (19)	1066 (21)	0.91 (0.80–1.03)	384 (12)	621 (13)	0.85 (0.73–1.00)
						P-trend 0.02

[a]Includes the Australian National Endometrial Cancer Study (ANECS), Connecticut Endometrial Cancer Study (CONN), FHCRC, PEDS (aspirin only), Iowa Women's Health Study (IOWA), NIH and Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO).
[b]Adjusted for age at diagnosis/interview (continuous), parity (continuous), BMI (kg/m^2, continuous) and oral contraceptive use (ever/never), highest level of education and smoking.

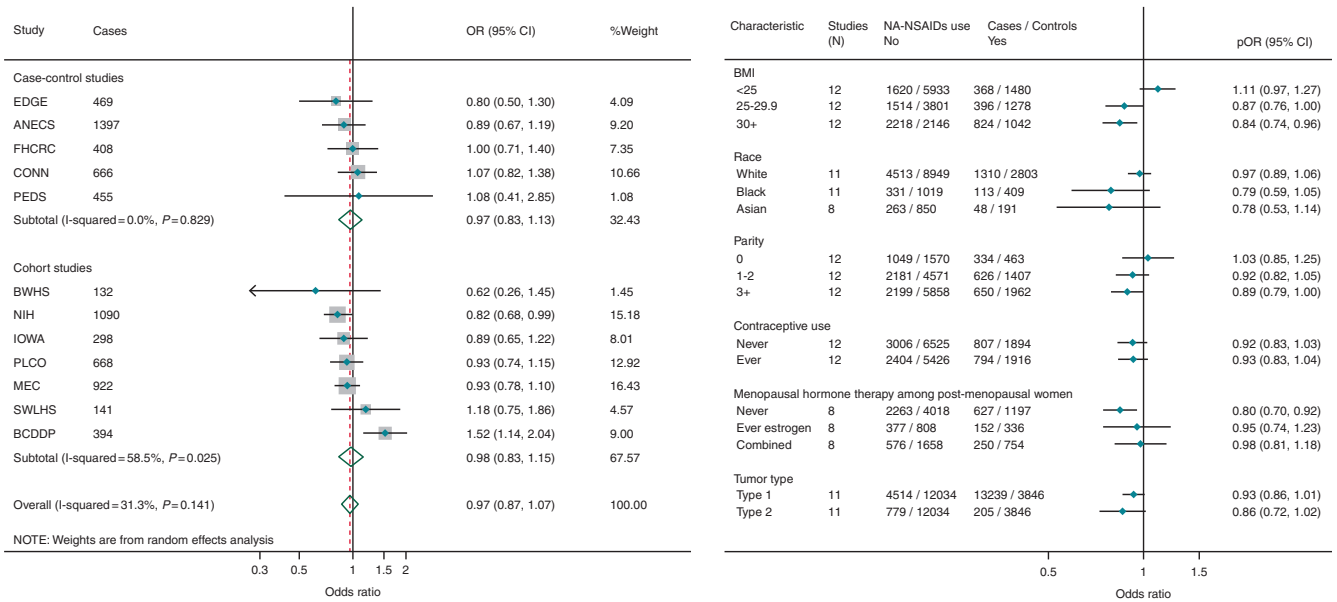


Figure 2. Forest plots showing adjusted estimates and 95% confidence intervals (CIs) for the association between regular use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of endometrial cancer (A) overall, by study design with estimates ordered from smallest to largest and (B) stratified by participant characteristics and tumor type. The size of the box indicates the weight of the study, the line represents the 95% CI and the diamonds represent the pooled estimates. BMI, body mass index; pOR, pooled odds ratios; EDGE, Estrogen, Diet, Genetics and Endometrial Cancer Study; ANECS, The Australian National Endometrial Cancer Study; FHCRC, Fred Hutchinson Cancer Research Center Study; CONN, Connecticut Endometrial Cancer Study; PEDS, Patient Epidemiologic Data System; BWHS, Black Women's Health Study; NIH, NIH AARP Diet and Health Study; IOWA, Iowa Women's Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; MEC, Multiethnic Cohort Study; SWLHS, Swedish Women's Lifestyle and Health Study; BCDDP, Breast Cancer Detection Demonstration Project.

difference between case–control and cohort studies, although the results from cohort studies were very heterogeneous (Figure 2A). However, similar to aspirin, NA-NSAID use was associated with a 13% reduction in risk among overweight women and a statistically significant 16% reduction in risk among obese women (Figure 2B, $P_{heterogenity} = 0.003$). The association did not differ significantly by race, parity, OC or MHT use or for type 1 and type 2 cancers.

Table 1 shows that in studies with information about frequency of use, there was no trend with increasing frequency of use overall or among women with BMI <25, but a suggestive trend toward lower risk with increasing frequency among women with BMI of 25 kg/m^2 or higher ($P_{trend} = 0.02$).

Acetaminophen

There was no association between regular use of acetaminophen and endometrial cancer risk in the seven studies with information available (supplementary Figure S1A, available at *Annals of Oncology* online). Stratification by BMI suggested an inverse association among overweight women (OR = 0.79, 95% CI 0.64–0.96) but no association among normal weight (1.10, 95% CI 0.91–1.33) or obese women (1.04, 95% CI 0.86–1.24) (supplementary Figure S1B, available at *Annals of Oncology* online). Estimates did not differ appreciably by the other variables considered. Too few studies had information about frequency of use to assess this.

Discussion

Our *a priori* hypothesis was that use of standard-dose aspirin and other NSAIDs would be associated with a reduced risk of endometrial cancer, particularly among obese women, but that there would be no association with low-dose aspirin or acetaminophen. Overall, our results largely support this hypothesis. Use of aspirin 2–6 times/week was associated with significantly reduced risk of endometrial cancer among overweight/obese women, but not among normal-weight women. Furthermore, the association with daily aspirin use, which likely includes most low-dose use [18], was weaker and in the two studies with dose information, the inverse association was restricted to standard-dose formulations. We also saw reductions in risk for regular use of non-aspirin NSAIDs among overweight/obese women, but no clear pattern with acetaminophen use. The results did not differ significantly between type 1 and type 2 cancers, although the associations with type 2 cancers were slightly stronger. Although the potential risk reduction with aspirin is modest (10%–20%), if this association is causal and all overweight/obese women used standard-dose aspirin at least once a week, this could translate into up to 4600 fewer endometrial cancers per year in the United States.

Our results for aspirin are consistent with two meta-analyses (including seven studies in the current analysis) which reported modest inverse associations between regular aspirin use and endometrial cancer among obese women although they could not distinguish between standard and low-dose use preparations [7, 9]. One meta-analysis also reported a non-significant risk reduction for NSAIDs but did not consider whether this might vary by BMI [7]. Limited randomized trial evidence is also consistent with a modest beneficial effect of standard-dose aspirin. A pooled analysis of data from trials of aspirin to prevent vascular events, reported no uterine cancers among women randomized to aspirin (versus 9 in the placebo group, $P = 0.003$) [19]. Similarly, in a trial of aspirin among patients with Lynch syndrome, only five endometrial cancers were diagnosed among 427 women randomized to 600 mg aspirin/day (versus 13 among 434 in the placebo group) [20]. This study also reported that aspirin reduced the adverse effects of obesity on colorectal cancer risk [21]. The weaker association with daily (presumed to be largely low-dose) aspirin use in our analysis is consistent with the Women's Health Study, which did not show any reduction in endometrial cancer risk among those randomized to 100 mg aspirin every second day [22]. Seven studies (ANECS, FHCRC, Patient Epidemiologic Data System, MEC and three others [23–25]) have previously reported no clear evidence for an association between acetaminophen use and endometrial cancer.

Strengths of our analysis include the large sample size, inclusion of published and unpublished data, and greater ability to standardize exposure levels and adjust consistently for confounders. Although previous meta-analyses reported inverse associations between aspirin use and endometrial cancer among obese women [6, 7, 9], these may be subject to publication bias if studies that saw no association had not published their data. Our analysis includes five studies that had not previously published data evaluating aspirin use in relation to endometrial cancer (Connecticut Endometrial Cancer Study, BCDDP, BWHS, PLCO, SWLHS) and we included 40%–50% more cases for two previously published studies (MEC and NIH). Although only two studies provided information about aspirin dose, we were able to assess this indirectly by looking separately at daily users who are most likely to use low-dose preparations.

Limitations of our study include the self-reported nature of the data for all studies except SWLHS (which used linkage to prescriptions data but could not capture over-the-counter use), and the possibilities of bias in individual studies. Also, despite the large sample, numbers were still limited for some sub-group analyses. Overall, the associations we observed with aspirin use were stronger among the case–control studies than the cohort studies although this difference disappeared when we stratified by BMI. Although case–control studies might overestimate the strength of association because of selection or recall bias, changing medication use over time in cohort studies would lead to misclassification which could attenuate associations. A systematic comparison of studies evaluating aspirin and cancer incidence concluded that results from case–control studies were highly correlated with those from randomized trials; in contrast, estimates from cohort studies were weaker if aspirin use was not updated during follow-up [26]. The fact that several cohort studies in this analysis did not update medication use after baseline (IOWA, MEC, NIH, PLCO), the difference between normal-weight and overweight/obese women was seen in both case–control and cohort studies, and no association was seen for acetaminophen, suggests that our results are not an artefact due to bias in the case-control studies.

An inverse association between use of anti-inflammatory medications and endometrial cancer risk among overweight/obese women is biologically plausible [27]. Several risk factors for endometrial cancer, including obesity [11], are associated with systemic chronic low-grade inflammation. Prospective studies have reported higher endometrial cancer risks among women

with higher concentrations of inflammatory markers [28–30] with one suggesting the risk was greatest for women who were both obese and had high levels of inflammatory markers [30]. Both aspirin and NSAIDs inhibit cyclooxygenase (COX), leading to a reduction in prostaglandin levels and, in breast cancer cell lines, COX inhibitors also down-regulate aromatase activity [12]. Cross-sectional studies suggest post-menopausal women who regularly use NSAIDs have lower estradiol levels than nonusers [31, 32]. *In vitro* studies suggest aspirin and NSAIDs also have antiproliferative and antineoplastic effects that are independent of COX inhibition [33, 34] and can inhibit the proliferation of endometrial cancer cells [35, 36].

In conclusion, our analysis provides further evidence that use of standard-dose aspirin or other NSAIDs might reduce the risk of endometrial cancer among overweight and obese women. Future studies should clarify the relationship with low-dose aspirin and should include regularly updated measures of medication use (dose, frequency), ideally in a well-powered randomized trial to minimize bias and confounding. If confirmed, clinicians could consider aspirin or NSAIDs as an option to reduce the greatly increased risk of endometrial cancer among obese women who have an intact uterus.

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Disclosure

The authors have declared no conflicts of interest.

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