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Aspirin, Non-Aspirin Nonsteroidal Anti-inflammatory Drugs, or Acetaminophen and risk of ovarian cancer

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Abstract

Background—Aspirin, non-aspirin nonsteroidal anti-inflammatory drugs (NA-NSAIDs) and acetaminophen all have biologic effects that might reduce the risk of ovarian cancer. However, epidemiologic data on this question are mixed.

Methods—A population-based, case-control study in western Pennsylvania, eastern Ohio, and western New York State included 902 women with incident epithelial ovarian cancer who were diagnosed between February 2003 to November 2008 and 1,802 matched controls. Regular use (at least 2 tablets per week for 6 months or more) of aspirin, NA-NSAIDs, and acetaminophen before the reference date (9 months before interview date) was assessed by in-person interview. We used logistic regression to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results—The OR for aspirin use was 0.81 (95% CI= 0.63–1.03). Decreased risks were found among women who used aspirin continuously (0.71 [0.54–0.94]) or at a low-standardized daily dose (0.72 [0.53–0.97]), who used aspirin for the prevention of cardiovascular disease (0.72 [0.57–0.97]), who used aspirin more recently, or who used selective COX-2 inhibitors (0.60 [0.39–0.94]). No associations were observed among women using non-selective NA-NSAIDs or acetaminophen.

Conclusions—Risk reductions of ovarian cancer were observed with use of aspirin or selective COX-2 inhibitors. However, the results should be interpreted with caution due to the inherent study limitations and biases.

Ovarian cancer is the second leading gynecologic cancer, following cancer of the uterine corpus, and causes more deaths per year than any other cancer of the female reproductive system.[1] It afflicts about 1 in 70 women, and is the fifth leading cause of cancer death among women in the United States.[1,2] Approximately 21,550 new cases of ovarian cancer are diagnosed annually, resulting in 14,600 deaths.[1,2] Thus, strategies that focus on prevention may provide the most rational approach for meaningful reductions in incidence and deaths attributable to ovarian cancer.

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Ovarian cancer has a poorly understood etiology and natural history. Two dominant hypotheses explain the genesis of the disease.[3] The ovulation hypothesis relates ovarian cancer risk to incessant ovulation, while the pituitary gonadotropin hypothesis implicates elevations in gonadotropin/estrogen levels. Epidemiologic and biologic observations do not entirely support either hypothesis. Previous work has suggested that ovarian cancer may be related to chronic pelvic inflammation that acts in concert with ovulation.[4] This theory could be an important consideration for prevention of ovarian cancer and is supported by the mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs, including aspirin and non-aspirin NSAIDs (NA-NSAIDs), act through non-competitive and irreversible inhibition of cycloxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes in the synthesis of prostaglandins to produce anti-inflammatory and anti-neoplastic effects.[5] In addition, NSAIDs may suppress ovulation and affect cell proliferation, angiogenesis, and apoptosis of the epithelium in ovarian cancer cell lines.[6] Acetaminophen, another commonly used analgesic and antipyretic drug, has weak anti-inflammatory activity and may have an anti-gonadotropic effect.[7] Acetaminophen may also inhibit ovarian carcinogenesis through the depletion of glutathione leading to necrosis.[8] Therefore, aspirin, NA-NSAIDs, or acetaminophen may be potential agents for the chemoprevention of ovarian cancer. NSAIDs and acetaminophen are two of the most frequently used classes of medication in the United States,[9,10] NSAIDs generated about $14 billion in sales world-wide in 2008.[11] Because of the widespread use of aspirin, NA-NSAIDs and acetaminophen, any association with an increased or decreased cancer risk may have important public health implications.

Several studies have described associations between aspirin or NA-NSAIDs use and the risk of ovarian cancer, but the findings are contradictory and inconclusive. Previous studies were relatively small and lacked information or statistical power to assess the effects of dose, duration, drug classes, or indications. The purpose of this study was to describe the associations of aspirin, NA-NSAIDs, or acetaminophen use with ovarian cancer risk, using the data from Hormones and Ovarian Cancer Prediction (HOPE) study, the second-largest population-based case-control study on ovarian cancer.

Methods

The HOPE study

Study population and recruitment details have been published previously.[12] Briefly, this is a case-control study involving 902 women with incident ovarian cancer (cases) from a contiguous region comprising western Pennsylvania, eastern Ohio, and western New York State. Cases were residents of this region with histologically confirmed, primary, epithelial ovarian, fallopian tube, or peritoneal cancer diagnosed between February 2003 and November 2008. Both borderline/low-malignant potential and invasive tumors were included. For brevity, the term “ovarian cancer” is used here to describe all cases. Women were referred from comprehensive hospital tumor registries, clinical practices, or pathology databases and contacted with the permission of their gynecologists. Age-adjusted incidence rates for 2003–2007 for the catchment counties in our study were similar to the rates based on the Surveillance and Epidemiology End Results (SEER) data (overall incidence rate in SEER was 14 vs. HOPE, 13 cases per 100,000). The ascertained cases were representative of the population from this region and considered as population-based. Eligible women had to be at least 25 years of age and recruited within 9 months of initial diagnosis. We excluded a total of 1,608 women (ineligible on the basis of age and time since diagnosis, residence outside of the counties in which referral hospitals were located, prior diagnosis of ovarian cancer, being non-English-speaking, or dead). Of 1,270 eligible cases, 902 completed the interview.

Controls were identified through random-digit-dialed phone numbers. Controls consisted of women at least age 25 who lived in the same telephone exchanges as cases. These women were further screened to ensure that they had no previous oophorectomy or diagnosis of ovarian cancer. Controls were frequency matched to cases by 5-year age groups and telephone exchange in approximately a 2:1 ratio. Overall, 1,802 eligible controls completed interviews (Figure). A standardized 2-hour interview (see eAppendix [http://links.lww.com] for questionnaire) was conducted by trained interviewers in the homes of participating women. The questionnaire included a reproductive and gynecologic history, a contraceptive history, a medical history, a family history, and information on lifestyle practices. A life-events calendar, which marked milestones such as marriages and births, was used to aid recall of reproductive history, infertility treatment, hormone use, and use of aspirin, over-the-counter (OTC) and prescription pain relievers until the reference date. The reference date was calculated as 9 months before the interview (for both cases and controls) to ensure that exposures occurred before the ovarian cancer diagnosis in cases and within a similar time frame for cases and controls.

The study protocol was approved by the University of Pittsburgh Institutional Review Board and by the human subject committees at each hospital where cases were identified. All study subjects gave informed consent.

Assessment of aspirin, NA-NSAIDs and acetaminophen use

Since most analgesic use is sporadic, regular use was defined as at least 2 tablets/week for 6 months or more. This definition created an exposure group that was homogeneous in its consistency of usage, and thus maximized the likelihood of detecting an association with ovarian cancer. Women who used less than this minimal level were defined as non-users. Participants were first asked if they took any aspirin, OTC pain relievers or NA-NSAIDs, or prescription medications for pain or inflammation on a regular basis before the reference date. Women who responded affirmatively were then asked the drug name, dose and frequency (numbers of pills taken per day, week, or month), the age at which they started, and duration (months or years) of use. For each episode, the primary reason for using the drug was recorded. The conditions were grouped as arthritis/burstitis/rheumatism, gout, menstrual cramps, injury, surgical/dental pain, back pain, headache, muscle ache, heart disease prevention (only listed for aspirin), others, or unknown. Aspirin products were defined as any product containing generic aspirin. NA-NSAIDs included celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumatone, naproxen/naproxen sodium, rofecoxib, sulindac, valdecoxib, or other NA-NSAIDs. Acetaminophen products were defined as any product containing acetaminophen.

Statistical Methods

Student’s t test was used for continuous variables, and the Chi-square test for categorical variables to compare differences between cases and controls. Unconditional logistic regression was used to calculate multivariable-adjusted odds ratios (ORs) as estimates of the relative risk and related 95% confidence intervals (95% CIs) for analgesics use. Potential confounders fell into 2 groups: those variables that (1) a priori were thought to be related to the exposure and also were risk factors for ovarian cancer and (2) those variables that previously published studies considered confounders. Confounders included the following: age (at reference year); interview year; region of residence (western Pennsylvania, eastern Ohio, and western New York); education; race; religion; parity; breastfeeding; history of infertility; contraceptive use and duration; menstrual status (age at menarche, menopausal status and age at menopause); use of postmenopausal hormone and duration; indications for aspirin, NA-NSAIDs, or acetaminophen use; prior hysterectomy or tubal ligation; history of

endometriosis; history of pelvic inflammatory disease; family history of breast cancer or ovarian cancer in first-degree relative; body mass index; cigarette smoking; alcohol consumption; comorbidities; and yearly household income.

Data were analyzed initially by constructing frequency counts of cases and controls by exposure variables and calculating ORs adjusted for age, region of residence, and interview year (Table 1). Second, confounders were forced into the models but were kept in the final regression model only if they changed the parameter estimates by at least 15%. The final multivariate model included age, region of residence, interview year, race, education, breastfeeding, numbers of full-term births, duration of oral contraceptive use, body mass index, postmenopausal hormone use, prior tubal ligation, arthritis, and diabetes (Tables 2–4). For the primary analyses of NSAIDs, women who had never used aspirin or NA-NSAIDs on a regular basis were the referent group. Risk was assessed separately among the subgroups of women who had used aspirin only, NA-NSAIDs only, and any NSAIDs (aspirin plus NA-NSAIDs). For the acetaminophen analyses, nonusers were considered as never having used acetaminophen regularly (but did not exclude aspirin or NA-NSAIDs use) before the reference date.

Duration of use was defined by three indicators as follows: (1) continuous (had used for at least 1 year and until or beyond the reference date); (2) current (used only less than a year and used on the reference date); and (3) past (discontinued use at least 1 year before the reference date). To examine dose-response effects, the average daily dose was calculated by multiplying the number of dosage forms per day with the strength of the medication taken during the most recent period before the reference date. For aspirin, the average daily dose was converted to a standardized daily dose by dividing it by 325 mg, assuming it was used as antithrombotic therapy for cardiovascular disease based on the dosage suggested by American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.[13] For NA-NSAIDs and acetaminophen, the average daily dose was then converted to a standardized daily dose by dividing it into minimal effective analgesic doses per day.[14] The minimal effective analgesic doses per day for individual agents were as follows: acetaminophen (1500 mg), celecoxib (200 mg), diclofenac (100 mg), etodolac (400 mg), fenoprofen (800 mg), flurbiprofen (150 mg), ibuprofen (1200 mg), indomethacin (75 mg), ketorolac (40 mg), ketoprofen (75 mg), mecolfenamate (150 mg), meloxicam (7.5 mg), nabumetone (1000 mg), naproxen (500 mg), piroxicam (20 mg), rofecoxib (25 mg), tolmetin (600 mg), sulindac (300 mg), and valdecoxib (10 mg).[15–17] Dosages were categorized into three clinically relevant categories: low-dose (≤ 0.5 standardized daily dose), moderate-dose (0.5–1 standardized dose) and high-dose (> 1 standardized dose).[14] Morever, the subgroup analyses were conducted by recency of use (e.g., age at first/last time use), self-reported indication and two types of NA-NSAIDs (i.e., non-selective NA-NSAIDs and selective COX-2 inhibitors). For the analysis on indications for analgesics, women who used different analgesics or the same analgesics but for different indications were considered separately. Analyses were also conducted separately among women with borderline and invasive epithelial ovarian tumors, and various histologic subgroups (i.e., serous, mucinous, endometrioid, clear cell, mixed cell and other epithelial cells); age less than 55 and 55 or more years; with and without arthritis; and with and without diabetes.

All analyses were carried out using STATA, version 11.0, statistical package (StataCorp LP, College Station, Texas, USA).

Results

Population characteristics are described in Table 1. Ninety-seven percent of the women were white; 61% of cases and 57% of controls were older than age 55. Cases were more likely to

be older, black, and nulliparous, and to have a body mass index of 30 kg/m^2 or more. Controls were more likely to be educated beyond high school, to have breastfed, have used oral contraceptives or postmenopausal hormones, have a history of tubal ligation, and have cormobidities including arthritis and diabetes. Overall, 491 cases and 1,018 controls reported having used aspirin, NA-NSAIDs, or acetaminophen on a regular basis.

Table 2 describes the regular use of aspirin or NA-NSAIDs and risks of ovarian cancer. The adjusted OR for regular use (versus never-use) of aspirin was 0.81 (95% CI= 0.63–1.03). ORs were reduced among continuous users (0.71 [0.54–0.94]), women who had used aspirin at low-standardized daily dose (0.72 [0.53–0.97]), women who began using aspirin only after age 45 (0.66 [0.50–0.88]), and women who stopped using after age 55 (0.70 [0.53–0.93]). Of those in the low-standardized daily dose group, the OR for using aspirin at daily doses of ≤81 mg was 0.66 (0.48–0.90). There were no associations between NA-NSAIDs or acetaminophen (eTable 1, http://links.lww.com) and ovarian cancer.

In Table 3, the adjusted OR for regular use of aspirin for prevention of cardiovascular disease was 0.72 (0.57–0.97). Seventy-one percent of women had used aspirin 81 mg daily for this purpose. A decreased OR was more evident among women who used aspirin for cardiovascular prevention for at least 5 years (0.66 [0.48–0.92]). Risk patterns remained essentially unchanged when stratified by indications for NA-NSAIDs use (eTable 2, http://links.lww.com).

ORs were reduced among women who used selective COX-2 inhibitors (0.60 [0.39–0.94]), but not in users of non-selective NA-NSAIDs (Table 4). The protective effects of selective COX-2 inhibitors were found only in women who used celecoxib (0.46 [0.25–0.84]), with no evidence of association in women who used rofecoxib or valdecoxib.

Cases included 677 women with invasive epithelial ovarian tumors, 97 with borderline or low-malignant potential epithelial ovarian tumors, 75 with peritoneal tumors, 32 with fallopian tumors, and 21 with “other/missing” type. Among the various histologic types of ovarian cancer, 516 cases were diagnosed with serous, 66 with mucinous, 100 with endometrioid, 54 with clear cell, 77 with mixed cells and 89 with other epithelial tumors. The results were similar for borderline or low-malignant potential and invasive tumors, and across categories of histologic types (eTable 3, http://links.lww.com). Stratification by age (less than 55 and 55 or more), arthritis status, and diabetes status, did not reveal any important differences in the associations between aspirin, NA-NSAIDs, or acetaminophen use and ovarian cancer.

Discussion

Aspirin or selective COX-2 inhibitors were associated with reduced risk of ovarian cancer, especially among middle aged and older women who took aspirin at low doses (or for prevention of cardiovascular disease) continuously over a long period of time. The results do not support the regular use of non-selective NA-NSAIDs and acetaminophen in the chemoprevention of ovarian cancer. We were able to evaluate dose-effects comprehensively among NSAIDs by using a standardized daily dose, and we had sufficient sample size to perform stratified analyses by indications of analgesic use and types of NA-NSAIDs.

Our results provide an additional direction for future study on the relationship between aspirin use and risk of ovarian cancer. Low-dose and continuous aspirin use had modest protective association with about 20 to 30% risk reduction, but without a dose-response relationship. A protective effect was not found in moderate to high-dose groups, which could have been due to smaller sample sizes with insufficient power. Our results agree with a study conducted by Hannibal et al.,[18] in which there were similar findings with aspirin use.

However, findings were null in a randomized controlled trial[19] and 5[21–24,26] of 8 cohort studies,[20–27] and inconsistent in 12 previous case-control studies.[7,18,28–37] Ten[7,20,22–24,28,30,31,34,35] studies found no association with aspirin use regardless of the duration or frequency of use, 4 studies found protective effects,[25,32,33,36] and 2 studies found harmful effects on ovarian cancer.[18,37] Our results of null associations with NA-NSAIDs use support findings in 5[7,23–25,30] of 9 previous studies.[7,20,23–25,27,30,32,37] Two studies[7,31] showed protective results of acetaminophen, not found in our study or 10 others.[18,20,21,23,24,26,29,32,33,37] These inconsistent findings may reflect inhibition of the progression, rather than the induction, of ovarian cancer; differences in the definition of regular analgesics use; incomplete or lack of information of dose, frequency, indication, and the list of medications queried; and different exposure assessments. Most analgesic use is sporadic, and recall of sporadic use may be less accurate. Furthermore, cumulative exposure could be assessed only approximately, due to incomplete information on dose and duration. Some studies evaluated dose in numbers of pills or tablets per week. However, different brands may not contain standardized amounts of the active ingredient. The list of NA-NSAIDs queried is heterogeneous and not comprehensive. This could lead to a misclassification of users and non-users, which would bias the results towards the null and attenuate the protective effect. The methodologic differences in assessing exposure remains an issue until validated operational definitions can be developed.

Given that most analgesic use may be episodic, it is conceivable that low-dose and continuous aspirin use for antithrombotic therapy may be more effective than sporadic use in reducing the synthesis of prostaglandins, further inhibiting chronic inflammation, cell proliferation, DNA synthesis, and suppressing immune response to neoplastic cells.[38] The biologic explanations for the protective association between aspirin or selective COX-2 inhibitors and ovarian cancer could be due to anti-carcinogenic effects via inhibition of COX-2 and COX-independent mechanisms. Aspirin and selective COX-2 inhibitors could also suppress carcinogenesis through pathways independent of prostaglandins. Increased COX-2 expression appears to be involved in the development of cancer by promoting cell division, inhibiting apoptosis, altering cell adhesion and stimulating angiogenesis. Some tumors expressing COX-2 are reported to exhibit more aggressive phenotype and poor clinical prognosis.[39] Recent preclinical data demonstrated that prostaglandin E2 is strongly associated with surrounding stroma in the tumor microenvironment in ovarian cancer and tumor progression.[40] COX-2 is expressed in epithelial ovarian cancer; the rate of expression ranges from 31% to 89% among various studies. Furthermore, aspirin and selective COX-2 inhibitors could act indirectly by inhibiting ovulation.[41] In our study, the protective effect of selective COX-2 inhibitors was only found in using celecoxib. Rofecoxib is a more potent COX-2 inhibitor than celecoxib, although Gorsch et al[42] found that celecoxib had unique and stronger anti-carcinogenic activity.

Our study is the second largest case-control study in ovarian cancer research, with a population-based design that contributes to generalizability of the results. The population had relatively high use of OTC and prescription analgesics, and provided detailed information on types, frequency, dose, duration and indications. The study collected data on a large number of potential confounders, which allowed for robust multivariate analyses. Complete dosage information allowed us to evaluate the risk by standardized daily doses and to conduct stratified analysis of selective COX-2 inhibitors.

Our study has certain limitations and biases that may have contributed to the observed results. First, we had no data on the characteristics of excluded and non-responding cases. Based on additional sensitivity analyses, the protective results for aspirin at low-standardized daily dose, continuously and recently, would be nullified if the responding controls had at least twice the exposure of non-responding controls, or if non-responding

cases had at least 1.7 times the exposure of the responding cases. Although responders and non-responders might not have the same analgesic exposure, it is unlikely that non-responders in either the case or control groups would have double or half of the exposure of the responders. Therefore, we believe the results are robust even with the non-responders. Second, cases may be more motivated to remember their analgesic use than controls. However, any tendency for the cases to better recall exposures would result in ORs greater than 1.0 rather than the protective effects observed here. Alternatively, controls might exaggerate their exposure relative to cases, if controls believed analgesics have a chemoprotective effect. This bias could over-estimate the protective effect. To reduce the impact of recall bias, a defined reference date was used for assessing exposures. The protective effects of recent aspirin use might be due to recall limitation since patients were more likely to recall the medications used recently. Third, measurement and misclassification errors are presumably present when relying on self-reported and single measurement of analgesics use without verification.[43] Regular use was defined to improve recall; however, this means that sporadic analgesic use could not be assessed. Including sporadic use in the non-user group, or evaluating aspirin/NA-NSAID use without excluding acetaminophen users, might attenuate the association and bias results toward the null. The results from additional analyses were similar when comparing non-regular users of any analgesics with 7 mutually exclusive groups (aspirin only, NA-NSAID only, aspirin plus NA-NSAID, acetaminophen only, aspirin plus acetaminophen, NA-NSAID plus acetaminophen, aspirin plus NA-NSAID plus acetaminophen) (eTable 4, http://links.lww.com). However, duration and dose-response effects could not be evaluated due to small sample sizes in the last 4 of these subgroups.

Fourth, we did not collect comprehensive information on medical co-morbidities related to cardiovascular disease, health-conscious behaviors, or factors related to adverse histories of aspirin use. Although the observed effect might be biased by the residual or unmeasured confounding, little change was found when two health-related behavior factors (i.e., how often having a routine gynecologic check-up or engaging in physical activities) were included in a separate analysis (for aspirin use, OR= 0.79 [95% CI= 0.62–0.99]; for NA-NSAIDs, 1.04 [0.82–1.32]). Fifth, while different NA-NSAIDs may have different effects on ovarian cancer, all were grouped into a single category. This limits our ability to evaluate the effect of individual NA-NSAIDs. Sixth, survival bias is possible. Since aspirin is used in the primary and secondary prevention of coronary heart disease, especially among high-risk women, it is possible that earlier mortality among aspirin users (e.g., from heart disease) precludes diagnosis of ovarian cancer and therefore produces a false impression of beneficial effect. Finally, the majority of women were white, limiting generalizability of the results to other ethnicities.

Our data suggest a lower risk of ovarian cancer among women who used aspirin at a low-standardized daily dose continuously, or who used selective COX-2 inhibitors. These results should be interpreted with caution due to inherent study limitations and biases. Future research on these associations should better characterize accompanying medical conditions, health and lifestyle behaviors, the dose, frequency, and duration of analgesic use, age of therapy initiation, genetic susceptibility, and the overall risk-benefit balance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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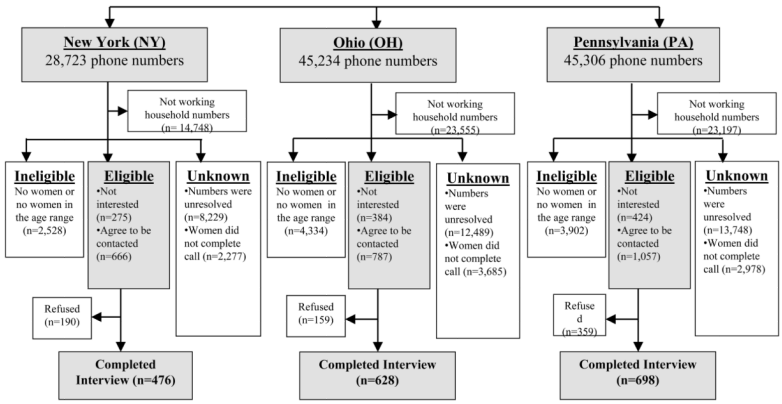

Figure 1.

Figure Selection Process for Community-Based Controls, Using Random-Digit Dialing. Response rate for screening phase = 64%; response rate for interview phase = 72%.

Table 1

Characteristics of Ovarian Cancer Cases and Controls in the HOPE Study

	Case (n = 902) No. (%)[a]	Control (n = 1,802) No. (%)[a]	OR[b] (95% CI)
Age (years); mean (SD)	58.29 (12.8)	57.02 (12.4)	-
Race			
White[c]	856 (95)	1758 (97)	1.00
Black	35 (4)	29 (2)	2.23 (1.35–3.68)
Other	11 (1)	15 (1)	1.43 (0.65–3.14)
Education			
Not high school graduate[c]	83 (9)	82 (4)	1.00
High school graduate	303 (34)	535 (30)	0.56 (0.40–0.78)
Post-high school	251 (28)	553 (31)	0.45 (0.32–0.64)
College graduate or post-college	265 (29)	632 (35)	0.43 (0.30–0.60)
Contraceptive use[d]			
Never use[c]	120 (13)	121 (7)	1.00
Any hormonal	481 (53)	1168 (65)	0.41 (0.31–0.55)
Non-hormonal	297 (33)	508 (28)	0.58 (0.43–0.77)
Oral contraception use[d], years			
Never use[c]	367 (41)	531 (30)	1.00
<1–4	321 (35)	667 (37)	0.69 (0.56–0.85)
<5–9	142 (16)	331 (18)	0.61 (0.47–0.78)
>9	71 (8)	273 (15)	0.37 (0.27–0.51)
No. of full-term births[e](%)			
Never pregnant[c]	167 (19)	167 (9)	1.00
0	46 (5)	63 (4)	0.75 (0.49–1.17)
1	120 (13)	231 (13)	0.52 (0.38–0.71)
2	264 (29)	601 (33)	0.43 (0.33–0.56)
≥3	305 (34)	740 (41)	0.37 (0.29–0.48)
Ever breastfeeding			
Never pregnant[c]	167 (18)	167 (9)	1.00
Ever pregnant but never breastfeeding	432 (48)	747 (42)	0.56 (0.44–0.72)
Any breastfeeding	303 (34)	888 (49)	0.33 (0.26–0.43)
Postmenopausal hormone use[d]			
Never use[c]	603 (67)	1137 (63)	1.00
Estrogen only	155 (17)	304 (17)	0.87 (0.69–1.09)
Estrogen + Progesterone	118 (13)	307 (17)	0.67 (0.53–0.85)
History of tubal ligation[d]			
No[c]	666 (74)	1162 (65)	1.00
Yes	201 (22)	616 (34)	0.57 (0.47–0.68)

	Case (n = 902) No. (%)[a]	Control (n = 1,802) No. (%)[a]	OR[b] (95% CI)
BMI (kg/m^2)[d]			
< 25[c]	300 (33)	670 (37)	1.00
25–29	267 (30)	528 (29)	1.12 (0.91–1.37)
≥30	334 (37)	603 (34)	1.25 (1.03–1.51)
Self-reported comorbidities[f]			
Arthritis	335 (37)	825 (46)	0.63 (0.51–0.73)
Hypertension	329 (37)	662 (37)	0.90 (0.76–1.09)
Diabetes	86 (10)	217 (12)	0.74 (0.57–0.96)
Family history of breast and ovarian cancers in first-degree relatives[g]			
No known family history[c]	715 (79)	1491 (83)	1.00
Breast cancer only	147 (16)	255 (14)	1.16 (0.93–1.45)
Ovarian cancer only	32 (4)	44 (2)	1.49 (0.93–2.37)
Breast and ovarian cancer	6 (1)	10 (1)	1.24 (0.45–3.46)
Annual household income			
< $20,000[c]	137 (15)	245 (14)	1.00
$20,000 $34,999	166 (19)	307 (17)	0.99 (0.74–1.31)
$35,000 $69,999	304 (34)	615 (35)	0.96 (0.74–1.24)
≥$70,000	201 (23)	436 (25)	0.87 (0.66–1.16)
Refused	75 (9)	151 (9)	0.96 (0.68–1.37)
NSAIDs[h] regular use[i]			
Non-users [c,j]	456 (51)	850 (47)	1.00
Aspirin only	169 (19)	360 (20)	0.79 (0.63–0.98)
NA-NSAIDs only	167 (18)	336 (19)	0.91 (0.73–1.13)
Aspirin plus NA-NSAIDs	110 (12)	256 (14)	0.74 (0.57–0.95)
Acetaminophen regular use[i]			
Non-users [c,k]	738 (82)	1447 (80)	1.00
Acetaminophen	164 (18)	355 (20)	0.90 (0.73–1.11)

[a] Except for age

[b]: Except for age, all the ORs were adjusted by age (continuous), region of residence, interview calendar year in the logistic regression.

[c] Reference category.

[d] Data were not summed to total due to the missing or unknown values.

[e] Number of full-term births, including both live and stillbirths; full-term is >6 months; twins and other multiples count as 1.

[f] Reference category is no arthritis, no hypertension, and no diabetes; respectively

[g] first-degree relatives including natural father and mother and blood-related brothers, sisters, sons and daughters.

[h] NSAID: includes aspirin or all other reported NA-NSAIDS.

[i] Regular use defined as ≥ 2 tablets/week for ≥ 6 months.

[j] Non-user: women who indicated that they didn't use aspirin or NA-NSAID (but might or might not have used acetaminophen) ≥ 2 tablets/week for ≥ 6 months ("minimal level").

[k] Non-user: women who indicated that they didn't used acetaminophen (but might or might not have used aspirin or NA-NSAID) ≥ 2 tablets/week for ≥ 6 months ("minimal level").

Table 2

Regular Use of Aspirin or NA-NSAIDs and Risk of Ovarian Cancer in the HOPE study

	Aspirin only			NA-NSAID only			Aspirin plus NA-NSAID		
	No. Cases	**No. Controls**	**OR (95% CI)[a]**	**No. Cases**	**No. Controls**	**OR (95% CI)[a]**	**No. Cases**	**No. Controls**	**OR (95% CI)[a]**
Nonusers [b]	456	850	1.00	456	850	1.00	456	850	1.00
Regular users [c]	169	360	0.81 (0.63–1.03)	167	336	1.06 (0.83–1.36)	110	256	0.95 (0.70–1.27)
Types of users [d]									
Continuous	121	283	0.71 (0.54–0.94)	96	199	1.10 (0.78–1.55)	93	211	0.99 (0.72–1.36)
Current	6	17	0.50 (0.19–1.32)	11	31	0.93 (0.64–1.37)	4	12	0.76 (0.23–2.57)
Past	42	60	1.34 (0.86–2.10)	60	106	1.19 (0.77–1.84)	13	33	0.76 (0.37–1.55)
Standardized-daily dose[e]									
Low	92	227	0.72 (0.53–0.97)	102	189	1.12 (0.83–1.51)	69	163	0.88 (0.62–1.24)
Moderate	46	81	0.84 (0.55–1.28)	42	97	0.96 (0.62–1.47)	26	57	1.21 (0.72–2.05)
High	31	52	1.08 (0.66–1.79)	23	50	1.01 (0.58–1.78)	15	36	0.90 (0.46–1.75)
Age at first use (years)									
< 45	50	75	1.32 (0.73–1.61)	77	162	1.04 (0.74–1.46)	62	79	1.10 (0.77–1.59)
≥45	119	285	0.66 (0.50–0.88)	90	174	1.08 (0.78–1.49)	48	177	0.79 (0.53–1.17)
Age at last use (years)									
< 55	48	90	1.08 (0.73–1.61)	91	200	1.04 (0.76–1.42)	40	79	1.12 (0.73–1.75)
≥55	121	270	0.70 (0.53–0.93)	76	136	1.10 (0.77–1.56)	70	177	0.85 (0.59–1.21)

[a]The ORs were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.

[b]Non-user: Women who indicated that they did not use aspirin or NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months (“minimal level”). Reference category.

[c]Regular user: women who indicated that they had used aspirin/NA-NSAIDs/aspirin plus NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months

[d]Duration of use was defined by three indicators: (1) continuous (had used for at least 1 year and until or beyond the reference date); (2) current (used only less than a year and used on the reference date); (3) past users (discontinued use at least 1 year before the reference date).

[e]To examine dose-response effects, the average daily dose was converted to a standardized daily dose by dividing by 325 mg for aspirin and minimal effective analgesic doses per day for other agents. Dosages were categorized into three clinically relevant categories: low-dose (≤ 0.5 standardized daily dose), moderate-dose (0.5–1 standardized daily dose) and high-dose (> 1 standardized daily dose).

Table 3

Regular use of Aspirin by Self-Reported Indications and Risk of Ovarian Cancer in the HOPE study

	No. Cases	No. Controls	OR (95% CI)[a]
Nonusers [b]	623	1186	1.00
Regular users[c] by indications[d]			
Prevention for CVD	159	392	0.72 (0.57–0.97)
Arthritis/bursitis, rheumatism	44	93	0.80 (0.53–1.21)
Headache	51	94	1.04 (0.71–1.52)
Other pain or injuries	50	75	1.27 (0.85–1.90)

[a] ORs and p-values were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.

[b] Non-user: women who indicated that they had not used aspirin ≥ 2 tablets/week for ≥ 6 months (“minimal level”). Reference category.

[c] Regular user: women who indicated that they had used aspirin ≥ 2 tablets/week for ≥ 6 months

[d] If patients used aspirin for different major indications before the reference date, each episode was counted separately

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Table 4

Regular Use of Non-Selective or Selective NA-NSAIDand Risk of Ovarian Cancer among NA-NSAID Only Users in the HOPE Study

	No. Cases	No. Controls	OR (95% CI)[a]
Nonusers [b]	456	850	1.00
Non-selective NA-NSAIDs [c] users	139	261	1.00 (0.78–1.30)
Selective COX-2 NA-NSAIDs [c] users	28	75	0.60 (0.39–0.94)

[a] ORs and p-values were adjusted by age at reference year, interview year, region of residence, race, education, breastfeeding, numbers of full-term births, duration of oral contraception use (years), body mass index, postmenopausal hormone use, arthritis, diabetes, and prior tubal ligation.

[b] Non-user: women who indicated that they had not used aspirin or NA-NSAIDs ≥ 2 tablets/week for ≥ 6 months (“minimal level”). Reference category.

[c] selective COX-2 NA-NSAIDs users include rofecoxib, celecoxib and valdecoxib, and the rest of NA-NSAIDs were included in non-selective NA-NSAIDs based on the most recent record