

MEDICATION USE AND RISK OF OVARIAN CARCINOMA: A PROSPECTIVE STUDY

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Inflammation and gonadotropins are hypothesized to influence ovarian carcinogenesis. In a prospective study, we evaluated ovarian cancer risk associated with self-reported use of medications that influence inflammation or gonadotropin levels. The Breast Cancer Detection Demonstration Project Follow-Up Study enrolled 61,431 women in 1979 and used telephone interviews and 3 mailed questionnaires through 1998 to update risk factor information and identify incident ovarian cancers. The 1992–95 questionnaire ascertained medication use, including duration and frequency of use for aspirin, acetaminophen, other nonsteroidal anti-inflammatory drugs (NSAIDs), tranquilizers and histamine-receptor antagonists. A Poisson regression analysis generated rate ratios (RRs) and 95% confidence intervals (CIs) for the 31,364 women who were at risk of ovarian cancer and responded to the questionnaire that queried regular medication use. One hundred sixteen women developed ovarian cancer during follow-up. None of the anti-inflammatory medications was associated with ovarian cancer, but the RR for more than 1 aspirin per day for 1 year or longer was 0.56 (95% CI 0.20–1.5) and the RR for more than 5 years of regular “other NSAID” use was 2.0 (95% CI 0.95–4.2). Regular tranquilizer use was not associated with ovarian cancer, but histamine-receptor antagonists used regularly for more than 5 years (RR = 3.6, 95% CI 1.4–9.1) or more than once daily (RR = 3.1, 95% CI 1.5–6.5) appeared to increase risk. In our study, neither anti-inflammatory medications nor anti-psychotic medications were associated with ovarian cancer. Potential associations with histamine-receptor antagonists may warrant further study.

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Ovarian cancer, the most lethal gynecologic tumor, has a poorly understood etiology and natural history.¹ No effective screening modalities exist,² and genetic predisposition appears to account for a small percentage of all ovarian cancers.³ Identification of modifiable risk factors could favorably influence cancer prevention, but only multiparity, long-term use of oral contraceptives and certain gynecologic surgeries are consistently associated with reduced risks of ovarian cancer in epidemiologic studies.⁴

Some reports identified acetaminophen (Tylenol) and anti-inflammatory medications as potential chemopreventive agents. In case-control^{5–7} and cohort^{8,9} studies, variable aspects of acetaminophen, aspirin or other nonsteroidal anti-inflammatory drug (NSAID) use were inversely associated with ovarian cancer. However, neither duration of use nor frequency of use was consistently associated with decreased risks, and other studies reported no association with medication use.^{10–12} Inflammation itself may play a role in ovarian carcinogenesis,¹³ and very high doses of NSAIDs inhibit *in vitro* ovarian cancer cell line growth.¹⁴ Although not an anti-inflammatory medication, acetaminophen may act through gonadotropin levels,⁵ which also influence ovarian cancer risk.¹⁵ Additional data would help to resolve the inconsistencies in the epidemiologic data.

Reports also link other medications to ovarian cancer. U.S. case-control studies showed positive associations with anti-psychotic medications,^{16,17} but other studies have been null.^{18,19} Anti-psychotic medications such as tranquilizers may also influence gonadotropin secretion, and cimetidine, a histamine-receptor antagonist (H₂ blocker) could influence ovarian carcinogenesis

through its effects on estrogen metabolism.²⁰ Using data from the Breast Cancer Detection Demonstration Project, a prospective cohort, we evaluated the potential association between these medications and ovarian cancer risk.

MATERIAL AND METHODS

Study participants were selected from the Breast Cancer Detection Demonstration Project (BCDDP), a mammography feasibility program conducted at 29 U.S. screening centers between 1973 and 1980 by the American Cancer Society and the U.S. National Cancer Institute (NCI).²¹ In 1979, NCI initiated a follow-up study of 64,182 of the original 283,222 participants: (i) all 4,275 women diagnosed with breast cancer during the BCDDP; (ii) all 25,114 women who underwent breast surgery during the BCDDP but had no evidence of malignant disease; (iii) all 9,628 women who were recommended by the BCDDP for surgical consultation but for whom neither biopsy nor aspiration was performed; (iv) 25,165 women sampled from participants who had neither surgery nor recommendation for surgical consultation during screening.²² The NCI Institutional Review Board approved the study. All participants provided informed consent.

The BCDDP Follow-Up Study consisted of 4 phases. Phase 1 (1979–86) involved a baseline telephone interview (completed by 61,431 women, or 96%) and up to 6 (usually 4) annual telephone follow-up interviews through 1986. Phases 2, 3 and 4 each used single, self-administered, mailed questionnaires (sent 1987–89, 1993–95 and 1995–98, respectively) sent to all respondents who were not known to be deceased at the end of the previous phase. Nonrespondents to mailed questionnaires were interviewed by telephone, if possible.

Exposure assessment

The phase 3 questionnaire asked about regular use (defined as “at least once a week for 1 year”) of aspirin (“Aspirin or other drugs containing aspirin products, such as Bufferin or Anacin”), Tylenol, other anti-inflammatories [“Pain relievers or anti-inflammation drugs that contain neither aspirin nor Tylenol, such as ibuprofen (Motrin, Advil, Nuprin); naproxen (Naprosyn); piroxicam (Feldene); indomethacin (Indocin); sulindac (Clinoril)”), tranquilizers (“Tranquilizers such as Valium or Librium”) and H₂

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blockers ["Cimetidine (Tagamet) or ranitidine (Zantac)"]. Participants reported their age at first regular use, the number of pills per day or per week and the number of years they took the medications regularly.

Each phase included questions about current menopausal status, gynecologic surgeries (including hysterectomy, partial or complete unilateral or bilateral oophorectomy and dates for each reported surgery) and other risk factors. Interviews during the screening phase (1973–80) collected demographic data (*e.g.*, education level and ethnicity) and measured height and weight, which were updated in phase 2.

Analytic data set

The analysis was restricted to women who completed the phase 3 questionnaire, the only phase in which medication data were collected. We considered these women at risk from the date they completed the previous (*i.e.*, phase 2) questionnaire until the end of the study (see Analysis below).

We excluded the 10,876 women who did not complete the phase 3 questionnaire because of death ($n = 4,601$) or nonresponse ($n = 6,275$; most because they were too ill). We excluded 14,049 women who reported a bilateral oophorectomy before the date of the phase 2 questionnaire, 226 women diagnosed with ovarian cancer before the date of the phase 2 questionnaire, 4,913 women diagnosed with breast cancer before they completed the phase 2 questionnaire and 3 women who developed nonepithelial ovarian cancers (see Case ascertainment below). Analysis therefore included 31,364 participants who completed the phase 3 questionnaire. Of these 31,364 women, 30,376 (97%) completed the phase 2 questionnaire, 273 (1%) refused to answer the phase 2 questionnaire and 715 (2%) were too ill or could not be contacted before the end of the phase 2 questionnaire period; 28,455 (91%) completed the phase 4 questionnaire, 1,113 (4%) had died, 612 (2%) refused and 1,184 (4%) were too ill or could not be contacted before the end of the phase 4 questionnaire period.

Case ascertainment

Lifetime history of ovarian cancer was first ascertained in phase 2. Phase 3 and 4 questionnaires ascertained ovarian cancer diagnoses since the previous interview. We verified reported ovarian cancer diagnoses through medical record review. Trained personnel completed standardized abstract forms when records were retrieved, and 2 of us (JVL Jr. and MES) re-reviewed those original records. We linked the cohort to state cancer registries to identify additional cancer diagnoses and to the National Death Index (NDI) to identify deaths during follow-up (with death certificate retrieval for study deaths).²³

The final analytic cohort included 116 women who developed ovarian cancer, verified by medical records ($n = 60$) or registry data ($n = 36$), or identified from death certificates ($n = 11$) or self-report ($n = 9$). Medical records were unavailable for self-reported cases because they were not received by the end of the study period. They were also unavailable due to nonresponse of physicians or hospitals or because participants did not grant permission for record retrieval. We further classified tumors according to histology data from records or cancer registries: serous (38), endometrioid (21), mucinous (4), clear cell (3), other unclassified (29) or unavailable (21; for cancers identified via death certificates or because medical records were not available).

Thirty-six additional women reported ovarian cancer, but medical record review revealed another primary tumor ($n = 30$), metastatic tumors ($n = 1$), benign lesions or tumors of low malignant potential ($n = 2$) or nonepithelial tumors ($n = 3$ sex-cord stromal tumors). We excluded the 3 women with nonepithelial tumors but included the other 33 women who were censored as noncases as described below. We defined diagnosis date hierarchically from medical records, state cancer registry data or self-report. When only death certificate information was available, we used time since cancer onset to estimate diagnosis date or used the

date of death. Thirty-five of the women who developed ovarian cancer were diagnosed in 1992 or earlier, 31 women were diagnosed in 1993 or 1994, and 50 women were diagnosed in 1995 or later.

Analysis

To maximize the observation period, follow-up began at the phase 2 questionnaire date. For the 988 women who did not complete this questionnaire (and all went on to complete the phase 3 questionnaire), we assigned start date to be the mean start date for all women who did complete the phase 2 questionnaire. Person-years accrued until the earliest of the following dates: ovarian cancer diagnosis, bilateral (or 2nd) oophorectomy, death from any cause, phase 4 questionnaire completion or end of study date. For women without a phase 4 questionnaire but with whom we had some contact (*e.g.*, telephone or notice of refusal) during phase 4, the end of study date was that contact date. We assumed all other women without a phase 4 questionnaire whom we could not contact and whom our NDI search did not identify as deceased were still alive. We assigned their study end dates by calculating the mean intervals between questionnaire completion dates for phases 2 through 4 (for all women who completed those questionnaires) and adding those mean intervals to the date of last completed questionnaire for these nonrespondents. To avoid biased endpoint ascertainment among these participants, deaths from NDI and cancer diagnoses from state cancer registries were included only if they occurred before the study end date.²³

Using Poisson regression in EPICURE software,²⁴ we modeled the rate of developing ovarian cancer during follow-up and generated rate ratios (RRs) with 95% confidence intervals (CIs) for categorized variables using standard likelihood ratio methods.²⁵ We assessed statistical significance of trends via score tests.

We based the time-dependent medication variables on the reported ages at which exposure occurred. To calculate person-years for each woman, we updated time-dependent medication and age covariates at 1-year intervals, but we used 5-year intervals to adjust for attained age in Poisson models. Women whose first use of medication occurred during follow-up contributed person-time to both the nonexposed and exposed groups during follow-up. Because we did not collect updated medication data in the phase 4 questionnaire, we assumed that exposure status remained constant from the date of the phase 3 questionnaire until the end of the study. Medication use was calculated to 1 year prior to attained (or current) age to eliminate exposure that was most likely not causal.

We calculated body mass index (kg/m^2 BMI) from measurements obtained during the screening visit closest in time to the baseline follow-up interview. To assess potential confounding, we assessed associations between exposures and ovarian cancer and then evaluated parameter estimate changes in models before and after stratification by (*i.e.*, adjustment for) potential confounding variables.

Ovarian cancer was associated with non-Caucasian race/ethnicity, hysterectomy, age at menopause, menopausal estrogen use, BMI and all variables representing parity and oral contraceptive use. Medication use was associated with older age, white race/ethnicity, later ages at first birth, being postmenopausal, older ages at menopause, long-term and heavy smoking, oral contraceptive use and menopausal estrogen use. Religion (Christian, Jewish or other), education, marital status, age at menarche, parity and family history of ovarian cancer were not associated with medication use and therefore did not confound the medication data. Models that adjusted only for attained age (<60, 60–64, 65–69, 70–74 or ≥ 75 years) produced essentially identical results compared to models also adjusted for race (white vs. nonwhite), oral contraceptive use (never, ever, unknown), family history of ovarian cancer (any, none or missing/unknown family history), menopause type (natural, surgical, or unknown type), and duration of menopausal estrogen use (none, ≤ 5 years, 6–10 years, >10 years or unknown) but we present fully adjusted models.

RESULTS

The 31,364 participants accrued 266,785 person-years of follow-up, with a mean follow-up of 8.5 years (minimum 1 month; maximum 10.9 years). The mean age at the start of follow-up was 61.3 years (range 40.3–91.4).

Demographic factors

Table I displays the person-years associated with individual medication use according to demographic and other factors. Medication use was generally associated with older age, higher BMI and longer duration of menopausal estrogen use.

Aspirin, acetaminophen and other nonsteroidal anti-inflammatory medications

The RR for regular aspirin use was 0.86 (95% CI 0.52–1.4; Table II). The RRs for more than 5 years of regular aspirin use (0.70, 95% CI 0.32–1.53) and for more than 1 aspirin per day for one year or longer (0.56, 95% CI 0.20–1.5) were below 1.0, but neither association was statistically significant. Of the 7 women who developed ovarian cancer and had regularly used aspirin for more than 5 years, 6 reported using 1 or fewer aspirin per day

(RR = 1.2, 95% CI 0.50–2.7), 1 reported using more than 1 aspirin per day (RR = 0.28, 95% CI 0.04–2.0).

Acetaminophen use was less common than aspirin use, but none of the RRs for regular use, duration of use or frequency of use materially differed from 1.0. Regular use of other NSAIDs was not associated with ovarian cancer. One-half (8 of 16) of the ovarian cancer patients who reported regular NSAID use did not know the duration of their NSAID use. The RR for more than 5 years of regular other NSAID use suggested an association with ovarian cancer (OR = 2.0, 95% CI 0.95–4.2), but the RRs for increasing frequency of use did not (≤ 1 pill per day, RR = 0.71, 95% CI 0.26–1.9; > 1 pill per day, RR = 1.3, 95% CI 0.68–2.6).

Tranquilizers and H₂ blockers

Reported regular tranquilizer use was low, and there was no evidence that increasing duration of use (RR = 1.3, 95% CI 0.49–3.7) or frequency of use (RR = 1.1, 95% CI 0.35–3.6) was associated with ovarian cancer (Table III). The RR for regular use of H₂ blockers was 1.7 (95% CI 0.92–3.1). Both increasing duration (> 5 years, RR = 3.6, 95% CI 1.4–9.1) and increasing frequency (≥ 1 pill per day, RR = 3.1, 95% CI 1.5–6.5) were associated with ovarian cancer.

TABLE I—PERCENTAGE OF PERSON-YEARS OF MEDICATION USE BY SELECTED FACTORS

	Aspirin		Tylenol		Other NSAIDs		H ₂ blockers		Tranquilizers		Total ¹
	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	
Age (years)											
<55	78	14	84	9	87	7	95	4	91	7	1,518
55–59	76	16	82	10	82	11	94	4	91	7	20,602
60–64	73	18	81	11	79	14	92	5	91	7	49,025
65–69	71	19	81	11	78	15	92	6	90	8	62,049
70–75	69	20	80	10	77	15	92	6	90	8	57,414
75–79	66	22	78	11	75	15	90	7	89	8	39,314
≥ 80	64	21	76	12	75	12	87	7	89	6	36,863
Ethnicity											
White	69	20	80	11	77	14	91	6	90	7	235,967
Other	76	13	78	11	80	10	91	5	91	6	30,817
Menopause type											
Natural	71	19	81	10	80	13	92	5	91	6	190,902
Surgical	66	22	76	13	73	17	88	9	87	10	70,768
Unknown	69	19	76	12	74	16	91	7	90	8	5,115
Age at menopause											
<45 years	66	22	76	13	74	17	88	8	87	10	67,657
45–49 years	70	19	81	10	78	13	91	6	91	7	72,772
50–53 years	71	19	81	9	79	13	93	5	91	7	87,257
≥ 54 years	71	18	82	9	79	14	93	4	91	6	38,732
Unknown ²	77	17	79	11	88	10	98	2	100	0	367
Oral contraceptives (years)											
None ²	69	19	80	11	78	13	91	6	90	7	181,174
≤ 2 yrs	71	20	80	11	77	15	92	6	89	9	85,372
> 2 yrs	59	20	71	15	65	13	87	10	89	0	239
Parity											
0	70	19	80	11	80	12	91	6	89	8	32,414
1	70	19	79	11	77	14	90	7	88	8	29,801
2	70	19	80	11	77	14	91	6	89	8	78,712
≥ 3	69	20	80	11	77	14	91	6	91	6	125,858
BMI (kg/m ²)											
≤ 21.4	74	17	84	9	83	11	94	4	90	8	69,085
21.5–23.4	70	19	81	10	79	13	92	5	90	8	69,720
23.5–26.6	68	20	79	11	76	14	90	7	90	7	65,822
> 26.6	66	21	75	13	71	18	89	8	90	7	62,158
Estrogen use (years)											
None	72	17	81	10	82	10	93	4	93	5	93,161
< 4	70	20	80	11	78	14	91	6	89	8	66,011
4–9	70	20	81	10	78	15	91	7	90	8	33,527
≥ 10	65	25	78	13	73	19	89	8	86	11	37,433
Unknown	67	20	76	12	72	16	89	7	87	9	36,652

NSAIDs, nonsteroidal anti-inflammatory drugs; BMI, body mass index.—¹For aspirin, unknown use accounted for 28,781 person-years. For acetaminophen, unknown use accounted for 25,286 person-years. For other NSAIDs, unknown use accounted for 22,817 person-years. For H₂ blockers, unknown use accounted for 7,518 person-years. For tranquilizers, unknown use accounted for 7,479 person-years. Percents may not sum to 100 because of rounding. Row totals include person-years for which individual regular medication use was unknown.—²Set to 57 years; see Material and Methods.

TABLE II – ANTI-INFLAMMATORY MEDICATION USE AND OVARIAN CANCER IN THE BCDDP FOLLOW-UP STUDY

	No regular use	Any regular use	Duration (years)		Frequency (per day)	
			≤5	>5	≤1	>1
Aspirin						
Person-years	185,787	52,217	18,837	23,834	29,713	16,396
No. of cancers	82	20	9	7	14	4
RR ¹	1.0	0.86	1.1	0.70	1.1	0.56
95% CI	(Ref)	(0.52–1.4)	(0.53–2.2)	(0.32–1.53)	(0.60–1.9)	(0.20–1.5)
Acetaminophen						
Person-years	212,970	28,529	10,427	10,855	13,415	10,332
No. of cancers	93	13	5	5	5	5
RR ¹	1.0	1.0	1.0	1.2	0.83	1.1
95% CI	(Ref)	(0.56–1.8)	(0.41–2.5)	(0.50–3.1)	(0.34–2.1)	(0.45–2.7)
Other NSAIDs						
Person-years	206,871	37,097	2,812	9,599	13,713	18,986
No. of cancers	90	16	0	8	4	10
RR ¹	1.0	1.0	N/A	2.0	0.71	1.3
95% CI	(Ref)	(0.60–1.8)		(0.95–4.2)	(0.26–1.9)	(0.68–2.6)

RR, relative risk; 95% CI, 95% confidence interval; NSAID, nonsteroidal anti-inflammatory drugs.¹ Adjusted for attained age, ethnicity, oral contraceptives, family history of ovarian cancer, menopausal status and duration of estrogen use. For aspirin, unknown use, unknown duration of use and unknown frequency of use accounted for 28,781 person-years and 14 ovarian cancers, 9,546 person-years and 4 ovarian cancers and 6,108 person-years and 2 ovarian cancers, respectively. For acetaminophen, unknown use, unknown duration of use and unknown frequency of use accounted for 25,286 person-years and 10 ovarian cancers, 7,247 person-years and 3 ovarian cancers and 4,779 person-years and 3 ovarian cancers, respectively. For other NSAIDs, unknown use, unknown duration of use and unknown frequency of use accounted for 22,817 person-years and 10 ovarian cancers, 24,686 person-years and 8 ovarian cancers and 4,398 person-years and 2 ovarian cancers, respectively.

TABLE III – ANTI-PSYCHOTIC AND H₂ BLOCKER MEDICATION USE AND OVARIAN CANCER IN THE BCDDP FOLLOW-UP STUDY

	No use	Any use	Duration (years)		Frequency (per day)	
			≤5	>5	≤1	>1
Tranquilizers						
Person-years	239,754	18,904	10,387	6,515	10,564	6,265
No. of cancers	101	10	5	4	5	3
RR ¹	1.0	1.2	1.2	1.3	1.1	1.1
95% CI	(Ref)	(0.60–2.2)	(0.47–2.9)	(0.49–3.7)	(0.45–2.7)	(0.35–3.6)
H₂ blockers						
Person-years	243,272	15,494	10,207	3,614	7,330	6,571
No. of cancers	100	12	6	5	4	8
RR	1.0	1.7	1.4	3.6	1.2	3.1
95% CI	(Ref)	(0.92–3.1)	(0.60–3.2)	(1.4–9.1)	(0.42–3.2)	(1.5–6.5)

RR, relative risk; 95% CI, 95% confidence interval.¹ Adjusted for attained age, ethnicity, oral contraceptives, family history of ovarian cancer, menopausal status and duration of estrogen use. For tranquilizers, unknown use, unknown duration of use and unknown frequency of use accounted for 7,479 person-years and 5 ovarian cancers, 2,650 person-years and 1 ovarian cancer and 2,723 person-years and 2 ovarian cancers, respectively. For H₂ blockers, unknown use, unknown duration of use and unknown frequency of use accounted for 7,518 person-years and 4 ovarian cancers, 2,175 person-years and 1 ovarian cancer and 1,915 person-years, respectively.

Other analyses

Limiting the analysis to the women who developed ovarian cancer after reporting their medication use (*i.e.*, excluding the 56 women who reported their ovarian cancer diagnosis and medication use on the 1992–95 questionnaire) produced similar, but less precise, results. Similar associations for regular medication use emerged after restricting the analysis to the mortality cases. The results were unchanged after we excluded the 988 women for whom we had to assign the date on which follow-up began because they did not complete the phase 2 questionnaire. We repeated the analyses after increasing the time lag between exposure and diagnosis (or attained age) from 1 year to 2 years, but results stayed the same (data not shown).

The questionnaire also queried regular use of diuretics (“diuretics or water pills”). After aspirin use, diuretic use was the next most commonly reported medication. Fifteen women who had regularly used diuretics developed ovarian cancer, but use was not associated with ovarian cancer (data not shown).

DISCUSSION

Regular use of acetaminophen, aspirin and other anti-inflammatory medications, which have been linked with decreased

ovarian cancer risk in several other reports, was not associated with ovarian cancer in this study. Frequent regular aspirin use generated a suggestive inverse association, and more than 5 years of other NSAID use generated an elevated rate ratio, but there was no consistent pattern of reduced risks among women who regularly used acetaminophen or anti-inflammatory medications.

Epidemiologic studies initially suggested anti-inflammatory medications might decrease ovarian cancer risk, but recent publications provide more support for a null association. One cohort study of 76,821 women, in whom 333 invasive ovarian cancers developed between 1976 and 1996, used multiple definitions based on self-reported medication use but concluded neither aspirin nor NSAIDs were associated with ovarian cancer.⁸ Ever-use of ibuprofen or other nonaspirin anti-inflammatory medications was inversely associated with ovarian cancer (rate ratio = 0.60, 95% CI 0.38–0.95) and there was a pattern of nonsignificant decreasing rate ratios with increasing monthly frequency of NSAID use. A cohort study of 1,573 fatal ovarian cancers among 616,189 women between 1982 and 1994 indicated a nonsignificant reduced risk (RR = 0.55, 95% CI 0.27–1.09) associated with daily acetaminophen use.⁹ Another cohort study of Danish women who filled acetaminophen prescriptions between 1989 and 1995 found no

evidence that ovarian cancer incidence rates were decreased compared to the expected incidence rates in the population.¹⁰

Case-control studies tend to show reduced ORs associated with some aspects of anti-inflammatory use, but the specific exposures for which ORs decline differ. Using 563 cases and 523 controls, Cramer *et al.*⁵ reported a null association with ever-use of ibuprofen (OR = 1.03) but inverse associations with ever-use of aspirin (OR = 0.75) and acetaminophen (OR = 0.52) with further decreased ORs for more frequent and longer-duration acetaminophen use. In a multicenter case-control study that included 780 ovarian cancer cases, 2,053 cancer controls and 2,570 noncancer controls, aspirin use and NSAID use for 5 or more years were inversely associated with ovarian cancer, but only the ORs based on cancer controls were statistically significant.⁷ Another study of 547 ovarian cancer cases and 1,094 controls concluded that aspirin use was not associated with risk, but regular, daily and 11 or more years of acetaminophen use decreased risk.⁶ A smaller case-control study of 68 ovarian cancers and 680 controls reported a nonsignificant OR of 0.60 (95% CI 0.26–1.38) for ever-use of aspirin and no associations with duration of use or time since last use.²⁶ An Italian hospital-based case-control study of 749 cases and 898 controls reported no association with aspirin use,¹² as did a United Kingdom General Practice Research Database study of 483 cases and 1,877 controls.¹¹ The persistent but inconsistent inverse associations that have surfaced in some of the epidemiologic studies may reflect true associations or spurious findings.

Definitions of regular acetaminophen, aspirin or anti-inflammatory use varied in previous studies, but whether those definitions alone account for the inconsistent epidemiologic data is not clear. Four studies^{5–7,12} defined regular use as weekly use for at least 6 months. Less than 15% of those study populations met that definition, but 3 of the 4 reported inverse associations.^{5–7} Inverse associations also appeared when exposure was based on a relatively strict definition (thrice or more weekly for at least 6 months)²⁶ or on recent use.⁹ We used a more conservative definition than most others—weekly use for at least 1 year—but roughly equivalent proportions of our participants reported regular use: of the BCDDP women who developed ovarian cancer, 12%, 17% and 15% regularly used acetaminophen, aspirin and other NSAIDs, respectively. Recent other null studies arose from a range of exposure definitions⁸ or from medication databases.^{10,11} Although focusing on regular use presumably captures the potentially relevant exposure(s), it has inevitably decreased the measured exposure prevalence—and thus the statistical power—of most questionnaire-based studies to date. The generalizability of exposure data will remain an issue until 1 operational definition emerges as the most appropriate measurement tool.

In contrast to the reported associations with anti-inflammatory medications, medications used to treat psychological conditions have been reported to increase ovarian cancer risk. A publication that combined 2 U.S. case-control studies reported elevated ORs for use of benzodiazepine tranquilizers and antidepressants, although both increases appeared limited to women whose first use occurred before age 50.¹⁶ A subsequent case-control study of 563 cases and 523 controls reported a significantly elevated OR for use of some psychotropic medications, such as dopamine reuptake inhibitors and gamma-amino butyric acid inhibitors, but not for serotonin reuptake inhibitors.¹⁷ A population-based Danish pharmacy linkage study of antidepressant medications showed no association with ovarian cancer.¹⁸ In a computerized pharmacy database with extensive exposure data to evaluate antidepressants, benzodiazepines and other “centrally acting medications” among 314 cases and 790 matched controls, increasing use of antidepressants, benzodiazepine and serotonin reuptake blockers, such as fluoxetine, were associated with reduced ORs.²⁷ An analysis of 47 ovarian cancers that developed in a cohort of 15,270 women indicated no association between psychotropic drug use at baseline (1985) and subsequent ovarian cancer through 1994.¹⁹ In our data, tranquilizer use was not associated with ovarian cancer.

We also assessed 2 other classes of medications. All associations with diuretics were null, but ovarian cancer was positively associated with H₂ blockers, with stronger associations among women who reported longer duration and more frequent use. H₂ blockers such as cimetidine (Tagamet) and ranitidine (Zantac) may inhibit experimental carcinogenesis²⁸ and have been linked to both increased and decreased risk of other hormonal cancers.²⁹ Our positive associations could simply be due to chance or might have emerged due to a reporting bias if women who already had symptoms of an undetected ovarian tumor used H₂ blockers in response to tumor-related gastrointestinal symptoms. To address this potential confounding by drug indication, we excluded exposures reported both 1 year and 2 years before diagnosis, but the results did not change.

Some factors limited our analytic data. Although the BCDDP study is relatively large and spans 20 years, these medication data were collected only in the 1992–95 mailed questionnaire. This restricted our analysis to the women who completed the 1992–95 questionnaire; just more than 100 ovarian cancers developed in this group. To increase the statistical power, we started follow-up at the previous (1987–89) questionnaire, which included women who reported their medication use after they had been diagnosed with ovarian cancer (*i.e.*, women who reported their ovarian cancer and their medication use on the 1992–95 questionnaire). We saw nearly identical associations after restricting the analyses to women who reported their medication use before they were diagnosed with ovarian cancer, but we cannot exclude the possibility of recall bias or potentially biased exposure ascertainment in a subset of women who developed ovarian cancer.

We relied on self-reported medication use. The questionnaire that queried regular medication use included names of commonly used medicines to facilitate recall, which is generally accurate for nonsteroidal anti-inflammatory medications.³⁰ Our questionnaire queried only “regular” use, which we defined as use for at least once a week for 1 year, and therefore we could not assess whether less consistent or periodic medication use was associated with ovarian cancer. We did not ascertain dose or inquire about the indications for use. Whether these 2 factors, or other unmeasured aspects of medication use, such as medications that combine aspirin and acetaminophen, are important for assessing medications and ovarian cancer is not known. Almost all women in this cohort reported their first regular medication use after menopause, and therefore we were not able to examine whether premenopausal use or use at younger ages might influence ovarian cancer. The lengthy period required for ovarian carcinogenesis raises the possibility that medication use well before diagnosis could influence tumor development, and future studies may wish to consider this prospect.

In conclusion, we saw no consistent evidence that acetaminophen, aspirin, other NSAIDs, H₂ blockers, tranquilizers or diuretics were associated with ovarian cancer. However, the suggestive results from other epidemiologic studies leave open the possibility that certain medications could modestly affect ovarian cancer risk.

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