Int. J. Cancer: 124, 1409–1415 (2009)

Markers of inflammation and risk of ovarian cancer in Los Angeles County

Anna H. Wu[1]*, Celeste L. Pearce[1], Chiu-Chen Tseng[1], Claire Templeman[2] and Malcolm C. Pike[1]

[1]*Department of Preventive Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA*
[2]*Department of Obstetric and Gynecology, University of Southern California, Keck School of Medicine, Los Angeles, CA*

Factors that increase inflammation have been suggested to influence the development of ovarian cancer, but these factors have not been well studied. To further investigate this question, we studied the role of talc use, history of endometrioisis and use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of ovarian cancer in a population-based case-control study in Los Angeles County involving 609 women with newly diagnosed epithelial ovarian cancer and 688 population-based control women. Risk of ovarian cancer increased significantly with increasing frequency and duration of talc use; compared to never users risk was highest among long-duration (20+ years), frequent (at least daily) talc users (adjusted relative risk (RR) = 2.08, 95% confidence interval (CI) = 1.34–3.23). A history of physician-diagnosed endometriosis was statistically significantly associated with risk (RR = 1.66, 95% CI = 1.01–2.75). Women who were talc users and had a history of endometriosis showed a 3-fold increased risk (RR = 3.12, 95% CI = 1.36–7.22). Contrary to the hypothesis that risk of ovarian cancer may be reduced by use of NSAIDs; risk increased with increasing frequency (per 7 times/week, RR = 1.27, 95% CI = 1.14–1.43) and years of NSAID use (per 5 years of use, RR = 1.25, 95% CI = 1.10–1.42); this was consistent across types of NSAIDs. We conclude that risk of ovarian cancer is significantly associated with talc use and with a history of endometriosis, as has been found in previous studies. The NSAID finding was unexpected and suggests that factors associated with inflammation are associated with ovarian cancer risk. This result needs confirmation with careful attention to the reasons for NSAID use.

Key words: talc; endometriosis; non-steroidal anti-inflammatory drugs; ovarian cancer

In 1999, Ness and Cottreau proposed that chronic inflammation may lead to the development of epithelial ovarian cancer.[1] They hypothesized that factors including talc exposure, endometriosis and pelvic inflammatory disease (PID) may increase risk by a common pathway, increasing local inflammation of the "ovarian epithelium." They also suggested that studying the effect of non-steroidal anti-inflammatory drugs (NSAIDs) may offer additional opportunities to evaluate the inflammation hypothesis. In a 2008 paper, Merritt *et al.*[2] studied the role of inflammation, based on histories of talc use, PID, endometriosis and use of NSAIDs in the same study. They concluded that chronic inflammation is unlikely to play an important role because risk of ovarian cancer was modestly increased in association with talc use and history of endometriosis and was unrelated to use of NSAIDs but they restricted attention to medication use in the 5 years prior to diagnosis of ovarian cancer, rather than long-term use.[2] No support for the use of NSAIDs was found in a recent study conducted in Seattle, Washington which collected information on lifetime medication use. These investigators found increased risk of ovarian cancer in association with use of acetaminophen, aspirin and other NSAIDs, particularly among long (10+ years) term users.[3] We have conducted a population-based case-control study of ovarian cancer in Los Angeles County to further investigate the role of inflammation in the risk of ovarian cancer. We focused our attention on risk in relation to lifetime use of talc, NSAIDs and history of various gynecological conditions. We are particularly interested in risk patterns associated with long duration of NSAID use. We report our results herein.

Material and methods

Study design

This was a population-based case-control study of ovarian cancer. Eligible patients were English speaking residents of Los Angeles County between the ages of 18 and 74 inclusive who had histologically confirmed invasive or borderline (low malignant potential; LMP) ovarian cancers that were first diagnosed from 1998 to 2002. The cases were identified by the Cancer Surveillance Program (CSP), part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, covering all residents of Los Angeles County.

A total of 1,097 patients meeting the pathological case definition were identified by the CSP. Of these, 136 patients had died or were too ill to be interviewed by the time we contacted them, 109 patients had moved away from Los Angeles County and could not be interviewed in person or they could not be located and 151 patients declined to be interviewed. Interviews were conducted with 701 ovarian cancer patients of whom 15 were later identified who did not have ovarian cancer and they were excluded from all analyses. Of the 686 ovarian cancer patients interviewed, 77 had a previous cancer (excluding non-melanoma skin cancer) before their diagnosis of ovarian cancer and were excluded from this report because their previous cancer diagnosis and/or treatment may have influenced use of NSAIDs and other risk factors. This left 609 ovarian cancer cases for the present analysis, 81% were invasive tumors [22% localized stage (Stage 1 or 2), 59% advanced stage (Stage 3 or greater) and 19% were LMP tumors. The cell type distribution is as follows: 58% serous, 14% clear cell/endometrioid, 12% mucinous and 16% other category.

Controls were identified through a well-established neighborhood recruitment algorithm, which we have used successfully in previous studies of breast, endometrial and other cancers to investigate the role of hormonal and non-hormonal medications and other factors.[4] For this study, controls were women with at least one intact ovary, with no history of cancer, except possibly non-melanoma skin cancer, and individually matched with patients on race/ethnicity (non-Hispanic White, African-American, Hispanic, Asians) and date of birth (+/−5 years). Neighborhood controls were sought by one of our staff who physically canvassed the neighborhood of the case using a systematic algorithm based on the address of the case. If the first eligible matched control declined to participate, the second eligible matched control in the sequence was asked, and so on. Letters were left when no one was at home, and follow-up by mail, telephone and further visits to the neighborhood continued until either an eligible control agreed to be interviewed or 150 housing units had been screened. When we failed to identify an exact race/ethnicity matched control, we

Grant sponsor: California Cancer Research Program; Grant number: 2II0200. Grant sponsor: National Cancer Institute; Grant number: P01 CA 17054. Grant sponsor: National Cancer Institute's Division of Cancer Prevention and Control's Surveillance, Epidemiology, and End Results (SEER) Program; Grant number: N01CN25403.

***Correspondence to:** University of Southern California/Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, MC 9175, Los Angeles, CA 90089-9175, USA. Fax: +[(323) 865-0139].
E-mail: annawu@usc.edu

Received 18 July 2008; Accepted after revision 1 October 2008
DOI 10.1002/ijc.24091
Published online 21 October 2008 in Wiley InterScience (www.interscience.wiley.com).

Publication of the International Union Against Cancer

accepted a control subject who was matched on age. A total of 688 control women were successfully interviewed by the closing date of the study. The first eligible match was interviewed for 76% of the patients, and the second match for another 17% and the third or later match for 6% of the patients. On average, we contacted a median number of 19 housing units to interview a matched control subjects for those neighborhoods with no refusal, a median of 36 housing units for those neighborhoods with 1 refusal and 58 housing units when there were 2 or more refusals.

Study participants were interviewed using a comprehensive questionnaire that covered medical, gynecological, reproductive and lifestyle history. All but 15 participants were interviewed in-person; cases and their matched controls were interviewed by the same person in almost all instances. A reference date was defined as 2 years before the date of diagnosis of the case. This same reference date was used for each case's matched control subject. Calendars were used to chart major life events and reproductive and contraceptive histories. Specifically, participants were asked if they were ever told by a physician that they had certain gynecological conditions including PID, gonorrhea, endometriosis, ovarian cysts, or uterine fibroids before the reference date. If the response was yes to any of the conditions, participants were then asked the age at which they were first diagnosed with the condition and if they had ever been treated for the condition. To determine the use of talcum powder, participants were asked if they ever used talc at least once per month for 6 months or more. If the response was positive, we then asked whether they had ever used talc in nonperineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm. Questions on talc use included age at first use, frequency of use (times per month) and years of talc use. Few of the talc users (13 cases, 11 controls) had a tubal ligation or hysterectomy before they started using talc; the numbers were too sparse to determine for certain the effect of talc use in this group and these 24 users were included with the nonusers in subsequent analyses on frequency and duration of talc use. Results were unchanged when we excluded these 24 users from the analysis (data not shown).

We asked the participants whether they took prescription or nonprescription NSAIDs for various conditions including back trouble, arthritis, headaches, migraine headaches, dental problems, sinus trouble, colds or sore throats, menstrual pain or cramps or any other reason. They were also asked if they took any of these medications for prevention reasons, such as for prevention of heart attack. We explicitly asked about usage patterns of 10 common over-the-counter NSAIDs (regular aspirin, buffered aspirin, Anacin, APC, Tylenol, Excedrin, Advil, Nuprin, Coricidin, Dristan), 12 prescription brand-name NSAIDs (Clinoril, Motrin, Anaprox, Feldene, Empirin with codeine, Tylenol with codeine, Darvocet, Indocin, Fiorinal, Percocet-5, Percodan, Naprosyn) and two COX-2 inhibitors (Celebrex, Vioxx). We also asked the participants if they had used any NSAIDs that were not on our list and recorded the drug name and details of use. Respondents were also asked about use of 4 common diuretics; these medications are not hypothesized to be related to ovarian cancer risk, but they were included as a check of differential recall between cases and controls. Taking a specific medication 2 or more times a week for 1 month or longer was categorized as "use"; otherwise participants were considered "non-users." Participants were asked about the ages at first and last use, duration of use, usual frequency of use and the primary reason for such use. All of the medications data were categorized into the following groups based on their components: aspirin, acetaminophen, other NSAIDs, COX-2 inhibitors and diuretics.

Total duration and frequency of the main classes of medication (aspirin, acetaminophen, other NSAIDs) were calculated by summing all use of the same class of medication for each person (there were few users of COX-2 inhibitors, thus results are not shown). We also created a combined variable representing use of all NSAIDs. Duration of use was categorized as no use, less than 5 years, 5–10 years and >10 years of use of the specific type of medication (years of use of different medications may be overlapping). The no use category included never users, occasional users and those who only started to use a particular medication within the interval beginning 2 years before date of diagnosis for case patients and the same reference period for controls to avoid including medication use because of early symptoms in cancer patients. We also repeated the analyses excluding first use of medication within 5 years of diagnosis. In addition, we evaluated effect modification of the NSAIDs-ovarian cancer association by race/ethnicity, education, menopausal status, tumor stage, history of endometriosis, talc use and frequency of Pap smears in the 10 years before reference date.

TABLE I – DEMOGRAPHIC AND OTHER CHARACTERISTICS OF OVARIAN CANCER PATIENTS AND CONTROLS

	Cases $N = 609$	Controls $N = 688$	RR	95% CI[1]
Race/ethnicity				
Non-Hispanic White	381	503		
Black	41	44		
Hispanic	136	103		
Asian	51	38		
Age				
≤34	40	36		
35–44	92	138		
45–54	162	227		
55–64	149	162		
65+	166	125		
Education				
≤high school	92	50		
Some college	109	81		
College graduate	223	242		
Graduate	185	315		
Family history of ovarian cancer				
No	581	672	1.00	
Yes	26	16	1.76	0.89–3.47
p-value			0.10	
Number of livebirth				
0	156	149	1.00	
1	98	110	0.76	0.52–1.12
2	157	202	0.61	0.43–0.86
3	109	118	0.61	0.41–0.90
4+	89	109	0.34	0.22–0.53
p trend			<0.0001	
Oral contraceptives				
0 yr	241	189	1.00	
>0 to <5 yr	259	261	0.98	0.73–1.32
≥5 to <10 yrs	57	112	0.54	0.36–0.82
≥10 yrs	52	126	0.40	0.26–0.61
p trend			<0.0001	
Tubal ligation				
No	531	553	1.00	
Yes	78	135	0.66	0.47–0.93
p value			0.017	

[1]Adjusted for race/ethnicity, age, education, tubal ligation, family history of ovarian cancer, menopausal status, use of oral contraceptives, and parity.

The study was approved by the Institutional Review Board of the Keck School of Medicine at the University of Southern California. Informed consent was obtained from each case and control before her interview.

Statistical methods

We calculated odds ratios as estimates of relative risk (RR), their corresponding 95% confidence intervals (CIs) and statistical significance (p) values. We used conditional stratified logistic regression analysis, with stratification sets defined jointly by age (<35, 35–44, 45–54, 55–64, ≥65) and race/ethnicity (non-Hispanic White, African-American, Hispanic, Asians). All regression models also included as categorical covariates education level (high school or less, some college, college graduate, >college),

TABLE II – MULTIVARIABLE RRS (95% CIS) FOR TALC USE AND RISK OF OVARIAN CANCER

	Cases	Controls	RR	95% CI[1]
Talc use				
No[2]	363	469	1.00	
Yes	242	219	1.48	1.15–1.91
Yes, non-perineal area[3]	112	103	1.43	1.03–1.98
Yes, perineal area	130	116	1.53	1.13–2.09
Frequency and duration of talc use				
No	363	469	1.00	
1 ≤20 yrs and ≤10 times/month	35	31	1.36	0.79–2.32
1 ≤20 yrs and >10 to ≤30 times/month	23	30	1.16	0.63–2.12
1 ≤20 yrs and >30 times/month	21	21	1.23	0.63–2.41
>20 yrs and ≤10 times/month	45	49	1.27	0.80–2.01
>20 yrs and >10 to ≤30 times/month	51	43	1.57	0.99–2.50
>20 yrs and >30 times/month	67	45	2.08	1.34–3.23
p (6 df)				$p = 0.032$
Total times of talc use				
No	363	469	1.00	
≤5200	49	52	1.20	0.77–1.88
>5200 to ≤15600	46	47	1.38	0.87–2.20
>15,600 to ≤52000	63	61	1.34	0.89–2.02
>52000	84	59	1.99	1.34–2.96
p (1 df)				$p = 0.0004$
Total times of talc use				
No	363	469	1.00	
Before 1975				
≤5200	24	35	0.84	0.47–1.51
>5200 to ≤15600	29	29	1.41	0.79–2.53
>15,600 to ≤52000	49	45	1.45	0.91–2.31
>52000	82	58	1.93	1.29–2.88
After 1975				
≤5200	25	17	1.95	0.98–3.89
>5200 to ≤15600	17	18	1.17	0.56–2.48
>15,600	16	17	0.98	0.45–2.13

[1]Adjusted for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity.–[2]Subjects (13 Cases, 11 Controls) reported tubal ligation and/or hysterectomy before started talc use and were included with the never users.–[3]Included arms and extremities.

age at menarche (<=11, 12, 13, 14+), parity (0, 1, 2, 3, 4+ births), use of oral contraceptives (none, >0 to <5, 5 to <10, 10+ years), family history of breast/ovarian cancer (no/yes), menopausal status (premenopausal, natural or surgical menopause) and tubal ligation (no/yes). Results obtained using stratified conditional logistic regression methods were consistent with those obtained in matched analyses that preserved the original case-control matching, and we show the results from the stratified analyses. All statistical significance p values quoted are two-sided and are standard chi-squared tests based on differences in log-likelihoods.

Results

The race/ethnicity, age and education of the ovarian cancer cases and controls are shown in Table I. Risk of ovarian cancer increased in association with family history of ovarian cancer (RR = 1.76, 95% CI = 0.89–3.47) and decreased significantly with increasing number of births (RR per birth = 0.79, 95% CI = 0.72–0.88), with increasing duration of oral contraceptive use (RR per 5 years of use = 0.73, 95% CI = 0.64–0.83) and with a history of tubal ligation (RR = 0.66, 95% CI = 0.47–0.93).

Table II shows risk associations with talc use. Ever use of talc was associated with a statistically significant increased risk (RR = 1.48, 95% CI = 1.15–1.91). This included talc that was applied to the perineal area (RR = 1.53, 95% CI = 1.13–2.09) and to the nonperineal area only (RR = 1.43, 95% CI = 1.03–1.98). Elevated risks were found among those who used talc on sanitary napkins (RR = 1.61, 95% CI = 0.93–2.78), underwear (RR = 1.71, 95% CI = 0.99–2.97) and on diaphragm/cervical caps (RR = 1.14, 95% CI = 0.46–2.87). When we examined risk patterns by frequency and duration of talc use, the effect of frequency of use was relatively modest among users of less than 20 years but there was a clear trend of increasing risk with increasing frequency of use among longer duration (>20 years) users. Compared with never users, risk was highest in long-term (>20 years), daily (>30 times/month) talc users (RR = 2.08, 95% CI = 1.34–3.23). Risk increased significantly with lifetime total times of talc use, but the association was limited to those who started talc use before 1975 (p_{trend} <0.001). The association between talc use and risk of ovarian cancer was strongest for serous ovarian cancer, the RR associated with any use was 1.70 (95% CI = 1.27–2.28). The risk associations for talc use and other histologic cell types overlapped with the finding for serous ovarian cancer (RRs were 0.99 for mucinous, 1.19 for clear/endometrioid and 1.46 for other cell types). Elevated risks in relation to talc use were found for those with invasive cancers (RR = 1.31, 95% CI = 0.85–2.01 for localized stage; RR = 1.66, 95% CI = 1.22–2.26 for advanced stage) and LMP tumors (RR = 1.32, 95% CI = 0.88–2.22).

Women with a history of physician-diagnosed endometriosis experienced a nearly 2-fold increased risk of ovarian cancer (RR = 1.95, 95% CI = 1.20–3.17). The risk associated with endometriosis remained statistically significant after adjustment for other gynecological conditions including PID, gonorrhea, ovarian cysts and uterine fibroids (adjusted RR = 1.66, 95% CI = 1.01–2.75) (Table III). Small (4–18%) increased risks were also associated with a history of the other gynecological conditions as mentioned earlier but none of these findings were statistically significant (data not shown). The risk of ovarian cancer increased significantly (RR = 2.58) for more recent diagnoses of endometriosis (2–10 years prior to cancer diagnosis) and was less strong (RR = 1.58) for women with diagnosis more than 10 years previously. The endometriosis-risk association was stronger for invasive cancers (RR = 1.80, 95% CI = 0.85–3.80 for localized stage, RR =

TABLE III – MULTIVARIABLE RRS (95% CIS) FOR PREVIOUS OVARIAN DISEASE AND RISK OF OVARIAN CANCER

		Cases	Controls	Adjusted RR[1]	Adjusted RR[2]
Pelvic inflammatory disease					
No		579	657	1.00	1.00
Yes		25	22	1.48 (0.78–2.82)	1.15 (0.60–2.21)
Gonorrhea					
No		553	619	1.00	1.00
Yes		51	60	1.19 (0.77–1.84)	1.04 (0.67–1.62)
Endometriosis					
No		553	642	1.00	1.00
Yes		51	37	1.95 (1.20–3.17)	1.66 (1.01–2.75)
Years since first diagnosed					
2–10		15	8	2.66 (1.06–6.64)	2.58 (1.03–6.48)
11+		36	29	1.56 (0.90–2.70)	1.58 (0.91–2.76)
Talc	Endometriosis				
No	No	332	435	1.00	1.00
No	Yes	29	28	1.68 (0.93–3.04)	1.67 (0.92–3.01)
Yes	No	221	207	1.50 (1.15–1.94)	1.49 (1.15–1.94)
Yes	Yes	22	9	3.17 (1.38–7.29)	3.12 (1.36–7.22)
p (3df)					0.001

[1]Adjusted for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity.–[2]Adjusted for other conditions including pelvic inflammatory diseases, gonorrhea, endometriosis, ovarian cyst and fibroids.

1.87, 95% CI = 1.04–3.35 for advanced stage) than for LMP tumors (RR = 1.28, 95% CI = 0.56–2.95). Although the point risk estimate was slightly higher for clear/endometrioid cancers (RR = 1.97), the risk associations for the other cell types were all around 1.70. Compared with women who did not have endometriosis and were nontalc users, risk increased 3-fold (RR = 3.12, 95% CI = 1.36–7.22) in women who had endometriosis and were talc users whereas about 50% increased risk was observed in women who had either exposure.

Risk of ovarian cancer increased significantly with increasing duration and frequency of use of all NSAIDs (*i.e.*, aspirin, acetaminophen, other NSAIDs). The risk per 5 years of NSAID use was 1.25 (95% CI = 1.10–1.42) and the risk per 7 times of NSAID use per week was 1.27 (95% CI = 1.14–1.43). The effect of total pill use was essentially identical to the effect of frequency of use. This pattern of risk elevation was found for aspirin, acetaminophen and other NSAIDs although the results were statistically significant only for other NSAIDs (Table IV). Risks patterns remained essentially unchanged when we adjusted for indication of use (*i.e.*, headaches, back pain, menstrual pain and others) or history of endometriosis and other gynecological conditions. Risk associations were only slightly reduced when we restricted our analyses to medication use at least 5 years before diagnosis; the RR per 5 years of all NSAID use was 1.20 (95% CI = 1.06–1.43) and the risk per 7 times of NSAID use per week was 1.23 (95% CI = 1.09–1.38). In contrast, risk of ovarian cancer was not significantly related to duration or frequency of use of diuretics (RRs were 1.00, 1.39, 0.89, 0.65, respectively for no, 1–5, >5–10, >10 years of use, $p_{trend} = 0.50$).

Table V presents stratified results, when we performed a series of analyses to evaluate whether the findings with NSAID use were consistent across levels of various subgroups of interest including race/ethnicity, education, menopausal status, tumor stage, endometriosis, talc use, use of oral contraceptives, parity and frequency of Pap smears in recent 10 years as a marker of access to care. Elevated risks in relation to NSAID use were found in all the subgroup analyses; findings were similar by race/ethnicity, menopausal status, talc use, oral contraceptive use, parity and history of Pap smear. There were some differences in risk estimates by education, tumor stage, history of endometriosis but they were not statistically significantly different. We considered these differences by tumor stage, history of endometriosis and education in our interpretation of these results.

Discussion

The main objective of this population-based case-control study was to comprehensively investigate the role of inflammation in risk of ovarian cancer by studying factors that have been hypothesized to increase inflammation (*e.g.*, talc, endometriosis) or to reduce inflammation (NSAIDs) simultaneously in the same population. Our findings on talc and endometriosis are consistent with previous findings and are compatible with the hypothesis that these factors increase the risk of ovarian cancer and that inflammation may be a common pathway.[1,2,5] However, contrary to the study hypothesis that NSAIDs may have chemopreventive effects by decreasing inflammation,[6] we found that risk of ovarian cancer increased significantly with increasing frequency and duration of NSAIDs use.

Our results on NSAID and risk are similar to the recent results reported in the population-based case-control study conducted in Seattle, Washington.[3] In both studies, women were asked to recall prescription and nonprescription medications taken over their lifetime for various conditions. In the Seattle study, risk of ovarian cancer increased significantly in association with 10+ years of use of acetaminophen (RR = 1.8, 95% CI = 1.3–2.6), aspirin (RR = 1.6, 95% CI = 1.1–2.2) and other NSAIDs (RR = 1.3, 95% CI = 1.0–1.7).[3] Mechanisms whereby use of NSAID may increase risk of ovarian cancer may be related, in part, to the underlying conditions associated with medication use.

However, our results and those from the Seattle study differed from most previous studies on this topic. As Cramer *et al.* reported risk reduction of ovarian cancer with ever use of aspirin, and acetaminophen, but not with use of ibuprofen,[7] 7 (3 case-control, 4 cohort) of 13 (7 case-control, 6 cohort) studies have found no significant relation with use of NSAID. The case-control studies showing null findings were conducted in Italy,[8] the UK[9] and Australia,[2] and they investigated risk associations with use of aspirin,[8] acetaminophen and other NSAID,[9] and aspirin and other NSAIDs,[2] respectively. There was also no relationship between acetaminophen use and risk in the Cancer Prevention II Mortality Study[10] or between risk and use of low-dose aspirin[11] and other NSAIDs[12] in a Danish prescription database study. In the Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP), risk was not significantly related to use of aspirin, acetaminophen and other NSAIDs but risk was increased with 5+ years of other NSAID use (RR = 2.0, 95% CI = 0.95–4.2).[13] Six other studies (4 case-control, 2 cohort) are supportive of an inverse

TABLE IV – MULTIVARIABLE RRS[1] (95% CIS) FOR USE OF ALL NSAIDs (ASPIRIN, ACETAMINOPHEN, OTHER NSAIDs) AND RISK OF OVARIAN CANCER

	Excluded medication use the 2 years before reference date		
	Cases	Controls	RR (95% CI)
All NSAIDs			
Years of use			
Never[2]	355	486	1.00
1 to 5 yr	117	99	1.71 (1.23–2.39)
>5 to ≤10 yr	37	33	1.59 (0.93–2.72)
>10 yr	79	57	1.81 (1.21–2.71)
p trend			<0.001
No. of pills per week			
Never[2]	355	486	1.00
1 to ≤7/wk	82	66	1.62 (1.11–2.39)
>7 to ≤14/wk	41	49	1.09 (0.67–1.78)
>14/wk	110	74	2.24 (1.56–3.21)
p trend			<0.001
Total no. of pills			
Never	355	486	1.00
1 to ≤1096	73	63	1.60 (1.08–2.38)
>1096 to 6428	73	66	1.43 (0.96–2.13)
>6428	87	60	2.22 (1.49–3.31)
p trend			<0.001
Years of use by type[3]			
Aspirin			
Never[2]	492	597	1.00
1 to 5 yr	46	25	2.13 (1.21–3.77)
>5 to ≤10 yr	13	18	0.70 (0.31–1.58)
>10 yr	31	28	1.15 (0.62–2.13)
p trend			0.43
Acetaminophen			
Never[2]	491	590	1.00
1 to 5 yr	47	53	0.87 (0.53–1.41)
>5 yr	44	25	1.71 (0.94–3.09)
p trend			0.12
Other NSAIDs			
Never[2]	450	575	1.00
1 to 5 yr	87	61	1.76 (1.18–2.63)
>5 to ≤10 yr	17	19	1.18 (0.55–2.53)
>10 yr	28	13	2.18 (1.03–4.63)
p trend			0.008
Frequency of use by type[3]			
Aspirin			
Never[2]	492	597	1.00
1 to ≤7/wk	61	48	1.49 (0.94–2.35)
>7	29	23	1.18 (0.61–2.29)
p trend			0.21
Acetaminophen			
Never[2]	491	590	1.00
1 to ≤7/wk	48	45	1.04 (0.63–1.71)
>7 /wk	43	33	1.36 (0.78–2.36)
p trend			0.33
Other NSAIDs			
Never[2]	450	575	1.00
1 to ≤7/wk	52	38	1.56 (0.95–2.56)
>7 to ≤14/wk	29	25	1.27 (0.68–2.40)
>14/wk	51	30	2.22 (1.30–3.79)
p trend			0.0009

[1]Adjusted for age, education, race, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives, parity and talc use.–[2]Included participants who started medication within 2 years of diagnosis/reference date.–[3]Additional adjustment for history of PID, gonorrhea, ovarian cysts, endometriosis, and fibroids. The RRs for aspirin, acetaminophen and other NSAIDs were mutually adjusted. Aspirin included regular aspirin, buffered aspirin; acetaminophen included Tylenol, coricidin, Dristan, darvocet, Percocet, Excedrin; other NSAID included advil, nuprin, clinoril, motrin, anaprox, feldene, indocin, naprosyn.

association with NSAIDs use, one reported significant risk reduction with acetaminophen use[14] while 4 studies found significant reduced risk with use of other NSAIDs[15–18] but there were differences in these results. In one study, an inverse association was found only in nulliparous and nonoral contraceptive users.[18] No dose-response relationship was observed in a second study,[15] and information on NSAID use was limited to the 5 years before diagnosis in a third study.[17] Aspirin use was not significantly associated with risk in these 5 studies.[14–17,19] Ascertainment of NSAID use was heterogeneous in these studies: different NSAIDs were included, the exposure period varied (*e.g.*, adult use, use in previous 20 years or previous 5 years before ovarian cancer diagnosis), and information on frequency and duration of NSAID use was asked in only some studies.

An advantage of our study is that we collected detailed information on adult usage history of both over the counter and prescription NSAIDs including duration and frequency of use and indication for use. Our results suggest increased risk associated with duration and frequency of use of aspirin, acetaminophen and other NSAIDs although only the findings for other NSAIDs were statistically significant on their own. We adjusted for potential confounders and indication for use; the latter was considered in only some previous studies. Nevertheless, our results should be interpreted with caution for the following reasons. Our assessment of NSAID use was based on self-report without assessment of reliability of recall. However, a drug validation study conducted by colleagues in Los Angeles County found high and comparable concordance rate of recall of analgesics in cancer patients and control subjects.[20] Regular NSAID use was reported by 29% (31% in non-Hispanic whites) of controls in our study; comparable with the rate reported in Wisconsin and Massachusetts (34%)[18] but lower than that in Seattle (41%).[3] Differences in the assessment of use of NSAID complicate comparison of prevalences of use between studies.

Although an increased risk was specific to NSAIDs use and no increased risk was found with diuretic use, we cannot rule out the possibility of selective recall bias among ovarian cancer cases. Given that many NSAIDs products are available and use may be episodic, it is conceivable that some cases may be more motivated to remember their NSAID use than control subjects. There is also the possibility of surveillance bias and that certain health conditions led to regular NSAID use, resulting in frequent doctor visits, which increased the chances of ovarian cancer detection. As noted earlier, the prevalence of NSAID use was higher in women with LMP tumors or localized cancer than those with advanced stage cancers, and the magnitude of association was stronger for earlier stage cancers. However, the proportion of LMP/localized stage cancers among those we interviewed (41%) and those we failed to interview (39%) was not dissimilar, suggesting there should be minimal overestimation of the overall effect of NSAID in relation to this reason. There also may be residual confounding by indication for use. Another possible explanation for our observed positive finding is that women with early symptoms of undiagnosed ovarian cancer take pain medications to relieve these symptoms. This seems less likely because our results were essentially unchanged when we excluded participants who first started using these medications within the 5 years of diagnosis. Finally, we consider possibly that selection bias of cases and controls may have affected our finding. Our response rate was modest; cases who participated may differ from those who did not participate. Although controls in our study had more years of education than cases, there was no consistent pattern in the NSAID-risk association by education. The NSAID-risk association was most apparent in women who were college graduates but was very similar in women with high school education or less and those who had more than college education. Thus, despite these limitations, our results raise the concern that NSAIDs, taken as aspirin, acetaminophen or other NSAIDs, may actually increase the risk of ovarian cancer.

In our study, history of self-reported history of endometriosis that was diagnosed by a physician was associated with a significant 66% increased risk of ovarian cancer. Given that the elevated risk was observed for those with previous endometriosis for at least 11+ years, it is unlikely that our finding is due to detection bias but suggests that endometriosis may have an etiological role.

TABLE V – PREVALENCE OF NSAID USE IN CASES AND CONTROLS AND RRS (95% CI)[1] PER 5 YEARS OF NSAID USE

		ever NSAID-cases (%)	ever NSAID-controls (%)	10+ yrs of NSAIDs-cases (%)	10+ yrs of NSAID-controls	RR (95% CI) per 5 years of NSAID
Race/ethnicity	Non-Hipsanic Whites	45%	31%	17%	10%	1.23 (1.07–1.42)
	Other	31%	19%	7%	4%	1.37 (1.03–1.84)
Education	<College	36%	29%	14%	10%	1.09 (0.84–1.41)
	College graduate	48%	27%	16%	7%	1.71 (1.36–2.15)
	Graduate	33%	28%	11%	9%	1.05 (0.85–1.30)
Menopause	Premenopause	34%	22%	7%	5%	1.35 (1.05–1.73)
	Postmenopause	43%	34%	17%	11%	1.22 (1.06–1.42)
Tumor stage	LMP	47%	28%	14%	8%	1.37 (1.11–1.69)
	Invasive, Stage 1 or 2	40%	28%	14%	8%	1.36 (1.11–1.67)
	Invasive, Stage ≥3	37%	28%	13%	8%	1.16 (1.01–1.35)
Endometriosis	No	39%	27%	12%	9%	1.23 (1.08–1.40)
	Yes	50%	44%	26%	8%	1.52 (0.96–2.43)
Talc	No	36%	25%	13%	6%	1.31 (1.10–1.55)
	Yes	45%	35%	15%	14%	1.14 (0.94–1.38)
Oral Contraceptives	No	35%	25%	13%	10%	1.10 (0.89–1.37)
	Yes	43%	29%	14%	8%	1.31 (1.12–1.53)
Parity	No	41%	31%	15%	9%	1.28 (0.98–1.68)
	Yes	40%	27%	13%	8%	1.25 (1.09–1.45)
Pap smear[2]	≤5 times	34%	24%	11%	7%	1.22 (0.94–1.59)
	>5 times	42%	30%	15%	9%	1.27 (1.09–1.47)

[1]Adjusted for age, education, race, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity.–[2]Frequency of Pap smears in the 10 years before reference date.

No association between endometriosis and ovarian cancer was reported in the Iowa Women's Health Study, but this may be because of the relatively limited number of ovarian cancers in this cohort and the low prevalence of endometriosis (~3%).[21] Endometriosis was associated with about a 30% increased risk in an Australian population-based case-control study[2] and in a pooled analysis of 2,098 cases and 2,953 controls from 4 US population-based case-control studies.[22] Although the prevalences of endometriosis among cases (8.4%) and controls (5.4%) in our study are very comparable with the figures reported in cases (8%) and controls (6%) in previous case-control studies,[2,22] a limitation of our study and other case-control studies on this topic is that history of endometriosis is not validated. We did not see meaningful differences in history of endometriosis by cell type (11% for endometrioid/clear cell *vs.* 8% for other cell types) of ovarian cancer while a higher prevalence of endometriosis in women with endometroid/clear cell has been usually reported in other studies.[2,23] Interestingly, when one of us (CT) reviewed the pathology reports of the 52 ovarian cancer patients who reported a history of endometriosis, endometriosis in the ovary was documented in only 15 patients (15 of 604 cases = 2.5%) but the percent was higher in women with clear cell/endometrioid (7 of 84 = 8.3%) ovarian cancer compared with the other cell types (8 of 520 = 2.3%). Additional information on the type of endometriosis and location of endometriosis would be helpful in future studies.

The role of talc in the development of ovarian cancer has been studied extensively. In a 2006 review by the International Agency for Research on Cancer (IARC), talc was classified as possibly carcinogenic to humans (*i.e.*, Group 2B) on the basis that most of the 20 epidemiological studies on talc and ovarian cancer show consistently a 30–60% increased risk associated with talc use.[24] However, only about half of the studies examined exposure-response relationships and the evidence for this is less consistent. Our study adds to the small group of studies that have investigated the combination of frequency and duration of talc use on ovarian cancer risk.[25–28] Our results show a significant trend with increasing number of total applications. Using a combined index of total applications or cumulative lifetime days of talc use, 2 studies showed a higher risk with greater exposure[27,29] but this was not observed in 2 other studies.[25,28] When we investigated the combined effect of frequency and duration, our results suggest that the effect of increasing frequency was modest in users of less than 20 years but that the effect of frequency was clearer in women who had used talc for 20 years or more. Our results also suggest that talc use prior to 1976 may be more important. In 1976, talcum powder manufacturers instituted voluntary guidelines to prevent asbestos contamination in talc products and thus formulations after 1976 may be less likely to be contaminated with asbestos fibers. Stronger associations with talc use in the 1960s and 1970s have been reported in some studies[25,27] but not in others.[2,28] Thus, lack of sufficient information on frequency, duration and calendar period of talc use may have contributed to misclassification of this exposure variable in some previous studies.

Our findings on talc use and endometriosis and ovarian cancer risk are compatible with previous studies. However, the NSAID finding in this study was unexpected and requires confirmation with further characterization of the association by frequency and duration of use, cumulative dose and timing of exposure. In addition, it will be important to evaluate the underlying conditions for medication use.

Acknowledgements

Incident ovarian cancer cases for this study were collected by the USC Cancer Surveillance Program (CSP), which is supported under subcontract by the California Department of Health. The authors are grateful to all the study participants for their contributions and support. They also thank the entire data collection team, especially Kat Mendoza, Heidi St. Royal, and Janelle Miller.

References

1. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 1999;91:1459–67.
2. Merritt MA, Green AC, Nagle CM, Webb PM. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int J Cancer 2008;122:170–6.
3. Hannibal CG, Rossing MA, Wicklund KG, Cushing-Haugen KL. Analgesic drug use and risk of epithelial ovarian cancer. Am J Epidemiol 2008;167:1430–7.
4. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, Wan PC, Mack TM. Estrogen-progestin replacement therapy and endometrial cancer. J Natl Cancer Inst 1997;89:1110–16.
5. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 2000;11:111–17.

6. Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. Br J Clin Pharmacol 2005;60:194–203.
7. Cramer DW, Harlow BL, Titus-Ernstoff L, Bohlke K, Welch WR, Greenberg ER. Over-the-counter analgesics and risk of ovarian cancer. Lancet 1998;351:104–7.
8. Tavani A, Gallus S, La Vecchia C, Conti E, Montella M, Franceschi S. Aspirin and ovarian cancer: an Italian case-control study. Ann Oncol 2000;11:1171–3.
9. Meier CR, Schmitz S, Jick H. Association between acetaminophen or nonsteroidal antiinflammatory drugs and risk of developing ovarian, breast, or colon cancer. Pharmacotherapy 2002;22:303–9.
10. Rodriguez C, Henley SJ, Calle EE, Thun MJ. Paracetamol and risk of ovarian cancer mortality in a prospective study of women in the USA. Lancet 1998;352:1354–5.
11. Friis S, Sorensen HT, McLaughlin JK, Johnsen SP, Blot WJ, Olsen JH. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. Br J Cancer 2003;88:684–8.
12. Sorensen HT, Friis S, Norgard B, Mellemkjaer L, Blot WJ, McLaughlin JK, Ekbom A, Baron JA. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. Br J Cancer 2003;88:1687–92.
13. Lacey JV, Jr, Sherman ME, Hartge P, Schatzkin A, Schairer C. Medication use and risk of ovarian carcinoma: a prospective study. Int J Cancer 2004;108:281–6.
14. Moysich KB, Mettlin C, Piver MS, Natarajan N, Menezes RJ, Swede H. Regular use of analgesic drugs and ovarian cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:903–6.
15. Fairfield KM, Hunter DJ, Fuchs CS, Colditz GA, Hankinson SE. Aspirin, other NSAIDs, and ovarian cancer risk (United States). Cancer Causes Control 2002;13:535–42.
16. Rosenberg L, Palmer JR, Rao RS, Coogan PF, Strom BL, Zauber AG, Stolley PD, Shapiro S. A case-control study of analgesic use and ovarian cancer. Cancer Epidemiol Biomarkers Prev 2000;9:933–7.
17. Schildkraut JM, Moorman PG, Halabi S, Calingaert B, Marks JR, Berchuck A. Analgesic drug use and risk of ovarian cancer. Epidemiology 2006;17:104–7.
18. Wernli KJ, Newcomb PA, Hampton JM, Trentham-Dietz A, Egan KM. Inverse association of NSAID use and ovarian cancer in relation to oral contraceptive use and parity. Br J Cancer 2008;98:1781–3.
19. Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, Kato I, Koenig KL, Shore RE. Aspirin and epithelial ovarian cancer. Prev Med 2001;33:682–7.
20. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC. Regular use of analgesics is a risk factor for renal cell carcinoma. Br J Cancer 1999;81:542–8.
21. Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. Cancer 2002;94:1612–18.
22. Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol 2004;191:733–40.
23. Brinton LA, Sakoda LC, Sherman ME, Frederiksen K, Kjaer SK, Graubard BI, Olsen JH, Mellemkjaer L. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. Cancer Epidemiol Biomarkers Prev 2005;14:2929–35.
24. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Cogliano V. Carcinogenicity of carbon black, titanium dioxide, and talc. Lancet Oncol 2006;7:295–6.
25. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol 1997;145:459–65.
26. Cramer DW. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol 1999;94:160–1.
27. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol 1992;80:19–26.
28. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the central valley of California. Int J Cancer 2004;112:458–64.
29. Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, Harlow BL. Genital talc exposure and risk of ovarian cancer. Int J Cancer 1999;81:351–6.