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

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Abstract

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 endometriosis, 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 longduration (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.

Keywords

talc; endometriosis; non-steroidal anti-inflammatory drugs; ovarian cancer

Introduction

In 1999, Ness and Coutreau proposed that chronic inflammation may lead to the development of epithelial ovarian cancer¹. 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 nonsteroidal anti-inflammatory drugs (NSAIDs) may offer additional opportunities to evaluate the inflammation hypothesis. In a 2008 paper, Merritt and co-workers² 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 since 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 five years prior to diagnosis of ovarian cancer, rather than long-term use². 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 users³. 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.

Materials 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 through 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 not to 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 since 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 factors⁴. 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 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 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 subjects were interviewed inperson; 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, subjects were asked if they were ever told by a physician that they had certain gynecological conditions including pelvic inflammatory disease (PID), gonorrhea, endometriosis, ovarian cysts, or uterine fibroids before the reference date. If the response was yes to any of the conditions, subjects 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 use of talcum powder, subjects 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 non-perineal 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 non-users 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 subjects whether they took prescription or non-prescription non-steroidal antiinflammatory drugs (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 subjects 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 one month or longer was categorized as 'use'; otherwise subjects were considered 'non-users'. Subjects 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 two 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.

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), age at menarche (≤ 11 , 12, 13, 14+), parity (0, 1, 2, 3, 4+ births), use of oral contraceptives (none, >0 to <5, 5-<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 1. Risk of ovarian cancer increased in association with family history of ovarian cancer (RR=1.77, 95% CI=0.89-3.49) 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=0.64, 95% CI=0.45-0.91).

Table 2 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 non-perineal 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 to 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 ($P_{\text{trend}} < 0.001$). 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/endometriosis, 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, gonorrhoea, ovarian cysts, and uterine fibroids (adjusted RR=1.66, 95% CI=1.01-2.75) (Table 3). Small (4-18%) increased risks were also associated with a history of the other gynecological conditions mentioned above 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=0.85-3.8 for localized stage, RR=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 to women who did not have endometriosis and were non-talc users, risk increased 3-fold (RR=3.12, 95% CI=1.35-7.22) in women who had endometriosis and were talc users while about a 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 1.26 (95% CI=1.11-1.43) and the risk per 7 times of NSAID use per week was 1.29 (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 4). 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 5 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 inflammation⁶, 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, Washington³. 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. Since Cramer and colleagues reported risk reduction of ovarian cancer with ever use of aspirin, and acetaminophen, but not with use of ibuprofen⁷, 7 (3 case-control, 4 cohort) of 13 (7 case-control, 6 cohort) studies have found no significant relation with use of NSAID. The casecontrol studies showing null findings were conducted in Italy⁸, the UK⁹ and Australia² and they investigated risk associations with use of aspirin⁸, acetaminophen and other NSAID⁹, and aspirin and other NSAIDs², respectively. There was also no relationship between acetaminophen use and risk in the Cancer Prevention II Mortality Study¹⁰ or between risk and use of low-dose aspirin¹¹ and other NSAIDs¹² 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 association with NSAIDs use, one reported significant risk reduction with acetaminophen use¹⁴ while four studies found significant reduced risk with use of other NSAIDs¹⁵⁻¹⁸ but there were differences in these results. In one study, an inverse association was found only in nulliparous and non-oral contraceptive users.¹⁸ No dose-response relationship was observed in a second study¹⁵ and information on NSAID use was limited to the 5 years before diagnosis in a third study¹⁷. 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

subjects²⁰. Regular NSAID use was reported by 29% (31% in non-Hispanic whites) of controls in our study; comparable to 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 above, 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 since our results were essentially unchanged when we excluded subjects who first started using these medications within the 5 years of diagnosis. Finally, we consider the 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. No association between endometriosis and ovarian cancer was reported in the Iowa Women's Health Study, but this may be due to 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 study² and in a pooled analysis of 2098 cases and 2953 controls from 4 US population-based case-control studies²². 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 casecontrol 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 endometrioid/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 to 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 use²⁴. 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 risk²⁵⁻²⁸. 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, two studies showed a higher risk with greater exposure^{27, 29} but this was not observed in two 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.

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Table 1
Demographic and other characteristics of ovarian cancer patients and controls

	Cases N=607	Controls N=688	RR	95% CI
Race /ethnicity				
White	381	503		
Black	41	44		
Hispanic	134	103		
Asian	51	38		
P (3df)				
Age				
<=34	40	36		
35-44	91	138		
45-54	161	227		
55-64	149	162		
65+	166	125		
P (4df)				
Education				
<=high school	91	50		
Some college	109	81		
College graduate	222	242		
Graduate	185	315		
P (4df)				
Family history of ovarian cancer				
No	581	672	1.00	
Yes	26	16	1.77	0.89-3.49
P value			0.17	
Number of livebirth				
0	156	149	1.00	
1	98	110	0.76	0.52-1.12
2	155	202	0.60	0.42-0.84
3	109	118	0.62	0.41-0.93
4+	89	109	0.34	0.21-0.53
P trend			<0.0001	
Oral contraceptives				
0 yr	241	189	1.00	
>0 to <5 yr	259	261	0.99	0.73-1.33
>=5 to <10 yrs	56	112	0.54	0.35-0.82
>=10 yrs	51	126	0.40	0.27-0.61
P trend			<0.0001	
Tubal ligation				
No	525	551	1.00	
Yes	76	135	0.64	0.45-0.91

	Cases N=607	Controls N=688	RR	95% CI
P value			0.012	

^a Adjusted for race/ethnicity, age, education, tubal ligation, family history of ovarian cancer, menopausal status, use of oral contraceptives and parity

Table 2
Multivariable RRs (95% CIs) for talc use and risk of ovarian cancer

	Cases	controls	RR	(95% CI) ^a
Talc use				
No ^b	363	469	1.00	
Yes	242	219	1.48	1.15-1.91
Yes, non-perineal area ^c	112	103	1.43	1.03-1.98
Yes, perineal area	130	116	1.53	1.13-2.09
Frequency & duration of talc use				
No	363	469	1.00	
1 <=20 yrs & <=10 times/month	35	31	1.36	0.79-2.32
1 <=20 yrs & >10- <=30 times/month	23	30	1.16	0.63-2.12
1 <=20 yrs & >30 times/month	21	21	1.23	0.63-2.41
>20 yrs & <=10 times/month	45	49	1.27	0.80-2.01
>20 yrs & >10- <=30 times/month	51	43	1.57	0.99-2.50
>20 yrs & >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	0.55-2.48
>15,600	16	17	0.98	0.45-2.13

^a Adjusted for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity

^b Subjects (13 cases, 11 controls) reported tubal ligation and/or hysterectomy before started talc use and were included with the never users.

^c Included arms and extremities.

Table 3
Multivariable RRs (95% CIs) previous ovarian disease and risk of ovarian cancer

	Cases	Controls	Adjusted RR ^a	Adjusted RR ^b
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	579	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	332	439	1.00	1.00
No	29	28	1.68 (0.93-3.04)	1.67 (0.92-3.01)
Yes	222	208	1.50 (1.15-1.94)	1.49 (1.15-1.94)
Yes	22	9	3.17 (1.38-7.29)	3.12 (1.36-7.22)
				P (3df)= 0.001

^a Adjusted for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity

^b Adjusted for other conditions including pelvic inflammatory diseases, gonorrhea, endometriosis, ovarian cyst, and fibroids

Table 4

Multivariable RRs^a (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 ^b	357	488	1.00
1 to 5 yr	117	100	1.70 (1.22-2.36)
>5 to <=10 yr	37	33	1.66 (0.98-2.83)
>10 yr	79	57	1.85 (1.24-2.77)
P trend			<0.001
# pills per week			
Never ^b	355	486	1.00
<=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 # pills			
Never	355	486	1.00
<=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 ^c			
Aspirin			
Never ^b	492	597	1.00
1 to 5 yr	46	25	2.13 (1.31-3.77)
>5 to <=10 yr	13	18	0.70 (0.31-1.58)
>10 yr	31	28	1.15 (0.62-2.13)
P trend			0.14
Acetaminophen			
Never ^b	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 ^b	450	575	1.00
1 to 5 yr	87	61	1.76 (1.18-2.63)
>5 yr	17	19	1.18 (0.55-2.53)
>10 yr	28	13	2.18 (1.03-4.63)

Excluded medication use the 2 years before reference date			
	Cases	controls	RR (95% CI)
P trend			0.008
Frequency of use by type ^c			
Aspirin			
Never ^b	492	597	1.00
<=7/wk	61	48	1.49 (0.94-2.35)
>7 to <=14/wk	29	23	1.18 (0.61-2.29)
P trend			0.21
Acetaminophen			
Never ^b	491	590	1.00
<=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 ^b	450	575	1.00
<=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

^a Adjusted for age, education, race, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives, parity, and talc use

^b Included subjects who started medication within 2 years of diagnosis/reference date

^c Additionally adjusted for the 4 types of medications simultaneously and 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, nurin, clinoril, motrin, anaprox, feldene, indocin, naprosyn.

Table 5
Prevalence of NSAID use in cases and controls and RRs (95% CI) ^a per 5 years of NSAID use

		% ever NSAID - cases	% ever NSAID- controls	% 10+ yrs of NSAIDs - cases	% 10+ yrs of NSAIDs - controls	RR (95% CI) per 5 years of NSAID
Race/ethnicity	Non-Hispanic	45%	31%	17%	10%	1.23 (1.07-1.42)
	Whites					
	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%	33%	17%	11%	1.22 (1.06-1.42)
Tumor stage	LMP	47%	28%	14%	8%	1.37 (1.11-1.69)
	Invasive, 1-2	40%	28%	14%	8%	1.36 (1.11-1.67)
	Invasive, 3-4	37%	28%	13%	8%	1.16 (1.01-1.35)
Endometriosis	No	39%	28%	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%	1.13 (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 ^b	<=5 times	34%	24%	11%	7%	1.22 (0.94-1.59)
	>5 times	42%	30%	15%	9%	1.27 (1.09-1.47)

^a Adjusted for age, education, race, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity

^b Frequency of Pap smears in the 10 years before reference date.