Published in final edited form as:

Gynecol Oncol. 2020 November ; 159(2): 522–526. doi:10.1016/j.ygyno.2020.08.038.

Aspirin use and ovarian cancer risk using extended follow-up of the PLCO Cancer Screening Trial

Lauren M. Hurwitz^{a,*}, Paul F. Pinsky^b, Wen-Yi Huang^a, Neal D. Freedman^a, Britton Trabert^a

^aDivision of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Rockville, MD 20850, U.S.A.

^bDivision of Cancer Prevention, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Rockville, MD 20850, U.S.A.

Abstract

Objective: Frequent use of aspirin has been associated with reduced ovarian cancer risk in observational studies, but it is unclear if only daily, low-dose aspirin confers a protective benefit. We examined associations between patterns of aspirin use and ovarian cancer risk among postmenopausal women in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Methods: Participants were enrolled in PLCO between 1993-2001 and followed for cancer outcomes through 2014. Detailed data on aspirin use (e.g., dose, frequency and duration) were ascertained via the supplemental questionnaire (SQX) administered in 2006-2007. We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between aspirin use (defined as use once/week) and incident ovarian cancer. We conducted analyses among all women in the study sample and stratified by age at the time of the SQX.

Results: There were 41,633 women included in this analysis, of whom 223 developed incident ovarian cancer. Overall, aspirin use was not significantly associated with ovarian cancer risk (HR: 0.93, 95% CI: 0.72-1.21). Among women <70 years, there was suggestion of an inverse association for daily use of aspirin (HR: 0.65, 95% CI: 0.40-1.05), low-dose aspirin (HR: 0.79, 95% CI: 0.51-1.24) and daily use of low-dose aspirin (HR: 0.64, 95% CI: 0.38-1.09).

*Corresponding author: Division of Cancer Epidemiology and Genetics, National Cancer Institute 9609 Medical Center Drive, Rockville, MD 20850, lauren.hurwitz@nih.gov.

Author contributions

Lauren M. Hurwitz: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft

Paul F. Pinsky: Conceptualization, Methodology, Investigation, Supervision, Critical revision of the article

Wen-Yi Huang: Methodology, Investigation, Supervision, Critical revision of the article

Neal D. Freedman: Methodology, Investigation, Supervision, Critical revision of the article

Britton Trabert: Conceptualization, Methodology, Investigation, Supervision, Critical revision of the article

All authors read and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts of interest to report.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions: These findings suggest a potential modest effect of daily, low-dose aspirin in reducing ovarian cancer risk. However, effect estimates were imprecise given the small number of events, and further research will be needed to confirm and extend these findings.

Keywords

Anti-inflammatory agents; non-steroidal; Aspirin; Chemoprevention; Ovarian neoplasms

Introduction

Ovarian cancer is the most fatal of the gynecologic malignancies. Due to the absence of effective modalities for screening and early detection, ovarian cancer is often detected at an advanced stage, when prognosis is poor. Primary prevention could help reduce the burden of ovarian cancer, but prevention strategies are currently limited by the paucity of established modifiable risk factors.

Aspirin is a commonly used anti-inflammatory and antiplatelet medication that may reduce ovarian cancer risk when taken frequently. Meta-analyses [1] and pooled analyses [2, 3] of case-control and cohort studies have reported an approximately 10-20% reduced risk of ovarian cancer among women who take aspirin daily or almost daily, compared to infrequent or non-users. However, individual study results, particularly in the prospective setting and for specific aspirin regimens, have been mixed. A longer duration of aspirin use was associated with reduced ovarian cancer risk in the Women's Health Initiative [4] but not in other cohorts [5-7]. In the Iowa Women's Health Study, an inverse trend was observed between frequency of aspirin use and ovarian cancer risk [8], but a similar trend was not observed in the Nurses' Health Study or Nurses' Health Study II [7, 9]. Consistent with case-control results [10, 11], risk reductions for ovarian cancer in the Nurses' Health Studies were limited to women who reported low-dose aspirin use as opposed to adult-strength aspirin use [7], but few other prospective studies have collected information on aspirin dose.

We examined associations between dose, frequency, and duration of aspirin use and ovarian cancer risk among postmenopausal women using extended follow-up from the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Cancer Screening Trial.

Methods

Study population

Study participants were from the PLCO Cancer Screening Trial, a multicenter randomized controlled trial designed to test the effect of cancer screening modalities on cancer-specific mortality [12]. Participants were ages 55-74 years at enrollment in 1993-2001. There were 78,216 women enrolled. We restricted our analysis to women who completed both the baseline questionnaire (BQ) and the supplemental questionnaire (SQX), administered in 2006-2007, and who were not diagnosed with ovarian cancer prior to the SQX (n=53,383). An additional 10,037 women were excluded for having a history of bilateral oophorectomy or unknown oophorectomy status at the time of the SQX, and 1,713 women were excluded for missing data on aspirin use or key covariates, yielding a sample size of 41,633 for this

study. The PLCO trial was approved by institutional review boards at all participating sites. All subjects provided written informed consent.

Ascertainment of aspirin use and other covariates

For this study, we used aspirin data from the SQX as opposed to the BQ because the BQ did not collect information on dose or duration of aspirin use. The SQX included three questionnaire items pertaining to aspirin use: “During the last 12 months, about how often did you usually take aspirin (examples of aspirin include Bayer, Bufferin, Anacin, and baby aspirin)? None or less than 1 time per month, 1 to 3 times per month, 1 to 2 times per week, 3 to 6 times per week, or 7 or more times per week,” “When you took aspirin, what strength or dose did you usually take? None, adult-strength (usually 325 mg), low-dose (usually 81 mg), some other strength, or don’t know the strength,” and “For how many years have you taken aspirin at least once a week? None, less than 10 years, 10 to 19 years, 20 to 39 years, or 40 or more years.” We defined aspirin users as those who reported aspirin use at least once per week during the past year on the SQX. A small percentage of women (1.7%) selected multiple responses to the question on aspirin dose; these women were grouped as low-dose users in our analysis, as almost all reported low-dose use in addition to another response.

Other covariates of interest were self-reported and included age, race/ethnicity, height, weight, oral contraceptives use, hormonal therapy use, parity, and history of heart attack or stroke. Parity was reported on the BQ; all other covariates were updated with data from the SQX. Body mass index (BMI) was calculated from the weight and height from the SQX as the weight in kilograms divided by height in meters squared.

Ascertainment of cancer outcomes

The primary outcome for this analysis was incident primary invasive ovarian, peritoneal, or fallopian tube cancer, henceforth jointly referred to as ovarian cancer. Through 2010, participants were actively followed by each study center for incident cancer cases and deaths. In 2011, PLCO transitioned to active follow-up by a centralized data center in combination with passive follow-up by linkage to state cancer registries and the National Death Index. Study participants were required to reconsent for additional follow-up at this time, and 14% of participants included in this study (n=5,924) refused.

Statistical analysis

Participant characteristics at study baseline (i.e. SQX) were compared by dose, frequency, and duration of aspirin use. Cox proportional hazards regression with age as the time scale was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between aspirin use, overall and by dose, frequency, and duration, and ovarian cancer risk. Models were left-truncated for age at the SQX; women contributed person time from age at the SQX to age at ovarian cancer diagnosis, death, or administrative censoring (end of 2010 for those who did not consent to additional follow-up, end of 2014 for everyone else). The proportional hazards assumption was checked via examination of Schoenfeld residuals and was found to hold for all aspirin variables. Models were adjusted for potential confounders selected *a priori* including study arm (intervention, usual care), race/ethnicity (non-Hispanic white, Hispanic or non-white), BMI (<25, 25-<30, ≥30 kg/m²,

treated ordinarily), duration of oral contraceptive use (none, ≤ 5 years, >5 years), hormonal therapy use (never, ever), and parity (no live births, ≥ 1 live birth). Additional adjustment for non-aspirin NSAID use at least once per week (yes, no) was also considered but was not found to alter effect estimates and was thus not included in the final models. Given that current guidelines recommend against aspirin use for primary prevention for older women [13], combined with trial results suggesting that the effect of aspirin on cancer outcomes may vary by age or timing of exposure [14, 15], we repeated all analyses stratified by age at the time of completion of the SQX (<70 years, ≥ 70 years). We also conducted two sensitivity analyses: one using inverse probability of selection weights (IPSW) to account for the fact that not all women consented for additional follow-up post-2010, and one in which we restricted to women without a history of heart attack or stroke. All statistical tests were two-sided, and analyses were conducted in SAS 9.4.

Results

Of the 41,633 postmenopausal women included in this study, 223 developed ovarian cancer during follow-up. The median (Q1-Q3) age at SQX was 71 (66-75) years, and the median (Q1-Q3) follow-up post-SQX was 8 (7-9) years. Fifty-two percent of women reported using aspirin at least once per week during the past year; of these aspirin users, 73% took low-dose aspirin, 71% took aspirin daily, and 56% reported both low-dose and daily use. Thirty-two percent of aspirin users reported using aspirin at least once per week for ≥ 10 years. Compared to non-users, aspirin users, and particularly daily users, were slightly older and more likely to be non-Hispanic white, overweight or obese, ever users of hormonal therapy, and have a history of heart attack or stroke (Table 1). Aspirin use characteristics by type of follow-up are displayed in Supplemental Table 1.

Overall, aspirin use at least once per week was not associated with ovarian cancer risk (HR: 0.93, 95% CI: 0.72-1.21, Table 2). Results were similar for low-dose use (HR: 0.88, 95% CI: 0.66-1.18), daily use (HR: 0.94, 95% CI: 0.70-1.25) and long-term use (≥ 10 years, HR: 0.75, 95% CI: 0.50-1.13).

Among women <70 years old at the time of the SQX, associations for any aspirin use at least once per week, low-dose use, and daily use strengthened, but confidence intervals still overlapped the null (Table 2). We observed suggestive inverse associations for daily use (HR: 0.65, 95% CI: 0.40-1.05), and specifically for daily use of low-dose aspirin (HR: 0.64, 95% CI: 0.38-1.09) for women <70 years old. In contrast, the association for non-daily use (HR: 1.26, 95% CI: 0.76-2.09) supported no benefit of this aspirin regimen for reducing ovarian cancer risk among women <70 years old. For women ≥ 70 years old, null associations were observed for all aspirin regimens.

Results were similar when we used IPSW and when we restricted to women without a history of heart attack or stroke (Supplemental Table 2).

Discussion

In this prospective cohort of postmenopausal women enrolled in the PLCO Cancer Screening Trial, we did not observe significant associations between aspirin use and ovarian

cancer risk overall. However, the direction and magnitude of the effect estimates for daily, low-dose aspirin use were consistent with prior reports, supporting a protective effect of this specific aspirin regimen.

A large pooled analysis of case-control data (median age at diagnosis/enrollment = 57) reported a 36% reduction in ovarian cancer risk with daily, low-dose aspirin [2]; our study estimate supported a consistent 36% risk reduction when we restricted to women of a similar age range (i.e. women <70 years). In contrast, a pooled analysis of cohort studies reported a more modest inverse association for daily aspirin (pooled HR 0.90 [0.82-1.00]) and no association for low-dose aspirin (pooled HR 0.99 [0.79-1.23]), though few included studies had data on aspirin dose [3]. These studies assessed aspirin use at baseline only (with mean baseline age ranging from 46-64 years), and may have misclassified aspirin use at older ages, more proximal to ovarian cancer diagnosis. A cohort study incorporating time-updated aspirin data observed an inverse association for frequent, low-dose aspirin use [7], suggesting that associations may emerge when misclassification is reduced. Though we only assessed aspirin use at a single time point, our results for women <70 years old mirror this finding, potentially because we assessed aspirin use in later adulthood. Collectively, these studies build support for the hypothesis that frequent, low-dose aspirin reduces ovarian cancer risk among younger postmenopausal women, though additional largescale studies are needed to confirm these results, obtain more precise effect estimates, and clarify how the age and timing of aspirin ascertainment influence risk.

Strengths of this study include the prospective study design, detailed information on aspirin use, and long-term follow-up for cancer outcomes. We leveraged data from a large cohort, though we still had limited power to examine associations for the rare outcome of ovarian cancer, particularly when we stratified by age and divided our exposed population into finer categories of aspirin use. Due to limited power, we were unable to examine associations by ovarian cancer histotype, though there has not been substantial etiologic heterogeneity by histotype in prior analyses [2, 3]. We were also unable to disentangle the effects of low-dose aspirin use from daily aspirin use since dose and frequency of use are highly correlated. Low-dose aspirin is sufficient to inhibit platelet activation but may have less of an anti-inflammatory effect than adult strength aspirin [16]; additional research is needed to determine whether biological effects specific to low-dose aspirin use lower ovarian cancer risk, or whether daily use regardless of dose is imperative. Finally, we did not have data on the number of aspirin tablets taken per day, which may have contributed to some measurement error in our assessment of aspirin dose.

Future studies should continue to examine the effects of daily, low-dose aspirin use on ovarian cancer risk and explore potential biological mechanisms. Given the low incidence of ovarian cancer and the dearth of prior studies with detailed aspirin data, such research will likely need to pool data from both existing and new studies. To facilitate such research, new studies should strive to collect detailed, time-updated data on aspirin use, including information on the dose, frequency, duration, and timing of use. Such research may eventually inform development of preventive strategies, particularly for women at high risk of developing an ovarian malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by the Intramural Research Program of the National Cancer Institute at the National Institutes of Health (ZIA CP010128).

Cancer incidence data have been provided by the Alabama Statewide Cancer Registry, Arizona Cancer Registry, Colorado Central Cancer Registry, District of Columbia Cancer Registry, Georgia Cancer Registry, Hawaii Cancer Registry, Cancer Data Registry of Idaho, Maryland Cancer Registry, Michigan Cancer Surveillance Program, Minnesota Cancer Surveillance System, Missouri Cancer Registry, Nevada Central Cancer Registry, Ohio Cancer Incidence Surveillance System, Pennsylvania Cancer Registry, Texas Cancer Registry, Utah Cancer Registry, Virginia Cancer Registry, and Wisconsin Cancer Reporting System. All are supported in part by funds from the Center for Disease Control and Prevention, National Program for Central Registries, local states or by the National Cancer Institute, Surveillance, Epidemiology, and End Results program. The results reported here and the conclusions derived are the sole responsibility of the authors.

Abbreviations:

BMI	body mass index
BQ	baseline questionnaire
CI	confidence interval
HR	hazard ratio
IPSW	inverse probability of selection weights
PLCO	Prostate Lung Colorectal and Ovarian Cancer Screening Trial
SQX	supplemental questionnaire

References

- [1]. Zhang D, Bai B, Xi Y, Wang T, Zhao Y. Is aspirin use associated with a decreased risk of ovarian cancer? A systematic review and meta-analysis of observational studies with dose-response analysis. *Gynecol Oncol*. 2016;142:368–77. doi: 10.1016/j.ygyno.2016.04.543. Epub May 15. [PubMed: 27151430]
- [2]. Trabert B, Ness RB, Lo-Ciganic WH, Murphy MA, Goode EL, Poole EM, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst*. 2014;106:djt431. doi: 10.1093/jnci/djt431. [PubMed: 24503200]
- [3]. Trabert B, Poole EM, White E, Visvanathan K, Adami HO, Anderson GL, et al. Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium. *J Natl Cancer Inst*. 2018;31.
- [4]. Brasky TM, Liu J, White E, Peters U, Potter JD, Walter RB, et al. Non-steroidal anti-inflammatory drugs and cancer risk in women: results from the Women's Health Initiative. *Int J Cancer*. 2014;135:1869–83. doi: 10.1002/ijc.28823. Epub 2014 Mar 20. [PubMed: 24599876]
- [5]. 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. doi: 10.1002/ijc.11538. [PubMed: 14639616]

- [6]. Setiawan VW, Matsuno RK, Lurie G, Wilkens LR, Carney ME, Henderson BE, et al. Use of nonsteroidal anti-inflammatory drugs and risk of ovarian and endometrial cancer: the Multiethnic Cohort. *Cancer Epidemiol Biomarkers Prev.* 2012;21:1441–9. doi: 10.158/055-9965.EPI-12-0390-T. Epub 2012 Jun 4. [PubMed: 22665579]
- [7]. Barnard ME, Poole EM, Curhan GC, Eliassen AH, Rosner BA, Terry KL, et al. Association of Analgesic Use With Risk of Ovarian Cancer in the Nurses' Health Studies. *JAMA Oncol.* 2018;4:1675–82. doi: 10.001/jamaoncol.2018.4149. [PubMed: 30286239]
- [8]. Prizment AE, Folsom AR, Anderson KE. Nonsteroidal anti-inflammatory drugs and risk for ovarian and endometrial cancers in the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev.* 2010;19:435–42. doi: 10.1158/055-9965.EPI-09-0976. [PubMed: 20142241]
- [9]. Pinheiro SP, Tworoger SS, Cramer DW, Rosner BA, Hankinson SE. Use of nonsteroidal antiinflammatory agents and incidence of ovarian cancer in 2 large prospective cohorts. *Am J Epidemiol.* 2009;169:1378–87. doi: 10.093/aje/kwp062. Epub 2009 Apr 2. [PubMed: 19342401]
- [10]. Baandrup L, Kjaer SK, Olsen JH, Dehlendorff C, Friis S. Low-dose aspirin use and the risk of ovarian cancer in Denmark. *Ann Oncol.* 2015;26:787–92. doi: 10.1093/annonc/mdu578. Epub 2014 Dec 23. [PubMed: 25538177]
- [11]. Peres LC, Camacho F, Abbott SE, Alberg AJ, Bandera EV, Barnholtz-Sloan J, et al. Analgesic medication use and risk of epithelial ovarian cancer in African American women. *Br J Cancer.* 2016;114:819–25. doi: 10.1038/bjc.2016.39. Epub Feb 23. [PubMed: 26908324]
- [12]. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials.* 2000;21:273S–309S. [PubMed: 11189684]
- [13]. Bibbins-Domingo K Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* 2016;164:836–45. doi: 10.7326/M16-0577. Epub 2016 Apr 12. [PubMed: 27064677]
- [14]. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med.* 2018;379:1519–28. doi: 10.056/NEJMoA1803955. Epub 2018 Sep 16. [PubMed: 30221595]
- [15]. Chan AT, McNeil J. Aspirin and Cancer Prevention in the Elderly: Where Do We Go From Here? *Gastroenterology.* 2019;156:534–8. doi: 10.1053/j.gastro.2018.11.063. Epub Dec 4. [PubMed: 30529298]
- [16]. Lichtenberger LM, Vijayan KV. Are Platelets the Primary Target of Aspirin's Remarkable Anticancer Activity? *Cancer Res.* 2019;79:3820–3. doi: 10.1158/0008-5472.CAN-19-0762. Epub 2019 Jul 12. [PubMed: 31300475]

Highlights:

- Aspirin has been associated with reduced ovarian cancer risk, but it is unclear what dose and frequency of use is needed.
- We addressed this gap using detailed aspirin data and extended follow-up from the PLCO Cancer Screening Trial.
- Our prospective study (n=41,633) builds support for the hypothesis that daily, low-dose aspirin reduces ovarian cancer risk.
- These results are promising given the high case-fatality and lack of preventive interventions for ovarian cancer.

Table 1.

Demographic and clinical characteristics, by aspirin use^{*} at the time of the PLCO Supplemental Questionnaire (SQX), 2006-2007

		No aspirin use		Aspirin use		Aspirin use, by dose ^{**}				Aspirin use, by frequency				Aspirin use, by duration ^{***}	
		(n=19925)		(n=21708)		Adult strength		Low-dose		Less than daily use		Daily use		<10 years of use	
		No. (%)		No. (%)		No. (%)		No. (%)		No. (%)		No. (%)		No. (%)	
Age at SQX, years	Median (Q1-Q3)	70	(66-75)	71	(67-76)	71	(66-76)	71	(67-76)	70	(66-75)	71	(67-76)	71	(66-75)
Years between BQ and SQX	Median (Q1-Q3)	9	(7-10)	9	(7-10)	9	(7-10)	9	(8-11)	9	(7-10)	9	(8-11)	9	(7-10)
Study arm	Intervention	9947	(50)	10817	(50)	2867	(50)	7618	(50)	3087	(50)	7730	(50)	7247	(50)
	Control	9978	(50)	10891	(50)	2868	(50)	7666	(50)	3144	(50)	7747	(50)	7323	(50)
Race	Non-Hispanic White	17397	(87)	19533	(90)	5197	(91)	13756	(90)	5522	(89)	14011	(91)	13021	(89)
	Non-White	2528	(13)	2175	(10)	538	(9)	1528	(10)	709	(11)	1466	(9)	1549	(11)
BMI at SQX, kg/m ²	<25	8624	(43)	8468	(39)	2124	(37)	6070	(40)	2665	(43)	5803	(37)	5709	(39)
	25->30	6784	(34)	7770	(36)	2013	(35)	5519	(36)	2193	(35)	5577	(36)	5230	(36)
	30	4517	(23)	5470	(25)	1598	(28)	3695	(24)	1373	(22)	4097	(26)	3631	(25)
Duration of oral contraceptive use	None	8579	(43)	9565	(44)	2574	(45)	6686	(44)	2713	(44)	6852	(44)	6265	(43)
	5 years	6896	(35)	7188	(33)	1863	(32)	5080	(33)	2101	(34)	5087	(33)	4934	(34)
	>5 years	4450	(22)	4955	(23)	1298	(23)	3518	(23)	1417	(23)	3538	(23)	3371	(23)
Hormone replacement therapy	Never	6195	(31)	6288	(29)	1829	(32)	4245	(28)	1863	(30)	4425	(29)	4152	(28)
	Ever	13730	(69)	15420	(71)	3906	(68)	11039	(72)	4368	(70)	11052	(71)	10418	(72)
Parity	No live births	1868	(9)	1866	(9)	473	(8)	1326	(9)	521	(8)	1345	(9)	1247	(9)
	1 live birth	18057	(91)	19842	(91)	5262	(92)	13958	(91)	5710	(92)	14132	(91)	13323	(91)
History of heart attack or stroke	No	18952	(95)	19256	(89)	4937	(86)	13712	(90)	5880	(94)	13376	(86)	13047	(90)
	Yes	973	(5)	2452	(11)	798	(14)	1572	(10)	351	(6)	2101	(14)	1523	(10)

SQX, supplemental questionnaire; BQ, baseline questionnaire; SD, standard deviation; BMI, body mass index

* Defined as use 1 time/week

** Excludes 689 aspirin users missing data on dose

*** Excludes 249 aspirin users missing data on duration

Table 2.

Associations between aspirin use* at the time of the PLCO Supplemental Questionnaire (SQX), 2006-2007, and ovarian cancer risk

	Overall study population				Age <70 at SQX				Age ≥70 at SQX			
	Events	Person-years	HR**	95% CI	Events	Person-years	HR**	95% CI	Events	Person-years	HR**	95% CI
No/infrequent aspirin use	110	144287	1.00	(ref)	56	72485	1.00	(ref)	54	71802	1.00	(ref)
Aspirin use ≥1 time/week	113	156179	0.93	(0.72-1.21)	45	67440	0.84	(0.57-1.25)	68	88739	1.02	(0.71-1.45)
By dose***												
Adult-strength	32	40672	1.03	(0.69-1.52)	12	17732	0.87	(0.47-1.62)	20	22940	1.17	(0.7-1.95)
Low-dose	76	110590	0.88	(0.66-1.18)	30	47586	0.79	(0.51-1.24)	46	63004	0.97	(0.65-1.43)
By frequency of use												
1-6 times/week	32	45300	0.92	(0.62-1.36)	21	21316	1.26	(0.76-2.08)	11	23984	0.61	(0.32-1.16)
7+ times/week	81	110879	0.94	(0.70-1.25)	24	46124	0.65	(0.40-1.05)	57	64755	1.17	(0.8-1.7)
By duration of use****												
<10 years	83	105675	1.02	(0.76-1.35)	34	48975	0.88	(0.58-1.35)	49	56700	1.15	(0.78-1.69)
≥10 years	29	48819	0.75	(0.50-1.13)	10	17937	0.69	(0.35-1.35)	19	30882	0.81	(0.48-1.37)
By dose and frequency****												
Adult-strength, 1-6 times/week	12	17034	0.92	(0.51-1.67)	6	8146	0.95	(0.41-2.21)	6	8888	0.89	(0.38-2.07)
Adult-strength, 7+ times/week	20	23638	1.10	(0.68-1.78)	6	9586	0.80	(0.34-1.85)	14	14052	1.35	(0.75-2.43)
Low-dose, 1-6 times/week	17	26227	0.84	(0.50-1.39)	12	12310	1.23	(0.66-2.29)	5	13917	0.48	(0.19-1.19)
Low-dose, 7+ times/week	59	84363	0.90	(0.65-1.23)	18	35276	0.64	(0.38-1.09)	41	49087	1.11	(0.74-1.66)

SQX, supplemental questionnaire; HR, hazard ratio; CI, confidence interval

* Defined as use ≥1 time/week

** Adjusted for study arm, race, BMI, oral contraceptive use, hormone replacement therapy, parity

*** Excludes 689 aspirin users missing data on dose

**** Excludes 249 aspirin users missing data on duration