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Aspirin Use and the Incidence of Breast, Colon, Ovarian and Pancreatic Cancers in elderly women in the Iowa Women's Health Study

Lisa E. Vaughan¹, Anna Prizment^{2,3}, Cindy K. Blair^{4,5}, William Thomas¹, and Kristin E. Anderson^{2,3}

¹Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota

²Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota

³Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota

⁴Department of Internal Medicine, University of New Mexico, Albuquerque, NM

⁵University of New Mexico Comprehensive Cancer Center, Albuquerque, NM

Introduction

In the U.S., 53% of cancers occur among individuals aged ≥ 65 years [1]. Eight percent of new cancers affect the oldest people (age 85+), a group expected to triple in size by 2040 [2, 3]. Overall, cancer incidence increases with age; rates generally peak and then decline between 75–90 years [4]. Cancer etiology and prevention in the elderly is relatively unexplored.

Both observational studies and randomized trials have found inverse associations between aspirin use and incidence of several site-specific cancers, as well as overall cancer incidence and mortality [5–15]. However, due to concerns about side effects, there have been limited general recommendations for widespread aspirin use for chemoprevention [13, 16]. Currently, the United States Preventive Services Task Force is the only major American organization that has issued a broad recommendation to take aspirin to prevent a form of cancer, finding that the benefits of aspirin to prevent colorectal cancer outweighed the risks in adults aged 50 to 69; recommendations were less definitive for older adults aged 70–79, since the risk of harmful bleeding due to aspirin use increases with age [17]. Aspirin use and cancer prevention in the elderly is particularly relevant given that the U.S. Preventive Services Task Force does not recommend mammography screening beyond age 74 years or routine colorectal screening over age 75 years [18, 19]. The incidence of these cancers is high at older ages and, thus reducing incidence could lower treatment costs and associated comorbidities. US preventive services concluded that the “current evidence is insufficient to

assess the balance of benefits and harms of initiating aspirin use for the primary prevention of cardiovascular disease and colorectal in adults aged 70 years or older” [17]. Therefore, more data on aspirin use in the elderly are needed, since older adults have not been included in aspirin trials and the risk-benefit profiles from trials in younger adults may not generalize to the elderly [20]. Additional data on the effective frequency, dose and duration are also needed, particularly among elderly women [16, 21, 22].

The Iowa Women’s Health Study (IWHS) is one of the few prospective, population-based studies to evaluate risk factors for incident cancers in a large sample of elderly women (aged 70 years and older). The IWHS has collected data on aspirin frequency, duration and dose, and thus, can address gaps about aspirin use and cancer outcomes in this population, which could be useful in informing risk-benefit decisions and cost-effectiveness analyses for recommended aspirin use in the elderly. In this IWHS analysis, we examined the patterns of aspirin use by elderly women (aged 73–87 years) and assessed whether or not aspirin use reduced the incidence of breast, colon, pancreatic and ovarian cancers. We focused on these cancers because aspirin use was associated with the risk of these cancers in earlier studies in this cohort in the postmenopausal women aged 61–75 years [6–9, 11–12, 28, 35], and supported by meta-analyses [5, 15, 18, 22, 27, 29–31].

Materials and Methods

The rationale and design of the IWHS have been presented elsewhere [23]. In 1986, a questionnaire was distributed to 98,030 women aged 55–69 who had been randomly selected from the Iowa driver’s license list. Those who completed a mailed questionnaire, 41,836 (42.7%), were enrolled in the cohort. Five subsequent questionnaires were mailed for follow-up from 1986–2004, with high response rates. The questionnaires asked about lifestyle behaviors, sociodemographic factors, medical histories, and anthropomorphic measures. Age, height, level of education and pack years of smoking were obtained at baseline, while smoking status, hormone replacement therapy (HRT) use and diabetes were reported at baseline and at each follow-up. Weight, calcium use, multivitamin use, level of physical activity, and diet - via a food frequency questionnaire - were obtained from follow-up in 2004. Diet quality scores were calculated as the sum of adherence (0=non-adherent, 0.5=partially adherent, 1=adherent) to the World Cancer Research Fund/American Institute for Cancer Research dietary recommendations for cancer prevention [24], which included six indicators: avoid high-sugar beverages; high fruit and vegetable intake, and dietary fiber intake; and limited consumption of red and processed meat, alcohol, and sodium [25].

The aim for this analysis, using data from 2004, was to characterize patterns of aspirin use in elderly women aged 73–87 years and examine associations with cancer incidence through 2011. The 2004 questionnaire included specific questions on the frequency, dose and duration of use for aspirin (e.g., Bufferin, Anacin, and enteric-coated aspirin) and other NSAIDs (e.g., Ibuprofen, Advil, Nuprin and Motrin), and reasons for use and avoidance of these drugs. Both questions specifically directed respondents to exclude use of Acetaminophen, Tylenol, Prednisone and Cortisone. The categories for frequency of use for both questions were: (a) nonusers; and current users with a frequency of (b) less than once per week; (c) once per week; (d) 2–5 times per week; (e) 6–7 times per week; (f) 8–14 times

per week; and (g) 15 or more times per week [7]. Categories for the number of years on each medication were (a) less than 1; (b) 1–4; (c) 5–9; (d) 10–19; (e) 20–39; and (f) 30 or more years. Possible doses of each medication were (a) low dose/children's/baby (81 mg); (b) regular (325 mg); and (c) extra strength (650 mg) for the aspirin-product group and (a) regular or (b) extra strength for the other NSAIDs group.

To more fully capture and integrate information regarding aspirin usage patterns for these women, the individual measures of exposure levels of these drugs – dose, duration and frequency – were combined to develop overall metrics to estimate aspirin use. An additional metric, “aspirin dose per year,” was calculated as the product of dose (mg) with median frequency of aspirin use. The following medians were used for frequency of aspirin use based on the categories listed above: (a) 0; (b) 0.5; (c) 1; (d) 3.5; (e) 6.5; (f) 11 and (g) 15. Similarly, “lifetime aspirin dose” was the sum of “aspirin dose per year” for the duration of use: (a) 0.5; (b) 2.5; (c) 7; (d) 14.5; (e) 29.5 and (f) 40. Women who responded that they never took aspirin were assigned an aspirin dose of “0” mg and a “0” years duration. We conducted separate analyses using aspirin dose per year and lifetime aspirin dose (both were categorized into quartiles).

Cancer incidence among this cohort through 2011 was obtained by linking to the State Health Registry of Iowa, which is part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program [1]. Cancer mortality through 2011 was ascertained through the National Death Index. Follow-up survey data indicated that the migration rate from Iowa among cohort members is <1% annually, allowing nearly complete follow-up for cancer incidence [26]. The primary focus was incidence of cancers that were shown to have the strongest inverse association with aspirin use among younger women in this and other cohorts which included first primaries of breast [8, 11, 21, 27], colon [15, 21, 27, 28], ovarian [12, 29, 30] or pancreatic cancer [6, 31] (hereafter, called aspirin-sensitive cancers). In the additional analysis, we used underlying cause of death to study death from all cancers as the endpoint.

Of the 41,836 women in the IWHs cohort in 1986, we excluded from analysis 20,992 who either died (n=11,739) before 2004, did not complete the 2004 questionnaire or were lost to follow up. Also excluded were women who had a cancer diagnosis other than non-melanoma skin cancer at baseline (n=1,511) or between baseline and 2005 (n=3,207), were no longer living in Iowa in 2004 (n=1,295) or whose response was inconsistent and thus deemed unreliable (aspirin frequency of use = never or left blank, but answered the dose or duration question (n=445)). This left 14,386 women with a total of 91,829 person-years of follow-up for analysis. This study was approved by the Institutional Review Board.

Statistical Analysis

Demographic characteristics were compared between groups using analysis of variance for continuous data and chi-square tests for categorical data. Two nested Cox proportional hazard models were used to test the association between metrics of aspirin use and incident aspirin-sensitive cancers. Model 1 included only age (continuous) as an adjusting covariate. Model 2 included age, BMI (continuous), smoking (ever vs never) and frequency of non-aspirin NSAIDs use (non-user, 1 time/week, 2–5 times/week, 6+ times/week). Women

were treated as censored at date of last follow-up, death, or non-aspirin sensitive cancer diagnosis, whichever occurred first. Parallel analyses compared categories of each aspirin metric (frequency, dose and duration), aspirin dose per year and lifetime aspirin dose.

Hazard ratios (HR) and confidence intervals (CI) were reported by level for the individual aspirin metrics and by quartile for the cumulative aspirin metrics. All P-values were derived using Wald tests to assess trends across the hazard ratios. The proportional hazards assumption was assessed for each model using chi-square tests and graphs derived from the scaled Schoenfeld residuals, and found to hold for all models. Additional analyses separately stratified by history of heart disease and used the endpoint of death from any cancer. Using a Cox proportional hazard model with adjustment for age and a 2-sided alpha level of 0.05, there was 80% power to detect a true HR of 0.72 or less between the highest quartile of aspirin users and non-users of aspirin.

A sensitivity analysis was conducted by restricting to consistent long-term users of aspirin based on a comparison of data from 1992, when frequency of aspirin use was first queried, and 2004. Additional sensitivity analyses were performed by excluding women who reported both using aspirin and reasons for avoiding aspirin in the 2004 data, as well as separately examining women with incident breast, pancreatic or ovarian cancer and colon cancer. All analyses were performed using R 3.0.2 [32, 33, 34].

Results

Among the 14,386 women (mean age 78.6 years, range 73–87) in our analytical cohort, 4,180 (30%) reported never using aspirin, 4,817 (34%) reported using low dose aspirin, and 5,083 (36%) reported using regular or high dose aspirin. A total of 719 aspirin-sensitive cancer cases were identified, of which 394 were breast, 222 were colon, 54 were pancreatic and 49 were ovarian cancers. Among these invasive cancers, the percentages with localized, regional, and distant stage of disease were 49%, 24%, and 14%, respectively. Select patient characteristics are reported in Table 1. Low-dose aspirin users were substantially more likely to have a higher diet quality score, and report multivitamin use, a higher level of physical activity, and a history of HRT use.

Among women who reported they did not use aspirin, the most common reason given for avoiding aspirin was because of other drugs taken (27%), followed by unpleasant side effects (12%), medical reasons (12%), other (10%), and religious or personal beliefs (1%). Forty four percent of non-users did not give a reason for avoiding aspirin. Among women who did report taking aspirin, the most frequent reason for reported use was for heart issues, in the regular/high dose group and especially the low-dose group.

After multivariable adjustment (Model 2), there was an indication of an inverse association between all metrics of aspirin use and cancer incidence, although trends were statistically non-significant (Table 2). Compared with aspirin nonusers, the HRs of incident aspirin-sensitive cancer for women who reported using aspirin 6+ times per week, using aspirin for 10+ years, and using a regular to high dose of aspirin were 0.95 (95% CI, 0.80–1.13), 0.93 (95% CI, 0.74–1.17) and 0.87 (95% CI, 0.72–1.06), respectively (Table 2). Using the

combined aspirin usage measures, compared to nonusers the HRs of incident aspirin-sensitive cancer for women who took >60,000 mg of aspirin per year and >280,000 mg of aspirin in their lifetime were 0.87 (95% CI, 0.70–1.09) and 0.95 (95% CI, 0.75–1.21), respectively. The inverse association was stronger for breast, pancreatic or ovarian cancer incidence; results were attenuated for colon cancer incidence (Supplemental Table 2). Results were similar after stratification by history of heart disease, with no evidence for effect modification (p-values ranged from 0.10–0.48 for the various aspirin metrics in the multivariable analysis) (Supplemental Table 3).

After excluding women who reported both using aspirin and reasons for avoiding aspirin in the 2004 questionnaire (N=791), HR estimates decreased in the group of women who used aspirin once per week or less (HR=0.79; 95% CI, 0.59–1.06). This suggests that the excluded women were infrequent users of low-dose aspirin for a short-duration; indeed, 83% of the women who were excluded and responded to all 3 individual aspirin metric questions reported using aspirin either <1/week, taking low dose aspirin, or taking aspirin for <1 year. No appreciable changes were observed in risk estimates after excluding women who reported regular aspirin use (defined as 2 or more times/week) in 1992, but reported not using aspirin in 2004.

Importantly, results were consistent when using death from any type of cancer as an endpoint (Supplemental Table 1), with HRs trending slightly lower than those for incident aspirin-sensitive cancers and a significant inverse association observed between lifetime aspirin dose and cancer mortality (<95,000 mg vs non-user HR=0.76; 95% CI, 0.61–0.95).

Discussion

In our study, we observed an overall pattern of reduced risk of incident aspirin-sensitive cancers with intake of aspirin using various metrics of dose, duration and frequency in elderly women over 7 years of follow-up. A protective effect was also shown for cancer mortality, with the strongest association observed using a cumulative lifetime dose aspirin metric.

Many studies, including previous studies in the IWHS cohort [6–8, 11, 30], have reported a benefit of aspirin use in middle-aged adults. Thus, with continued follow-up, more definitive evidence of inverse associations with cancer incidence may be seen in this study. The ability to detect an association between aspirin use and cancer was not an initial aim of the IWHS; thus, detailed information on aspirin usage patterns were only collected in 2004. Previous IWHS analyses, based on frequency of use, have reported inverse associations between frequent aspirin users (6+ times/week) and incident cancer of the breast (HR=0.72; 95% CI, 0.61–0.84), ovaries, (HR=0.61; 95% CI, 0.37–0.99), pancreas (HR=0.40; 95% CI, 0.20–0.82), and colon (HR=0.76; 95% CI, 0.58–1.00) compared to nonusers; however, women in these studies were 61–75 years old at the start of follow-up, and aspirin dose and duration measures were not available from that questionnaire [7, 30].

The findings of a reduced risk for several types of cancer among middle-aged adult aspirin users are supported by several meta-analyses [15, 27, 29–31]. Frequent aspirin use (6+

times/week) was associated with reduced pancreatic cancer incidence (OR=0.57; 95% CI, 0.39–0.83) [31]. The meta-analysis of all cancer types by Bosetti et al. (2012) reported reduced risks of both colorectal cancer and breast cancer for regular aspirin use vs nonuse of RR=0.73 (95% CI, 0.67–0.79) and RR=0.90 (95% CI, 0.85–0.95), respectively [27]. However, results were heterogeneous across studies and included all ages; moreover, dose-risk and duration-risk were not clearly elucidated. In other meta-analyses, regular aspirin use, compared to non-regular use, was associated with a significantly reduced risk of invasive ovarian cancer (RR=0.88; 95% CI, 0.79–0.98) [30], and colorectal cancer (RR=0.81; 95% CI, 0.75–0.88) [15]. The meta-analysis by Algra et al. (2012) included randomized studies; they found that the 20-year risk of death due to colorectal cancer was reduced in patients who used aspirin daily (OR=0.58; 95% CI, 0.44–0.78). However, due to the limited number of women enrolled in the randomized trials, estimates of the effect of aspirin use on cancers such as breast and ovarian could not be reliably obtained [22]. Although several meta-analyses included adults over 70 years of age as part of their analyses, none specifically investigated the associations in this older age group. Thus, to build evidence-based research data to inform policy on the use of aspirin in adults aged 70 years and older, additional studies of aspirin use, specifically, in this age group are needed.

As a relatively healthy 80-year old woman has 8–10 years of remaining life [33], the high incidence rates of cancer during those years and the high cost of treatment underscore the need for research to identify preventive factors. The ongoing ASPREE trial will assess effects of aspirin use in adults aged ≥ 65 years, but results (for just a single dosage) will not be available until 2018 [34]. Importantly, the IWHS cohort is more representative of the overall population than clinical trials. Moreover, unlike numerous aspirin trials, IWHS was specifically designed to assess cancer incidence.

One of the limitations of this analysis was low power to detect small effects. We would have needed 13,234 events in our sample in order to achieve 80% power to detect a hazard ratio of 0.95 such as we found between the highest quartile of lifetime aspirin dose and non-users (Table 2). In this analysis, we aimed to evaluate whether or not there was a moderate to large effect of aspirin use on incident cancers; studies with larger sample sizes and longer follow-up time are needed to evaluate potential small to modest effects. The findings from our study can contribute to the future meta-analyses.

Another limitation is the potential selection bias in our cohort. The elderly women who responded to the 2004 survey tended to be healthier than non-responders [36]. Therefore, it is possible that the women who were included in our study may benefit less from aspirin compared to the women who, for example, had systemic or other types of inflammation or cardiovascular disease by 2004 and did not respond to the survey.

In summary, this study indicates that aspirin use in elderly women may provide prophylactic benefit with respect to incident breast, colon, pancreatic and ovarian cancers. These findings require confirmation in further research. In the future, participants in the IWHS cohort could be linked to outcomes in the Centers for Medicare & Medicaid Services (CMS) database that includes cardiovascular disease events and gastrointestinal bleeding, thus allowing for analyses of the potential benefits versus risks of aspirin use in this age group. To our

knowledge, no other studies have evaluated aspirin use and incident cancer in elderly women over 70 years. Reducing cancer incidence with aspirin could lower costs and associated comorbidities, which is particularly important in the elderly in the absence of screening and the underrepresentation in cancer trials of individuals 65 years of age or older [20]. Studying aspirin use in the prevention of colon, pancreatic, breast and ovarian cancers is significant because inexpensive, safe strategies are needed to maintain health, enhance quality of life and reduce medical interventions in the elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Howlader, N.; Noone, AM.; Krepcho, M., et al. [Accessed 11 April 2016] SEER Cancer Statistics Review, 1975–2010. National Cancer Institute. 2013. http://seer.cancer.gov/csr/1975_2010/
- Administration on Aging. A profile of older Americans: 2012. U.S. Department of Health and Human Services; 2012.
- Suzman, R.; Willis, DP., editors. Introducing the Oldest Old. New York: Oxford University Press; 1992.
- Harding C, Pompei F, Wilson R. Peak and decline in cancer incidence, mortality, and prevalence at old ages. *Cancer*. 2009; 118(5):1371–1386.
- Rothwell PM, Fowkes GR, Belch JFF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet*. 2011; 377(9759):31–41. [PubMed: 21144578]
- Anderson KE, Johnson TW, Lazovich D, Folsom AR. Association Between Nonsteroidal Anti-Inflammatory Drug Use and the Incidence of Pancreatic Cancer. *J Natl Cancer Inst*. 2002; 94(15): 1168–1171. [PubMed: 12165642]
- Bardia A, Ebbert JO, Vierkant RA, et al. Association of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs with cancer incidence and mortality. *J Natl Cancer Inst*. 2007; 99(11):881–889. [PubMed: 17551148]
- Bardia A, Olson JE, Vachon CM, et al. Effect of aspirin and other NSAIDs on postmenopausal breast cancer incidence by hormone receptor status: results from a prospective cohort study. *Breast Cancer Res Treat*. 2011; 126(1):149–155. [PubMed: 20669045]
- Cerhan JR, Anderson KE, Janney CA, Vachon CM, Witzig TE, Habermann TM. Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma. *Int J Cancer*. 2003; 106(5):784–788. [PubMed: 12866040]
- Jacobs EJ. Will an aspirin a day help keep fatal cancer away? *Lancet*. 2011; 377(9759):3–4. [PubMed: 21195237]
- Johnson TW, Anderson KE, Lazovich D, Folsom AR. Association of aspirin and nonsteroidal anti-inflammatory drug use with breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2002; 11(12): 1586–1591. [PubMed: 12496048]
- 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(2):435–442. [PubMed: 20142241]
- Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. *Nat Rev Clin Oncol*. 2012; 9(5):259–267. [PubMed: 22473097]

14. Rose S. A role for aspirin in cancer prevention? *Cancer Discov.* 2013; 3(12):1324. [PubMed: 24327682]
15. Cao Y, Nishihara R, Wu K, et al. Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer. *JAMA Oncol.* 2016
16. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics-2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2006; 113(6):e85–e151. [PubMed: 16407573]
17. Chubak J, Whitlock EP, Williams SB, et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2016 [Epub ahead of print].
18. Rothwell PM, Price JF, Fowkes GR, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet.* 2012; 379(9826):1602–1612. [PubMed: 22440946]
19. USPSTF. U.S. Preventive Service Task Force. Screening for Colorectal Cancer. Current Recommendation. 2008 [Accessed 1.12.2014] <http://www.uspreventiveservicestaskforce.org/uspstf/uspscolo.htm>.
20. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med.* 1999; 341:2061–2067. [PubMed: 10615079]
21. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet Oncol.* 2009; 10(5):501–507. [PubMed: 19410194]
22. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol.* 2012; 13(5):518–527. [PubMed: 22440112]
23. Bisgard KM, Folsom AR, Hong CP, Sellers TA. Mortality and cancer rates in nonrespondents to a prospective study of older women: 5- year follow-up. *Am J Epidemiol.* 1994; (139):990–1000. [PubMed: 8178787]
24. WCRF/AICR. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: World Cancer Research Fund/American Institute for Cancer Research; 2007.
25. Inoue-Choi M, Ward MH, Cerhan JR, Weyer PH, Anderson KE, Robien K. Adherence to the WCRF/AICR guidelines for cancer prevention is associated with lower mortality among older female cancer survivors. *Cancer Epidemiol Biomarkers Prev.* 2013; 22(5):792–802. [PubMed: 23462914]
26. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. The Iowa Women's Health Study. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. *Cancer.* 1995; 76:275–283. [PubMed: 8625103]
27. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol.* 2012; 23(6):1403–1415. [PubMed: 22517822]
28. Mahipal A, Anderson KE, Limburg PJ, Folsom AR. Nonsteroidal Anti-inflammatory Drugs and Subsite-Specific Colorectal Cancer Incidence in the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(10):1785–1790. [PubMed: 17035383]
29. Trabert B, Ness RB, Lo-Ciganic W, et al. Aspirin, non-aspirin 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(2)
30. Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand.* 2013; 92(3):245–255. [PubMed: 23240575]
31. Zhang YP, Wan YD, Sun YL, Li J, Zhu RT. Aspirin might reduce the incidence of pancreatic cancer: A meta-analysis of observational studies. *Sci Rep.* 2015; 5:15460. [PubMed: 26486090]
32. Qiu W, Chavarro J, Lazarus R, Rosner B, Ma J. powerSurvEpi: Power and sample size calculation for survival analysis of epidemiological studies. R package version 0.0.6. 2012 <http://CRAN.R-project.org/package=powerSurvEpi>.

33. R Core Team. R Foundation for Statistical Computing. Vienna, Austria: 2013. R: A language and environment for statistical computing. ISBN 3-900051-07-0, URL <http://www.R-project.org/>
34. Therneau T, Lumley T. A package for Survival Analysis in S. R package version 2.37-7. 2014 <http://CRAN.R-project.org/package=survival>.
35. Bardia A, Keenan TE, Ebbert JO, et al. Personalizing Aspirin Use for Targeted Breast Cancer Chemoprevention in Postmenopausal Women. Mayo Clin Proc. 2015; 91(1):71–80. [PubMed: 26678006]
36. USPSTF. U.S. Preventive Service Task Force. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Preventive Medication. Final Update Summary. 2016 [Accessed 4.15.2016] <http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer?ds=1&s=aspirin>.
37. Cho H, Klabunde C, Yabroff KR, et al. Comorbidity-adjusted life expectancy: a new tool to inform recommendations for optimal screening strategies. Ann Intern Med. 2013; 159:667–676. [PubMed: 24247672]
38. ASPREE Investigator Group. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. Contemp Clin Trials. 2013; 36:555–564. [PubMed: 24113028]
39. Lazovich D, Robien K, Cutler G, Virnig B, Sweeney C. Quality of Life in a Prospective Cohort of Elderly Women With and Without Cancer. Cancer. 2009; 115(18 suppl):4283–4297. [PubMed: 19731348]

Table 1

Participant characteristics by frequency of aspirin use, IWHS 2004

Patient Characteristic	Aspirin Dose ^a		
	Non-User	Low Dose	Regular/High Dose
Prevalence of use ^b , n (%)	4180(30%)	4817(34%)	5038(36%)
Age in 2004 (y) ^c , mean(SD)	78.8(4.0)	78.5(3.9)	78.6(4.0)
Obese (BMI ≥ 30 kg/m ²) ^e , n (%)	706(17%)	744(16%)	872(18%)
Education ^c , n (%)			
<HS	635(15%)	684(14%)	839(17%)
High school graduate	1777(43%)	2021(42%)	2147(43%)
Some college +	1765(42%)	2105(44%)	2041(41%)
Pack years of smoking ^c , mean(SD)	6.2(14.1)	6.6(14.4)	6.5(14.1)
History of smoking ^{c,g} , n (%)	1144(28%)	1346(28%)	1416(29%)
Calcium (mg) ^b , mean(SD)	845(476)	879(494)	842(494)
Diet quality score ^b , mean(SD)	45.9(10.3)	47.3(10.3)	46.3(9.9)
Diet quality score (tertiles) ^b , mean(SD)			
42	1367(37%)	1366(32%)	1540(35%)
(42,50]	1130(31%)	1349(31%)	1381(31%)
>50	1198(32%)	1623(37%)	1496(34%)
Multivitamin Use ^b , n (%)	2414(60%)	3229(69%)	2980(61%)
Level of physical activity ^b , n (%)			
Low	2101(51%)	2026(42%)	2338(47%)
Medium	1094(26%)	1428(30%)	1464(29%)
High	969(23%)	1347(28%)	1226(24%)
History of HRT use ^f , n (%)	1988(48%)	2525(52%)	2413(48%)
History of Diabetes ^f , n (%)	578(14%)	773(16%)	752(15%)
Reason for aspirin use ^{bd} , n (%)			
Headaches	NA	209(4%)	1107(22%)
Body aches/pains, arthritis	NA	621(13%)	2246(45%)
Heart issues	NA	4172(87%)	2721(54%)
Other	NA	397(8%)	446(9%)
Avoid aspirin use ^{bd} , n (%)			
Unpleasant side effects	515(12%)	NA	NA
Because of other drugs taken	1109(27%)	NA	NA
Medical reasons	480(12%)	NA	NA
Religious or personal beliefs	23(1%)	NA	NA
Other	409(10%)	NA	NA
Unknown	1821(44%)	NA	NA

Abbreviations: HRT, hormone replacement therapy

^aLow dose=81 mg; regular dose=325mg; high dose= 650mg

^bReported in 2004

^cReported at baseline (1986)

^dFor these questions, participants were instructed to select all that apply

^eWeight reported in 2004; height reported at baseline (1986)

^fReported up to 2004

^gHistory of smoking: never vs current or former smoker

Table 2

Age- and multivariable-adjusted associations between self-reported aspirin frequency, duration, and dose and incident aspirin-sensitive cancers, IWHs 2004–2011^a

Aspirin Metric	No. cancer cases	Model 1 HR (95% CI) ^b	Model 2 HR (95% CI) ^c
Dose			
Non-users	209	1.00 (reference)	1.00 (reference)
Low dose ^d	257	1.03 (0.86–1.24)	1.01 (0.84–1.22)
Regular/high dose ^d	242	0.94 (0.78–1.13)	0.87 (0.72–1.06)
	<i>Total: 708</i>	<i>P_{trend}=0.47</i>	<i>P_{trend}=0.15</i>
Frequency			
Non-users	209	1.00 (reference)	1.00 (reference)
1 time/week	88	0.92 (0.71–1.17)	0.87 (0.67–1.13)
2–5 times/week	71	0.99 (0.76–1.30)	0.94 (0.71–1.24)
6 times/week	344	0.99 (0.84–1.18)	0.95 (0.80–1.13)
	<i>Total: 712</i>	<i>P_{trend}=0.91</i>	<i>P_{trend}=0.71</i>
Duration			
Non-users	209	1.00 (reference)	1.00 (reference)
<5 years	257	0.99 (0.82–1.18)	0.96 (0.80–1.16)
5–9 years	112	0.98 (0.78–1.23)	0.88 (0.69–1.12)
10 years	125	0.97 (0.78–1.21)	0.93 (0.74–1.17)
	<i>Total: 703</i>	<i>P_{trend}=0.79</i>	<i>P_{trend}=0.39</i>
Aspirin dose per year (quartiles)			
Non-user	209	1.00 (reference)	1.00 (reference)
0<–25,000 mg	121	0.99 (0.80–1.24)	0.94 (0.74–1.18)
25,001<–60,000 mg	234	0.99 (0.82–1.20)	0.99 (0.81–1.19)
>60,000 mg	144	0.96 (0.78–1.19)	0.87 (0.70–1.09)
	<i>Total: 708</i>	<i>P_{trend}=0.75</i>	<i>P_{trend}=0.35</i>
Lifetime aspirin dose (quartiles)			
Non-user	209	1.00 (reference)	1.00 (reference)
0<–95,000 mg	203	1.01 (0.83–1.22)	0.99 (0.81–1.20)
95,000<–280,000 mg	131	1.00 (0.81–1.25)	0.95 (0.76–1.19)
>280,000 mg	116	1.03 (0.82–1.30)	0.95 (0.75–1.21)
	<i>Total: 659</i>	<i>P_{trend}=0.82</i>	<i>P_{trend}=0.59</i>

^a Aspirin sensitive cancers included breast, colon or rectal, ovarian and pancreatic cancer.

^b Adjusted for age

^c Adjusted for age, smoking, BMI, and non-aspirin NSAIDs use.

^d Low dose=81 mg; regular dose=325mg; high dose= 650mg