3-1-2021

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OXFORD

JNCI J Natl Cancer Inst (2021) 113(3): djaa114

doi: 10.1093/jnci/djaa114
First published online August 11, 2020
Article

Effect of Aspirin on Cancer Incidence and Mortality in Older Adults

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ARTICLE

Abstract

Background: ASPirin in Reducing Events in the Elderly, a randomized, double-blind, placebo-controlled trial of daily low-dose aspirin (100 mg) in older adults, showed an increase in all-cause mortality, primarily due to cancer. In contrast, prior randomized controlled trials, mainly involving younger individuals, demonstrated a delayed cancer benefit with aspirin. We now report a detailed analysis of cancer incidence and mortality. **Methods:** 19 114 Australian and US community-dwelling participants aged 70 years and older (US minorities 65 years and older) without cardiovascular disease, dementia, or physical disability were randomly assigned and followed for a median of 4.7 years. Fatal and nonfatal cancer events, a prespecified secondary endpoint, were adjudicated based on clinical records. **Results:** 981 cancer events occurred in the aspirin and 952 in the placebo groups. There was no statistically significant difference between groups for all incident cancers (hazard ratio [HR] = 1.04, 95% confidence interval [CI] = 0.95 to 1.14), hematological cancer (HR = 0.98, 95% CI = 0.73 to 1.30), or all solid cancers (HR = 1.05, 95% CI = 0.95 to 1.15), including by specific tumor type. However, aspirin was associated with an increased risk of incident cancer that had metastasized (HR = 1.19, 95% CI = 1.00 to 1.43) or was stage 4 at diagnosis (HR = 1.22, 95% CI = 1.02 to 1.45), and with higher risk of death for cancers that presented at stages 3 (HR = 2.11, 95% CI = 1.03 to 4.33) or 4 (HR = 1.31, 95% CI = 1.04 to 1.64). **Conclusions:** In older adults, aspirin treatment had an adverse effect on later stages of cancer evolution. These findings suggest that in older persons, aspirin may accelerate the progression of cancer and, thus, suggest caution with its use in this age group.

Received: March 9, 2020; **Revised:** June 22, 2020; **Accepted:** July 30, 2020

The ASPirin in Reducing Events in the Elderly (ASPREE) was a randomized controlled trial (RCT) comparing daily low-dose aspirin (100 mg) vs placebo in 19 114 Australian and US adults aged 70 years or older (or aged 65 years or older among US African Americans and Hispanics) who were free of known cardiovascular disease, dementia, or physical disability at trial entry (1,2). We recently reported that ASPREE participants randomized to aspirin experienced higher all-cause mortality (3). This became evident at 3 years postrandomization and was largely attributable to death from cancer.

This finding was unexpected in the context of results from prior RCTs and meta-analyses (4–6). Generally, these studies, conducted in a younger average age group, reported that aspirin did not affect the short-term risk of cancer although Rothwell et al. (7) recently reported an increase in cancer incidence during the early years of follow-up among older trial participants. With more prolonged follow-up, participants randomized to daily aspirin had a reduced risk of incident cancer and death from cancer, particularly colorectal cancer (7,8). This led the US Preventive Services Task Force in 2016 to recommend low-dose aspirin for primary prevention of cardiovascular events and colorectal cancer among US adults aged 50-59 years with a greater than 10% 10-year risk of a cardiovascular event (9). However, this advice did not extend to adults aged 70 years and older where the evidence was considered insufficient (9).

The present report now provides a more detailed analysis of the effect of aspirin on cancer incidence and mortality occurring in the ASPREE participants with the aim of better understanding the findings and implications of the study.

Methods

Trial Design

Details of the ASPREE trial have been described elsewhere (Trial Registration No.: ASPREE ClinicalTrials.gov No. NCT01038583) (1,2). From March 2010 through December 2014, a total of 19 114 participants across Australia (n = 16 703) and the United States (n = 2411) gave written informed consent and were randomly assigned to receive daily 100 mg of enteric-coated aspirin (n = 9525) or matching placebo (n = 9589). A previous history of cancer was not an exclusion criterion and was present in 19% of those randomly assigned. However, all participants were required to be in good health and free of major diseases and expected to survive for at least 5 years (details of follow-up and compliance in Supplementary Methods, available online) (10).

Ascertainment of Cancer Outcomes

Fatal and nonfatal cancers occurring during the randomized treatment phase were a prespecified secondary endpoint. Detailed clinical records, including histopathology reports, were sought from treating practitioners and health-care institutions when evidence of a new or recurrent cancer was recorded, or after a participant had died. If available, TNM staging and histological grading were also collected. When death certificates were the only source of information, cases where cancer was included as the underlying cause of death were included within the dataset (details of blinded adjudication and definitions in Supplementary Methods, Supplementary Box 1 and Supplementary Figure 1, available online).

Analyses were conducted by "person" and by "incident cancer," the former analysis accounting for the number of individuals developing 1 or more "cancer events" (either a new incident cancer that could be localized or distant, or a metastatic recurrence of a cancer diagnosed prior to study entry) during the period of the trial. The incident cancer analysis included each new cancer subtype diagnosis reported and confirmed after random assignment and included the possibility for participants to contribute 2 or more distinct cancer endpoints if the subtype differed. For example, a participant diagnosed with prostate cancer after being randomly assigned, who subsequently developed pancreatic cancer, would contribute 2 incident cancers. If a subsequent death was considered the result of cancer, the cancer considered most likely to have led to the death was determined. Among those who entered the trial with a history of cancer, any new cancer type was included among incident cancers, whereas a local recurrence of the same type was not (see Supplementary Figure 2, available online). Distant recurrence of a primary tumor present at baseline was included as a new metastatic cancer (details in Supplementary Methods, available online).

Statistical Analysis

Cox proportional-hazards models were used in intention-to-treat analyses to compare aspirin and placebo groups on time-to-event cancer outcomes during the intervention phase of the trial (on or prior to June 12, 2017, median of 4.7 years follow-up for both groups). An analysis was performed for the event of "first diagnosis" of cancer of any type (ie, incident cancers) that occurred during the trial, and a separate set of analyses, 1 for each anatomical cancer type, was also conducted. These analyses were all time to first event, and if participants experienced multiple anatomical cancer types, then only their first occurrence contributed to the analysis of "cancer of any type," and their first occurrence of each specific anatomical type contributed to that anatomical type's analysis. Cause-specific hazard ratios (HR) were determined for total cancer, nonmetastatic cancer, metastatic cancer, and specific cancer types with censoring at the time of the competing risk of death. The proportional hazards assumption was checked for all models by using a test based on Schoenfeld residuals. A competing risk model was used to develop the cumulative incidence plots.

Subgroups that were prespecified in the trial protocol included country of residence, age, sex, ethnicity, smoking status, body mass index category, prior regular use of aspirin, baseline history of diabetes, hypertension, dyslipidemia, and prior cancer history (1,2,11). Effect heterogeneity between subgroups was assessed with omnibus tests of whether coefficients for interaction terms in Cox proportional-hazards models were different from zero. All P values are 2-sided, with cut point for statistical significance P less than .05, and all analyses were restricted to events that occurred on, or prior to, the end of the treatment phase.

Compliance With Ethical Standards

The ASPREE trial was conducted in accordance with the Declaration of Helsinki 1964 as revised in 2008, the National Health and Medical Research Council Guidelines on Human Experimentation, the federal patient privacy (Health Insurance Portability and Accountability Act) law, and the International Conference of Harmonization guidelines for Good Clinical Practice. ASPREE also follows the Code of Federal Regulations as it relates to areas of clinical research.

Results

Participants

Baseline characteristics of the participants are presented in Table 1 showing treatment groups well balanced in terms of established or putative risk factors for cancer (2). Prior aspirin use was low (11.0%) and balanced across groups (aspirin n = 1053, placebo n = 1041). At the end of the trial, the total number of years during which participants were at risk of cancer mortality was 44 007 person-years in the aspirin group and 44 382 person-years in the placebo group. At trial entry, 3660 (19.1%) had a prior diagnosis of cancer (excluding nonmelanoma skin cancer), 15 375 (80.4%) were not known to have cancer prior to random assignment, and the cancer history status was unknown for 79 (0.4%) (see Table 1). The compliance to study medication, expressed as a proportion of the time in study that an individual spent taking randomized medication, was on average 72.7% for the aspirin group and 74.5% for the placebo group.

Incidence

Table 2 indicates that 981 individuals in the aspirin group and 952 in the placebo group had a first incident cancer after random assignment, regardless of whether they had a past cancer history at baseline. Corresponding numbers of deaths adjudicated as caused by cancer are also shown. During the in-trial follow-up, 1933 (10.1%) were diagnosed with a new incident cancer. Among these, 1270 (65.7%) presented with localized cancer (ie, nonmetastatic cancer), 363 (18.8%) presented with new metastatic disease (ie, incident metastatic disease), 113 (5.8%) presented with metastatic disease of a cancer type already present before study entry (ie, metastatic recurrence), and 187 (9.7%) with a hematological or lymphatic cancer (subgroup analyses Supplementary Tables 1 and 2, available online). A total of 495 (25.6%) participants died as a result of their malignancy; of these, 52 died from progression of a cancer initially diagnosed prior to trial entry (Table 2; CONSORT diagram, Supplementary Figure 3, available online).

Aspirin was not associated with risk of diagnosis of a first incident cancer event (HR = 1.04, 95% CI = 0.95 to 1.14), an incident localized cancer (HR= 0.99, 95% CI = 0·89 to 1.11), or an incident hematological or lymphatic cancer (HR = 0.98, 95% CI = 0.73 to 1.30). However, the number of participants with metastatic cancer at diagnosis (HR= 1.19, 95% CI = 1.00 to 1.43) was increased among those randomly assigned to aspirin.

Table 3 compares the impact of aspirin and placebo on the incidence of, and mortality from, solid tumors (ie, excluding hematological and lymphatic cancers) according to stage and anatomical origin, and Figure 1 shows the cumulative incidence of solid tumor cancers according to stage at diagnosis. There was no association of aspirin with the overall incidence of solid tumors (HR = 1.05, 95% CI = 0.95 to 1.15) or with the incidence of cancers that were diagnosed at stages 1, 2, or 3. By contrast, aspirin was associated with an increase in the incidence of cancers presenting at stage 4 (HR = 1.22, 95% CI = 1.02 to 1.45).

Deaths

An increased progression to death was observed among those randomly assigned to aspirin, regardless of whether the initial cancer presentation had been localized or metastatic (Table 2 and Figure 2). Table 3 demonstrates a higher death rate among the aspirin group presenting with stage 3 (HR = 2.11, 95% CI = 1.03 to 4.33) or stage 4 disease (HR = 1.31, 95% CI = 1.04 to 1.64).

Prostate, colorectal, breast, melanoma, and lung were the most common incident cancers, accounting for 80% of all solid tumor cancers. There was no association of aspirin with the incidence of cancer in any anatomic subtype. However, the aspirin-treated group was observed to have more deaths from solid tumors irrespective of anatomical site, including colorectal cancer deaths (35 vs 20, HR = 1.77, 95% CI = 1.02 to 3.06). In absolute terms, the rate of solid tumor cancers with subsequent death was increased from 4.4 cases per 1000 person-years of observation among those randomly assigned to placebo to 5.9 cases per 1000 person-years among those receiving aspirin (HR = 1.33, 95% CI = 1.11 to 1.61).

Table 1. Baseline characteristics of the ASPREE population by treatment group

Characteristic	Aspirin (n = 9525) No. (%)	Placebo (n = 9589) No. (%)
Age, y		
65-69	284 (3.0)	280 (2.9)
70-74	5243 (55.0)	5356 (55.9)
75-79	2533 (26.6)	2490 (26.0)
80-84	1085 (11.4)	1111 (11.6)
≥85	380 (4.0)	352 (3.7)
Male sex	4152 (43.6)	4180 (43.6)
BMI ≥25, kg/m^2	6981 (73.6)	7080 (74.2)
Smoking		
Current	352 (3.7)	383 (4.0)
Former	3909 (41.0)	3890 (40.6)
Never	5264 (55.3)	5316 (55.4)
Alcohol use		
Current	7309 (76.7)	7333 (76.5)
Former	566 (5.9)	570 (5.9)
Never	1650 (17.3)	1686 (17.6)
Previous regular aspirin use[a]	1053 (11.1)	1041 (10.9)
Personal cancer history	1827 (19.2)	1833 (19.1)
Family cancer history[b]	5554 (58.5)	5605 (58.3)
Previous cancer screening, % of asked[c]	2924 (96.6)	2934 (96.7)

[a]Previous regular aspirin use was defined according to participant-reported regular use of aspirin immediately before entering the study. ASPREE = ASPirin in Reducing Events in the Elderly; BMI = body mass index.
[b]Family cancer history includes a history of cancer in the participant's mother, father, siblings, and children, as reported by each participant at baseline.
[c]Previous cancer screening questions asked of 3022 participants in the aspirin group and 3035 participants in the placebo group.

Subgroup Analyses

The effect of aspirin on solid tumor incidence (Figure 3,A), solid tumor mortality (Figure 3,B), and all incident cancers (Supplementary Figure 4, available online) appeared similar across a series of prespecified and nonprespecified subgroups. Notably, an aspirin-associated non-statistically significant trend toward increasing cancer mortality, but not cancer incidence, was observed with age.

Compliance-Adjusted Treatment Effects

Adjusting for compliance (Supplementary Tables 3 and 4, available online) did not diminish the intention-to-treat aspirin effects presented in Tables 2 and 3.

Table 2. Number of individuals with incident cancer (n = 1933) and deaths from cancer (n = 495), by presentation of first cancer event, in the aspirin or placebo study arms (summarized as rates per 1000 person-years of follow-up)

	Cancer incidence[a]			Cancer mortality[b,c]		
	No. individuals with cancer diagnosis (rate per 1000 person-years)		Aspirin vs placebo	No. individuals dying from cancer (rate per 1000 person-years)		Aspirin vs placebo
Cancer endpoint	Aspirin	Placebo	HR (95% CI)	Aspirin	Placebo	HR (95% CI)
First incident cancer	981 (23.9)	952 (23.0)	1.04 (0.95 to 1.14)	283 (6.4)	212 (4.8)	1.35 (1.13 to 1.61)
Incident localized cancer	631 (15.2)	639 (15.3)	0.99 (0.89 to 1.11)	93 (2.1)	64 (1.4)	1.47 (1.07 to 2.02)
Metastatic cancer	258 (6.1)	218 (5.1)	1.19 (1.00 to 1.43)	171 (3.9)	133 (3.0)	1.30 (1.03 to 1.63)
Incident metastatic cancer	196 (4.6)	167 (3.9)	1.18 (0.96 to 1.46)	143 (3.2)	109 (2.5)	1.32 (1.03 to 1.70)
Metastatic spread from cancer reported prior to random assignment[d]	62 (1.5)	51 (1.2)	1.23 (0.85 to 1.77)	28 (0.6)	24 (0.5)	1.18 (0.68 to 2.03)
Hematological or lymphatic cancer	92 (2.2)	95 (2.2)	0.98 (0.73 to 1.30)	19 (0.4)	15 (0.3)	1.28 (0.65 to 2.51)

[a]Based on time from random assignment to first incident cancer. CI = confidence interval; HR = hazard ratio.
[b]Based on time from random assignment to cancer-related death in those who developed cancer.
[c]Mortality definitions: Adjudicated cancer deaths only are included in this table. Note: 522 cancer-related deaths are reported in the recent publication by the same first author (McNeil et al., *N Eng J Med*, 2018, "Effect of aspirin on all-cause mortality in the healthy elderly"; ref. 2), whereas only 495 deaths are reported here. Deaths that could not be adjudicated but were attributed to cancer using death certificate codes are not included (n = 7). Cancer deaths in participants who did not present with cancer prior to death are not included (n = 20).
[d]Metastatic cancer of the same type as preexisting (prior to random assignment) cancer.

Discussion

We previously reported that among older adults taking low-dose aspirin for primary prevention in the ASPREE RCT, there was an increased mortality rate, largely attributed to a higher death rate from cancer (3). More deaths were observed among aspirin-treated participants from cancers originating from a variety of anatomical sites, and these deaths were not attributable to a specific "proximal" cause of death such as bleeding (3).

In this paper, we provide a more detailed assessment of the cancer incidence and mortality from cancer among the major cancer subtypes according to stage of disease at presentation to help provide a better understanding of the mortality findings. Essentially, whereas the incidence of new localized cancer was similar in those randomly assigned to aspirin or placebo, the number of individuals diagnosed with malignancy at an advanced stage (including those with metastatic cancer at diagnosis) was higher in the aspirin group.

Additionally, a higher death rate from cancer among those randomly assigned to low-dose aspirin was observed for all solid tumors, regardless of whether the cancer was localized or metastatic at presentation. This was most evident for cancers that were stage 3 or 4 at diagnosis and for colorectal cancer. No similar effect was seen with blood and lymphatic cancers. There was no evidence of effect modification on mortality by age, sex, or risk factors for malignancy. The impact on mortality from colorectal cancer was at least equal in magnitude to that at other sites, and the findings were similar among subgroups from both Australia and the United States.

The observed increase in risk of cancers presenting at an advanced stage and the increased death rate among those diagnosed with a later stage cancer, consistently observed across multiple primary sites, suggest that aspirin may promote the progression of advanced malignancies in this age group. Possible explanations for this finding include aspirin suppressing (or blunting) antitumor inflammatory or immune responses critical to controlling later stage growth and spread (12–14). Such an effect may be particularly evident among an older population for which underlying antitumor immunity may already be compromised (15).

Differences in the biology and behavior of tumors in older adults are also well described. For example, among older adults, colorectal cancer occurs more commonly in the right side of the colon (16) and has a higher prevalence of specific molecular changes, including deficiencies in mismatch repair and BRAF mutations (17). In a previous study, we observed that regular aspirin use was associated with a lower risk of *BRAF*–wild-type colorectal cancer but not *BRAF*-mutated colorectal cancer (18). Additionally, age has been shown to impact the types of mutations found within specific genes of tumors, such as the greater incidence of the G12 mutation of *KRAS* in those younger than 40 years compared with the more common Q61 *KRAS* mutation in older patients (19), along with a difference in the mutated gene itself (20). Other molecular changes have also been shown to be more prominent in cancers of older people, such as the methylation state of certain genes (20, 21).

These reports make it plausible that aspirin might also act differently, at the cellular or molecular level, in older individuals. Our results contrast with other data from previous RCTs, summarized in earlier systematic reviews by Rothwell et al. (4), the US Preventive Services Task Force (22), and Haykal et al. (23). Pooled analysis of trials, which included populations with a mean age of approximately 10 years younger than in ASPREE, found that aspirin neither increased nor decreased cancer incidence or mortality during the period of aspirin intervention, typically 5 years (23). The recent ASCEND primary prevention trial, conducted in somewhat younger individuals with diabetes mellitus, also found no evidence of increased cancer mortality after 7.4 years of follow-up (24). However, the most recently published meta-analysis by Rothwell et al. (7) reported an increase in risk of cancer diagnosis with low-dose aspirin among individuals aged 70 years and older, when follow-up was limited

Table 3. Cancer incidence and cancer mortality by stage, anatomical site, and treatment arm, as rates per 1000 person-years of observation

	Cancer incidence[a]			Cancer mortality[a]		
	Aspirin	Placebo	Aspirin vs placebo	Aspirin	Placebo	Aspirin vs placebo
Cancer stage at diagnosis or anatomical site	No. cancer events (rate per 1000 person-years)	No. cancer events (rate per 1000 person-years)	HR (95% CI)	No. cancer events (rate per 1000 person-years)	No. cancer events (rate per 1000 person-years)	HR (95% CI)
All solid tumors[b]	893 (21.7)	859 (20.7)	1.05 (0.95 to 1.15)	259 (5.9)	196 (4.4)	1.33 (1.11 to 1.61)
Stage 1	210 (5.0)	225 (5.3)	0.94 (0.78 to 1.13)	5 (0.1)	9 (0.2)	0.56 (0.19 to 1.67)
Stage 2	219 (5.2)	236 (5.5)	0.94 (0.78 to 1.12)	16 (0.4)	9 (0.2)	1.80 (0.79 to 4.06)
Stage 3	98 (2.3)	99 (2.3)	1.00 (0.75 to 1.32)	23 (0.5)	11 (0.2)	2.11 (1.03 to 4.33)
Stage 4[c]	275 (6.5)	228 (5.3)	1.22 (1.02 to 1.45)	172 (3.9)	133 (3.00)	1.31 (1.04 to 1.64)
Uncertain stage	91 (2.1)	71 (1.7)	1.29 (0.95 to 1.76)	30 (0.7)	16 (0.4)	1.89 (1.03 to 3.47)
Anatomic site of origin[d]						
Prostate[e]	199 (11.1)	202 (11.1)	1.00 (0.82 to 1.21)	17 (0.9)	17 (0.9)	1.02 (0.52 to 2.01)
Colorectal	139 (3.3)	137 (3.2)	1.02 (0.81 to 1.30)	35 (0.8)	20 (0.5)	1.77 (1.02 to 3.06)
Breast[f]	127 (5.3)	124 (5.1)	1.03 (0.80 to 1.32)	15 (0.6)	7 (0.3)	2.15 (0.88 to 5.27)
Melanoma	87 (2.0)	106 (2.5)	0.83 (0.62 to 1.10)	12 (0.3)	8 (0.2)	1.51 (0.62 to 3.69)
Lung	86 (2.0)	84 (2.0)	1.03 (0.76 to 1.40)	55 (1.2)	51 (1.1)	1.09 (0.74 to 1.59)
Bladder	37 (0.9)	38 (0.9)	0.98 (0.62 to 1.54)	8 (0.2)	9 (0.2)	0.90 (0.35 to 2.33)
Brain	18 (0.4)	9 (0.2)	2.02 (0.91 to 4.49)	14 (0.3)	9 (0.2)	1.57 (0.68 to 3.62)
Cervical[f]	2 (0.1)	1 (0.04)	2.01 (0.18 to 22.13)	0 (0.0)	0 (0.0)	n/a
Gallbladder or bile duct	11 (0.3)	12 (0.3)	0.93 (0.41 to 2.10)	8 (0.2)	8 (0.2)	1.01 (0.38 to 2.69)
Kidney	25 (0.6)	18 (0.4)	1.40 (0.76 to 2.57)	9 (0.2)	4 (0.1)	2.28 (0.70 to 7.39)
Liver	7 (0.2)	1 (0.02)	n/a	4 (0.1)	0 (0.0)	n/a
Mesothelioma	9 (0.2)	6 (0.1)	1.52 (0.54 to 4.26)	5 (0.1)	2 (0.05)	2.53 (0.49 to 13.03)
Esophageal	11 (0.3)	18 (0.4)	0.62 (0.29 to 1.30)	7 (0.2)	13 (0.3)	0.54 (0.22 to 1.36)
Ovary or endometrium[f]	40 (1.6)	37 (1.5)	1.09 (0.69 to 1.70)	15 (0.6)	13 (0.5)	1.16 (0.55 to 2.43)
Pancreatic	37 (0.9)	29 (0.7)	1.29 (0.79 to 2.09)	29 (0.7)	21 (0.5)	1.39 (0.80 to 2.45)
Stomach	18 (0.4)	11 (0.3)	1.65 (0.78 to 3.49)	9 (0.2)	4 (0.1)	2.27 (0.70 to 7.38)
Thyroid	6 (0.1)	5 (0.1)	1.21 (0.37 to 3.97)	0 (0.0)	0 (0.0)	n/a
Other	66 (1.5)	55 (1.3)	1.21 (0.85 to 1.73)	15 (0.3)	8 (0.2)	1.89 (0.80 to 4.46)
Unknown	20 (0.5)	13 (0.3)	1.55 (0.77 to 3.12)	12 (0.3)	9 (0.2)	1.35 (0.57 to 3.19)

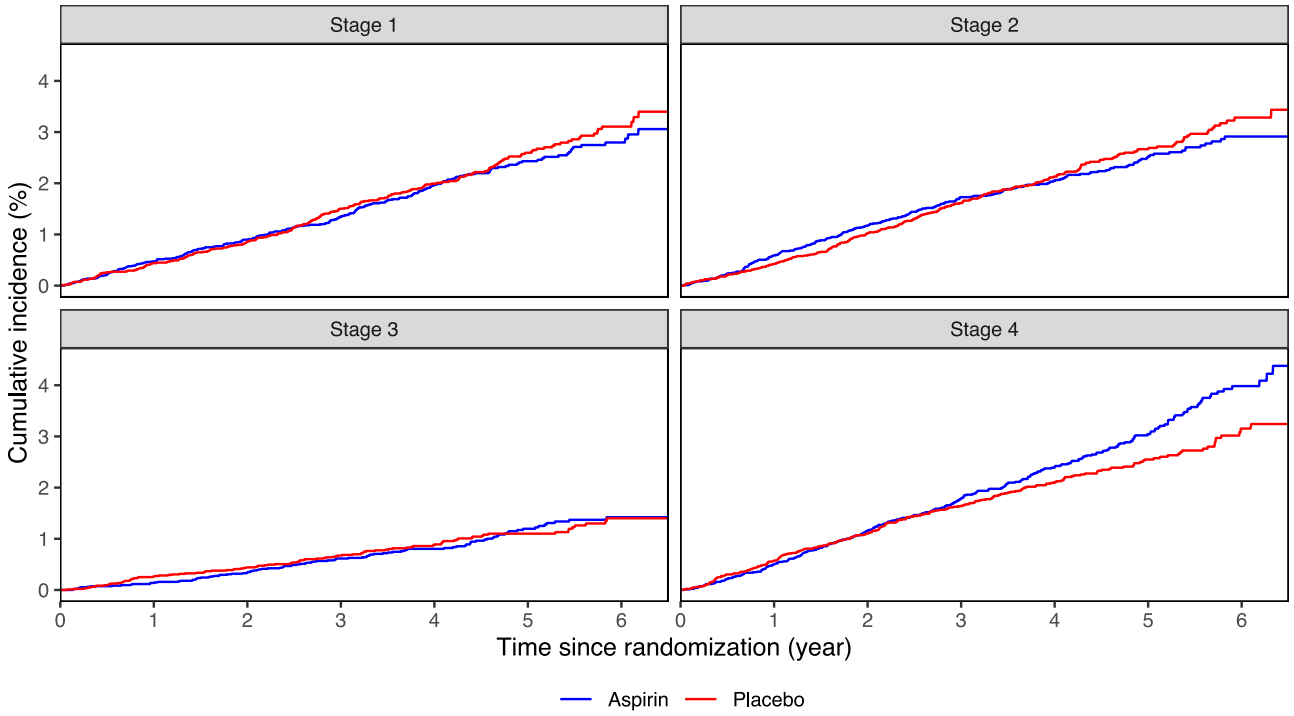
[a]Cancer incidence is the first cancer event of anatomical type, noting that participants with more than 1 cancer type will be counted for each type. Cancer mortality reports deaths from the same individuals included in the same row under incidence. CI = confidence interval; HR = hazard ratio.
[b]Excludes hematological cancer and hematological cancer death. Stage 1 cancer incidence includes the first presentation with a cancer that was stage 1 at presentation. Cancer mortality is death from a cancer that was stage 1 at presentation. This format is repeated for stages 2-4 and uncertain stage.
[c]Some cancer types (eg, prostate and bladder) can have nonmetastatic disease staged as stage 4.
[d]Cancer type is ordered with the top 5 most prevalent cancers by incident listed first, then listed alphabetically.
[e]Males only.
[f]Females only.

to 3 years. The authors noted this effect was observed only in those with low body weight. Statistically significant effects from aspirin were not seen in cancer deaths.

Given the multiple analyses undertaken without statistical control for multiple testing, the possibility that findings have arisen by chance, or from a bias in the ascertainment of relevant outcomes, must also be considered. However, the objective endpoint of all-cause mortality was statistically significantly higher among those randomly assigned to aspirin and is less likely to be a chance finding. The difference in cancer mortality explained virtually all of this difference. The process for allocating cause of death required blinded adjudicators to confirm all cancer diagnoses and determine the underlying reason for the trajectory to death, which reduced the likelihood of biased ascertainment of cancer endpoints. In an older age group, where multimorbidity is common and clinical investigations may be limited, the illness ultimately leading to death frequently requires a review of clinical documentation to determine the most likely pathology. This process was undertaken to review all deaths occurring during ASPREE, in contrast with earlier aspirin trials.

The results might also be explained if there was a bias in the ascertainment of the outcome, most obviously, if aspirin led to a systematic delay in the recognition of cancer, so that among those taking aspirin, cancer was diagnosed at a more advanced stage. However, this is unlikely because we did not observe a time-dependent compensatory decrease in incidence of stages 1-3 cancers that would offset the observed increase in the incidence of stage 4 cancer. As reported previously, the difference also did not appear to be explained by differences in the mode of death, for example, if aspirin increased the likelihood of a patient with cancer dying prematurely from hemorrhage or infection (3).

During more prolonged follow-up of participants in earlier primary and secondary prevention trials, a delayed protective effect of aspirin on cancer incidence and mortality has been observed, particularly for colorectal cancers (8,22). In 2010, Rothwell and colleagues (8) reported a long-term follow-up of



Number at risk

	Entry	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Aspirin	9525	9268	8944	7635	5667	3434	1193
Placebo	9589	9326	9012	7697	5722	3473	1164

Figure 1. Cumulative incidence of first incidence of solid tumor cancer, by stage and treatment group.

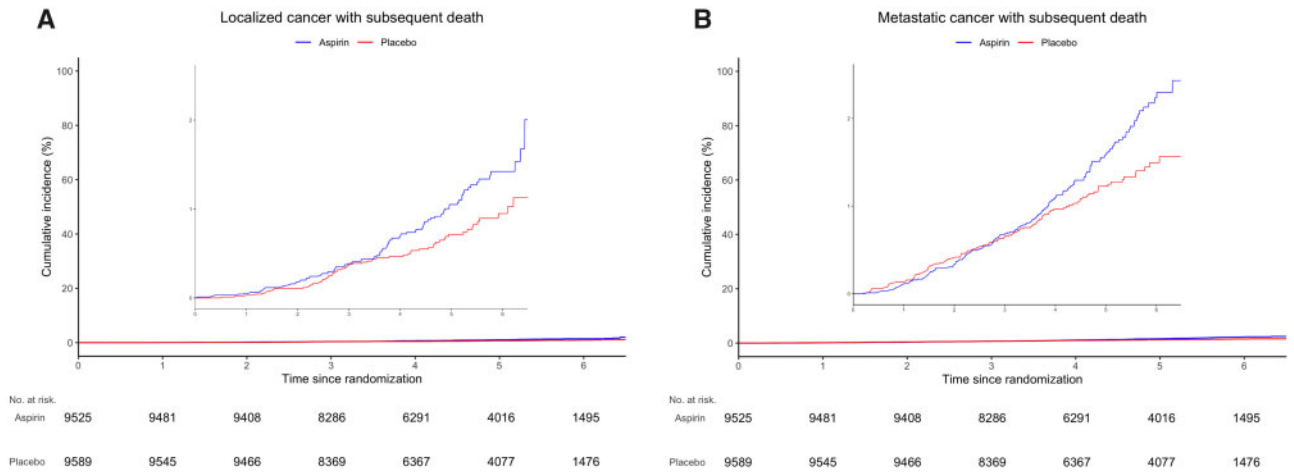


Figure 2. Cumulative incidence of cancer-related death following a first presentation of localized or metastatic cancer. Panel **(A)** shows localized cancer, and panel **(B)** shows metastatic cancer. Time is from random assignment to the occurrence of death following the cancer event.

participants from 4 large random assignment trials of aspirin (75-300 mg/d), which found that allocation to aspirin reduced the 20-year risk of cancer mortality (HR = 0.65, 95% CI = 0.48 to 0.88), and the benefit increased with treatment duration. In the Women's Health Study (alternate-day 100 mg aspirin), aspirin was associated with reduced colorectal cancer incidence that became apparent during subsequent posttrial follow-up 10 years after random assignment (25). These results are suggestive of a delayed benefit of aspirin and emphasize the importance of ongoing follow-up of the ASPREE cohort.

Strengths of ASPREE include the use of blinded expert reviewers to categorize both tumor stage and causes of death, thus minimizing bias or misclassification. However, limited statistical power was available to examine the effect of aspirin within subgroups or on specific cancer subtypes, and consideration about the multiplicity of statistical analyses also

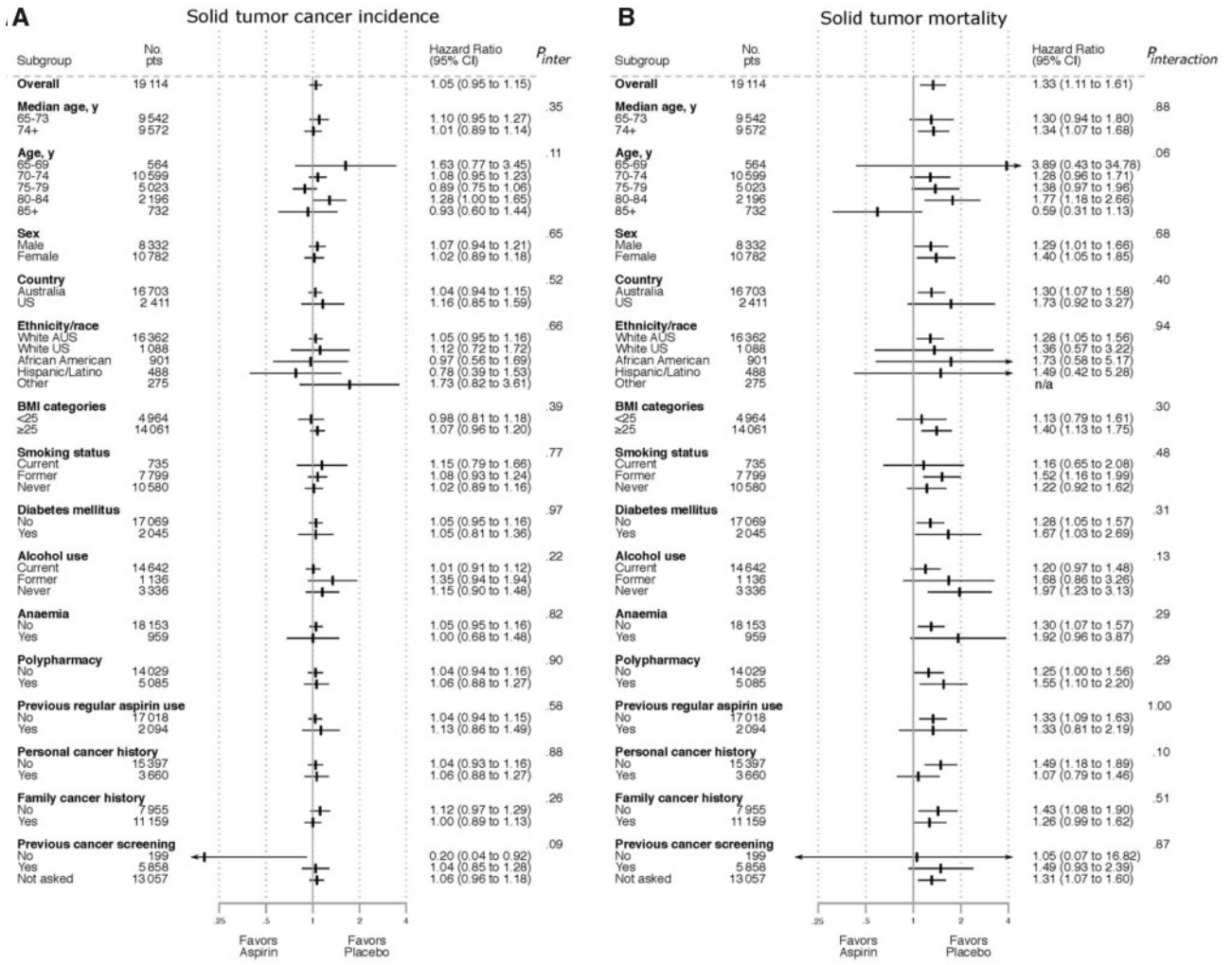


Figure 3. Forest plots of solid tumor cancer incidence and mortality by subgroup. Solid tumor cancer incidence is shown **(A)** and mortality is shown **(B)**. Subgroups are classed from baseline (enrollment) and include age in years, BMI (in kg/m^2), prior cancer history, and family cancer history. For 'Other', within the ethnicity/race subgroup, all events occurred in the aspirin arm (ie, no events in the placebo arm), and thus, HR cannot be estimated. Not all participants were asked about cancer-related medical screening (questionnaire introduced late in recruitment, 2013). AUS = Australian; BMI = body mass index; CI = confidence interval; HR = hazard ratio; pts = participant; NA = not applicable.

constrains some of our conclusions. Finally, although we did not observe a differential effect of aspirin on cancer mortality according to a history of prior aspirin use, our overall results do not specifically address whether aspirin use initiated at a younger age should be discontinued after ages 65 to 70 years.

If confirmed, the clinical implications of these findings could be important for the use of aspirin in an older population. If low-dose aspirin were to hasten the progression of cancers, its role as a primary prevention agent would be further diminished. However, the increased risk in ASPREE was small (an extra 1.5 deaths from cancer per 1000 person-years) in comparison with the risk of mortality from other causes. Several RCTs are currently underway to address the use of aspirin after diagnosis and treatment of cancer with curative intent, and these results may be of particular value in supporting or refuting these findings, provided they include sufficient numbers of older subjects (26–30).

In summary, among generally healthy adults predominantly 70 years of age or older at enrollment and followed for a median of 4.7 years, daily low-dose aspirin was associated with an increased risk of incident solid cancers presenting at an advanced stage. Mortality from both localized and advanced cancers was higher in those taking aspirin, suggesting a possible adverse effect of aspirin on cancer evolution in older adults. Cancer molecular and genetic data give reason to suggest that the potential adverse impact of aspirin identified in ASPREE might be specific to this age group. The cohort continues to be followed to explore the possibility of a delayed reduction in cancer incidence and/or mortality that may emerge with longer-term observation.

Funding

This work was supported by grants from the National Institute on Aging (U01AG029824, U19AG062682), from the National Cancer Institute (R01CA137178 and R35CA253185 to ATC), from the National Health and Medical Research Council of Australia (334047 and 1127060), and from Monash

University and the Victorian Cancer Agency. Dr Chan is a Stuart and Suzanne Steele MGH Research Scholar.

Notes

Role of the funders: No sponsor had any role in the study design, data collection, analysis, interpretation, the writing, and decision to submit the manuscript.

Disclosure: Drs Chan, Murray, and Nelson received travel compensation and a consulting fee for presentation of results of the ASPREE primary papers at a Bayer PharmaAG–sponsored conference in October 2018. Drs Chan and Zalcberg have received research funding for unrelated studies from Bayer Pharma AG. All other authors certify that there is no actual or potential conflict of interest in relation to this article. Dr McNeil had full access to the data in the study and takes final responsibility for the decision to publish. He was not paid to write this article.

Author contributions: **JMcN**: conceptualization, methodology, supervision, resources funding acquisition, writing—original draft. **PG**: methodology, validation, investigation. **SO**: methodology, project administration, data collection, writing, supervision, investigation. **JL:** methodology, investigation, software, data curation, supervision, validation. **WB:** investigation, validation. **YC:** investigation, validation. **AH:** investigation, validation. **FM:** investigation, validation. **CM:** investigation, validation. **JM:** investigation, validation. **LMR:** investigation, validation. **JT:** investigation, validation. **AU:** methodolgy. **JvL:** investigation, validation. **JZ:** investigation, validation. **LF:** methodology. **ER:** methodology. methodology. **BK:** methodology, investigation, project administration. **AM:** investigation, project administration. **MN:** investigation, project administration. **CR:** investigation, project administration. **RS:** investigation, project administration. **KR:** writing (review and editing). **GP:** data analysis, data interpretation, visualization. **RW:** data analysis, data interpretation, visualization. **RLW:** methodology, investigation, supervision, resources funding acquisition, project administration. **ATC:** conceptualization, methodology, supervision, writing. All authors were involved in writing (review and editing).

Acknowledgments: The authors would like to thank the participants, the collaborating general practitioners and other clinical staff, the data monitoring committee, Catherine Smith who conducted the compliance-adjusted analyses, and all the administrative and other staff who helped conduct the trial. A full listing of the ASPREE collaborators is listed at www.aspree.org.

Data availability

The data underlying this article will be shared on reasonable request addressed to ASPREE.AMS@monash.edu.

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