

Effect of aspirin on cancer incidence and mortality in older adults

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Abstract

Background

ASpirin in Reducing Events in the Elderly (ASPREE), a randomized double-blind placebo-controlled trial (RCT) of daily low-dose aspirin (100 mg) in older adults, showed an increase in all-cause mortality, primarily due to cancer. In contrast prior RCTs, 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 U.S. community-dwelling participants aged 70+ years (U.S. minorities 65+ years) without cardiovascular disease, dementia or physical disability were randomized and followed for a median of 4.7 years. Fatal and non-fatal 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 (HR = 1.04, 95% 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.

The ASPirin in Reducing Events in the Elderly (ASPREE) was a randomized controlled trial (RCT) comparing daily low-dose aspirin (100mg) *versus* placebo in 19,114 Australian and U.S. adults aged 70 years or older (or ≥ 65 years of age among U.S. 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 three years post-randomization 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.* recently reported an increase in cancer incidence during the early years of follow-up amongst older trial participants.⁷ 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 United States Preventive Services Task Force (USPSTF) in 2016 to recommend low-dose aspirin for primary prevention of cardiovascular (CVD) events and colorectal cancer among U.S. adults aged 50-59 with a greater than 10% ten-year risk of a CVD event.⁹ However, this advice did not extend to adults aged 70+ 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 Number: ASPREE ClinicalTrials.gov number NCT01038583).^{1,2} From March 2010 through December 2014, a total of 19,114 participants across Australia (n=16,703) and the U.S. (n=2,411) gave written informed consent and were randomly assigned to receive daily 100mg of enteric coated aspirin (n=9,525) or matching placebo (n=9,589). A previous history of cancer was not an exclusion criterion and was present in 19% of those randomized.

However, all participants were required to be in good health, free of major diseases and expected to survive for at least five years (details of follow-up and compliance in Supplementary Methods).¹⁰

Ascertainment of cancer outcomes

Fatal and non-fatal cancers occurring during the randomized treatment phase were a prespecified secondary endpoint. Detailed clinical records, including histopathology reports, were sought from treating practitioners and healthcare 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).

Analyses were conducted by ‘person’ and by ‘incident cancer’, the former analysis accounting for the numbers of individuals developing one or more ‘cancer events’ (either a new incident cancer which 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 randomization, and included the possibility for participants to contribute two or more distinct cancer endpoints if the subtype differed. For example, a participant diagnosed after randomization with prostate cancer, who subsequently developed pancreatic cancer, would contribute two 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. Amongst those who entered the trial with a history of cancer, any new cancer type was included amongst incident cancers while a local recurrence of the same type was not (see Supplementary Figure 2). Distant recurrence of a primary tumor present at baseline was included as a new metastatic cancer (details in Supplementary Methods).

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 12th June 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 (*i.e.* incident cancers) that occurred during the trial, and a separate set of analyses, one for each anatomical cancer type, was also conducted. These analyses were all time to first event, and if a participant experienced multiple anatomical cancer types then only their first occurrence contributed to the analysis of “cancer of any type”, while 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, non-metastatic 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.

Sub-groups that were pre-specified in the trial protocol included country of residence, age, sex, ethnicity, smoking status, body mass index (BMI) 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 two-sided, with cut-point for statistical significance $p < 0.05$, 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 NHMRC Guidelines on Human Experimentation, the federal patient privacy (HIPAA) law and ICH-GCP guidelines and the International Conference of Harmonisation 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 numbers of years during which participants were at risk of cancer mortality were 44,007 person-years in the aspirin group and 44,382 person-

years in the placebo group. At trial entry 3,660 (19.1%) had a prior diagnosis of cancer (excluding non-melanoma skin cancer) while 15,375 (80.4%) were not known to have cancer prior to randomization, with the cancer history status unknown for 79 (0.4%) (Table 1). The compliance to study medication, expressed as a proportion of the time in study that an individual spent taking their 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 randomization, 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, 1,933 (10.1%) were diagnosed with a new incident cancer. Amongst these, 1,270 (65.7%) presented with localized cancer (*i.e.* non-metastatic cancer), 363 (18.8%) presented with new metastatic disease (*i.e.* incident metastatic disease), 113 (5.8%) presented with metastatic disease of a cancer type already present before study entry (*i.e.* metastatic recurrence) and 187 (9.7%) with a hematological or lymphatic cancer (subgroup analyses Supplementary Tables 1 and 2). 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).

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 = 0.89-1.11), 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 amongst those randomized to aspirin.

Table 3 compares the impact of aspirin and placebo on the incidence of, and mortality from, solid tumors (*i.e.* excluding hematological/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) nor 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 amongst those randomized to aspirin, regardless of whether the initial cancer presentation had been localized or metastatic (Table 2, Figure 2). Table 3 demonstrates a higher death rate amongst 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 *versus* 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 amongst those randomized to placebo to 5.9 cases per 1000 person-years amongst those receiving aspirin (HR = 1.33, 95% CI = 1.11 to 1.61).

Subgroup analyses

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

Compliance-adjusted treatment effects

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

DISCUSSION

We previously reported that amongst 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 amongst 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 amongst the major cancer subtypes according to stage of disease at presentation, to help provide a better understanding of the mortality findings. Essentially while the incidence of new localized cancer was similar in those randomized 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 amongst those randomized to low-dose aspirin was observed for all solid tumors, regardless of whether the cancer was localised 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 U.S.

The observed increase in risk of cancers presenting at an advanced stage and the increased death rate amongst 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’) anti-tumor 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 anti-tumor immunity may already be compromised.¹⁵

Differences in the biology and behaviour 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 colon¹⁶ 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 under 40 compared to the more common Q16 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.* (2012)⁴ and the USPSTF (2016)²² and Haykal *et al.* (2019).²³ Pooled analysis of trials, which included populations with a mean age ~10 years younger than in ASPREE, found that aspirin neither increased or 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.* (2018) reported an increase in risk of cancer diagnosis with low-dose aspirin amongst individuals aged 70 years and over, when follow-up was limited to 3 years.⁷ The authors noted this effect was observed only in those with low bodyweight. 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 end-point of all-cause mortality was statistically significantly higher amongst those randomized 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 end-points. 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 amongst those taking aspirin cancer was diagnosed at a more advanced stage. However, this is unlikely as we did not observe a time-

dependent compensatory decrease in incidence of stage 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, as 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 reported a long-term follow-up of participants from four large randomized trials of aspirin (75-300mg/d) which found that allocation to aspirin reduced the 20-year risk of cancer mortality (HR 0.65, 95% CI 0.48-0.88) and the benefit increased with treatment duration.²⁵ In the Women's Health Study (WHS, alternate-day 100-mg aspirin), aspirin was associated with reduced colorectal cancer incidence that became apparent during subsequent post-trial follow-up 10 years after randomization.²⁶ 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 constrain 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 age 65 to 70.

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.²⁷⁻³¹

In summary, among generally healthy adults predominantly 70 years of age or older at enrolment 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.

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NOTES

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~~Compliance with Ethical Standards:~~

Conflict of Interest: Drs. Chan, Murray and Nelson received travel compensation and a consulting fee for presentation of results of the ASPREE primary papers at a Bayer Pharma-AG-sponsored conference in October 2018. Drs. Chan and Zalberg 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.

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

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REFERENCES

1. ASPREE Study Group. Study design of ASPIrin in Reducing Events in the Elderly (ASPREE): a randomised controlled trial. *Contemp Clin Trials* 2013;**36**:555–64.
2. McNeil JJ, Woods RL, Nelson MR, et al. Baseline Characteristics of Participants in the ASPREE (ASPIrin in Reducing Events in the Elderly) Study. *J Gerontol A Biol Sci Med Sci* 2017;**72**:1586–93.
3. McNeil JJ, Nelson MR, Woods RL, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med* 2018;**379**:1519–28.
4. Rothwell PM, Price JF, Fowkes FG, 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**:1602–12.

5. Rothwell PM, Fowkes FG, Belch JF, 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**:31–41.
6. Mills EJ, Wu P, Alberman M, Kanters S, Lanas A, Lester R. Low-dose Aspirin and Cancer Mortality: A meta-analysis of randomized trials. *Amer J Med* 2012;**125**:560–7.
7. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 2018;**392**:387–99.
8. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010;**376**:1741–50.
9. 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.
10. McNeil JJ, Woods RL, Nelson MR, et al. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. *N Engl J Med* 2018;**379**:1499–508.
11. Wolfe R, Murray AM, Woods RL, et al. The aspirin in reducing events in the elderly trial: Statistical analysis plan. *Int J Stroke* 2018;**13**:335–8.12.
12. Umar A, Steele VE, Menter DG, Hawk ET. Mechanisms of nonsteroidal anti-inflammatory drugs in cancer prevention. *Semin Oncol* 2016; **43**:65–77.
13. Hussain M, Javeed A, Ashraf M, Zhao Y, Mukhtar MM, Rehman MU. Aspirin and immune system. *Int Immunopharmacol* 2012;**12**:10–20.
14. Gilligan MM, Gartung A, Sulciner ML, et al. Aspirin-triggered proresolving mediators stimulate resolution in cancer. *Proc Natl Acad Sci U S A* 2019;**116**:6292–7.
15. Hong H, Wang Q, Li J, Liu H, Meng X, Zhang H. Aging, Cancer and Immunity. *J Cancer* 2019; **10**(13):3021–7. Doi: 10.7150/jca.30723.
16. Shellnut JK, Wasvary HJ, Grodsky MB, Boura JA, Priest SG. Evaluating the age distribution of patients with colorectal cancer: are the United States Preventative Services Task Force guidelines for

colorectal cancer screening appropriate? *Dis Colon Rectum* 2010; **53**(1):5-8. Doi:

10.1007/DCR.0b013e3181bc01d1.

17. Aparicio T, Schischmanoff O, Poupardin C, Mary F, Soufir N, Barrat C, Bellaiche G, Boubaya M, Choudat L, Cucherousset J, DesGuetz G, Wind P, Benamouzig R. High prevalence of deficient mismatch repair phenotype and the V600E BRAF mutation in elderly patients with colorectal cancer. *J Geriatr Oncol.* 2014; **5**(4):384-8. Doi: 10.1016/j.jgo.2014.08.002.

18. Nishihara R, Lochhead P, Kuchiba A, Jung S, Yamauchi M, Liao X, Imamura Y, Qian ZR, Morikawa T, Wang M, Spiegelman D, Cho E, Giovannucci E, Fuchs CS, Chan AT, Ogino S. Aspirin use and risk of colorectal cancer according to BRAF mutation status. *JAMA* 2013; **309**(24):2563-71. doi: 10.1001/jama.2013.6599.

19. Serebriiskii IG, Connelly C, Frampton G, et al. Comprehensive characterization of RAS mutations in colon and rectal cancers in old and young patients. *Nature Commun* 2019; 10(1): #3722. Doi: 10.1038/s41467-019-11530-0

20. Wang M, Ren J, Tang L, Ren Z. Molecular features in young vs elderly breast cancer patients and the impacts on survival disparities by age at diagnosis. *Cancer Medicine* 2018; **7**:3269–77.

21. Xu Z, Taylor JA. Genome-wide age-related DNA methylation changes in blood and other tissues relate to histone modification, expression, and cancer. *Carcinogenesis* 2014; **35**(2):356-64, doi:10.1093/carcin/bgt391

22. Chubak J, Whitlock EP, Williams SB, Kamineni A, Burda BU, Buist DS, Anderson ML. Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016; **164**(12):814-25.

23. Haykal T, Barbarawi M, Zayed Y, Yelangi A, Dhillon H, Goranta S, Kheiri B, Chahine A, Samji V, Kerbage J, Katato K, Bachuwa G. Safety and efficacy of aspirin for primary prevention of cancer: a meta-analysis of randomized controlled trials. *J Cancer Res Clin Oncol.* 2019; **145**(7):1795-1809. doi: 10.1007/s00432-019-02932-0.

24. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018;**379**:1529–39.

25. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010; **376**(9754):1741-50. doi: 10.1016/S0140-6736(10)61543-7.
26. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Ann Intern Med* 2013;**159**:77–85.
27. Ali R, Toh H-C, Chia W-K, The ASCOLT trial investigators. The utility of Aspirin in Dukes C and high risk Dukes B colorectal cancer - The ASCOLT study: study protocol for a randomized controlled trial. *Trials* 2011;12:261.
28. Coyle C, Cafferty FH, Rowley S, et al. ADD-ASPIRIN: A phase III, double-blind, placebo controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours. *Contemp Clin Trials* 2016;51:56–64.
29. Chen W et al. Aspirin in Preventing Recurrence of Cancer in Patients with HER2 Negative Stage II-III Breast Cancer After Chemotherapy, Surgery, and/or Radiation Therapy. ClinicalTrials.gov Identifier: NCT02927249. Accessed 19 June 2019 at <https://clinicaltrials.gov/ct2/show/NCT02927249>.
30. Petrera M, Paleari L, Clavarezza M, et al. The ASAMET trial: a randomized, phase II, double-blind, placebo-controlled, multicenter, 2 x 2 factorial biomarker study of tertiary prevention with low-dose aspirin and metformin in stage I-III colorectal cancer patients. *BMC cancer* 2018;18:1210.
31. Michel P, Boige V, Andre T, et al. Aspirin versus placebo in stage III or high-risk stage II colon cancer with PIK3CA mutation: A French randomised double-blind phase III trial (PRODIGE 50-ASPIK). *Dig Liver Dis* 2018;50:305–7.

TABLE 1: Baseline characteristics of the ASPREE population by treatment group

Characteristic	Aspirin (n=9525)	Placebo (n=9589)
	No. (%)	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*	1053 (11.1)	1041 (10.9)
Personal cancer history	1827 (19.2)	1833 (19.1)
Family cancer history†	5605 (58.3)	5554 (58.5)
Previous cancer screening, % of asked ‡	2934 (96.7)	2924 (96.6)

*Previous regular aspirin use was defined according to participant-reported regular use of aspirin immediately before entering the study.

†Family cancer history includes a history of cancer in the participant's mother, father, siblings and children, as reported by each participant at baseline.

‡Previous cancer screening questions asked of 3022 participants in the aspirin group and 3035 participants in the placebo group

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 endpoint	Cancer incidence*			Cancer mortality†‡		
	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
	Aspirin	Placebo	Hazard Ratio (95% CI)	Aspirin	Placebo	Hazard Ratio (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 randomization§	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)

* Based on time from randomization to first incident cancer

† Based on time from randomization to cancer-related death in those who developed cancer

‡ 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, NEJM 2018, “Effect of Aspirin on All-Cause Mortality in the Healthy Elderly”; reference 2), whilst 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).

§ Metastatic cancer of the same type as pre-existing (prior to randomization) cancer

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

Cancer stage at diagnosis or anatomical site	Cancer incidence*			Cancer mortality*		
	Aspirin	Placebo	Aspirin vs Placebo	Aspirin	Placebo	Aspirin vs Placebo
	No. cancer events (rate per 1000 person-years)	No. cancer events(rate per 1000 person-years)	Hazard Ratio (95% CI)	No. cancer events (rate per 1000 person-years)	No. cancer events (rate per 1000 person-years)	Hazard Ratio (95% CI)
All solid tumors†	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‡	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						
Prostate§	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	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)
Cervicall	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)
Oesophageal	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	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)

*Cancer incidence is the first cancer event of anatomical type, noting that participants with more than one cancer type will be counted for each type. Cancer mortality reports deaths from the same individuals included in the same row under incidence.

†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.

‡Some cancer types, *e.g.* prostate and bladder, can have non-metastatic disease staged as Stage 4.

Cancer type is ordered with the top 5 most prevalent cancers by incident listed first, then listed alphabetically.

§ - males only; ¶ - females only;

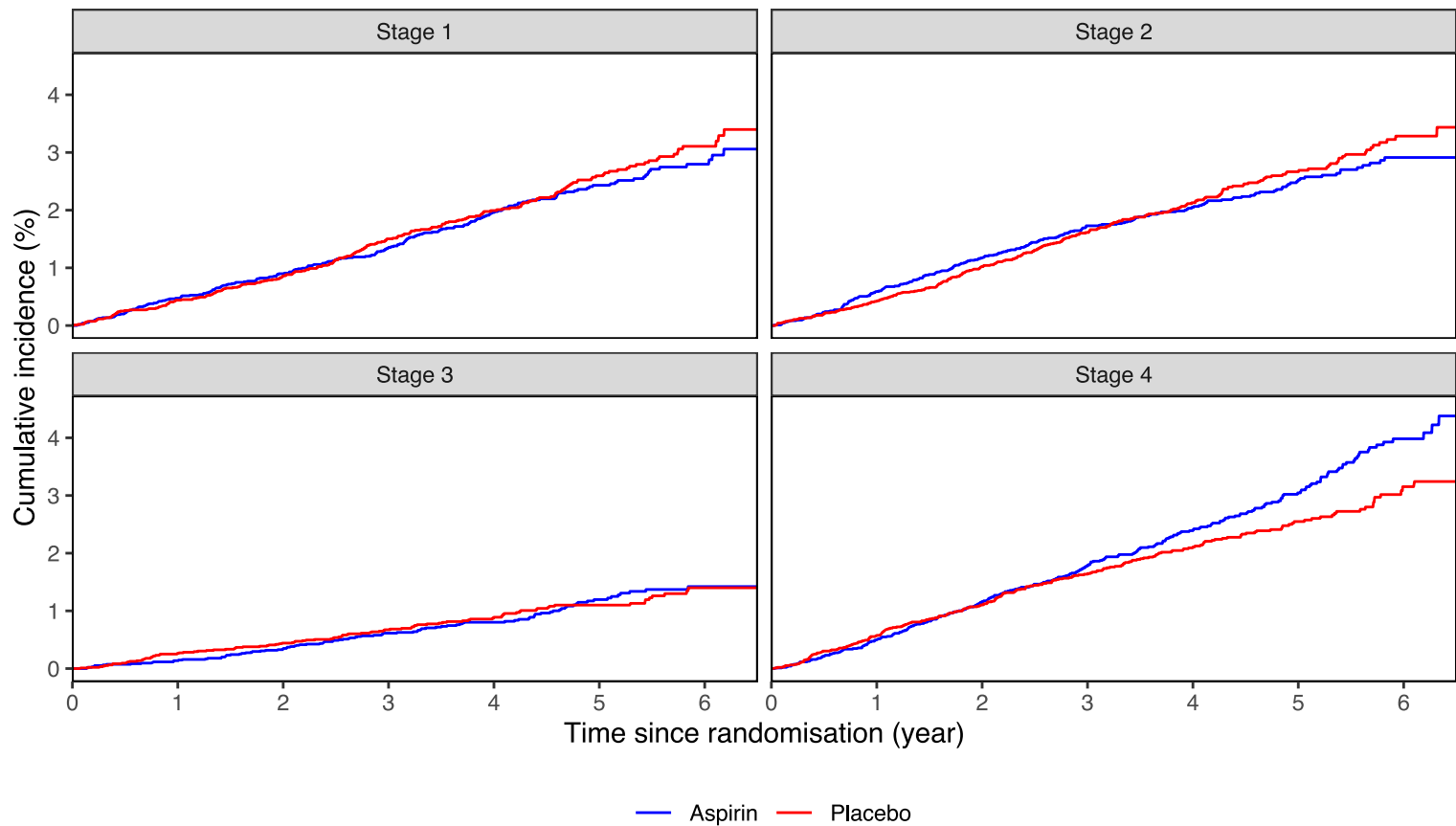
FIGURE LEGENDS

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 randomization to the occurrence of death following the cancer event.

FIGURE 3: Forest plots of solid tumor cancer incidence and mortality by sub-group. Solid tumor cancer incidence is shown Panel A and mortality is shown in Panel B. Subgroups are classed from baseline (enrolment) and include age in years, BMI (in kg/m^2), prior cancer history and family cancer history. Not all participants were asked about cancer-related medical screening (questionnaire introduced late in recruitment, 2013).

Figure 1--FINAL
Figure 1.



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

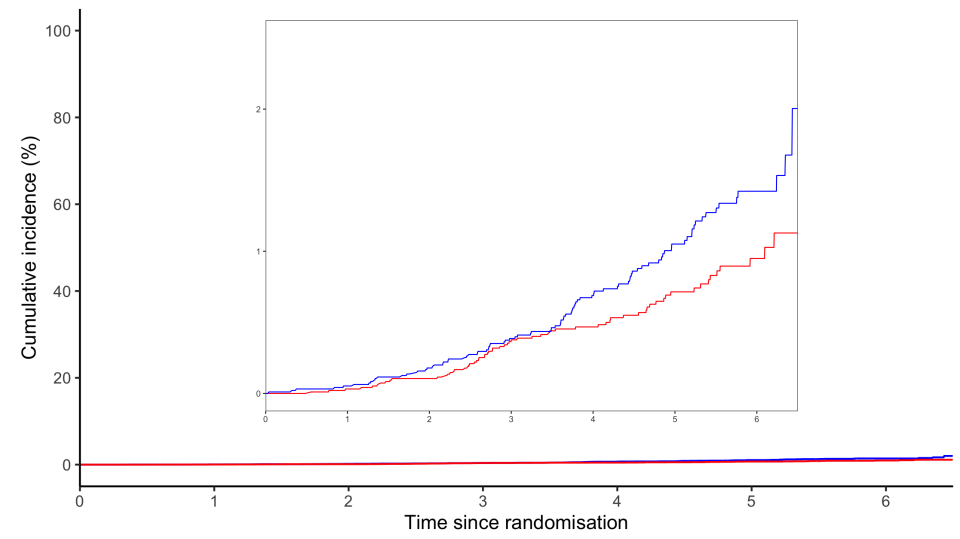
Figure 2--FINAL
Figure 2.



A

Localized cancer with subsequent death

Aspirin Placebo

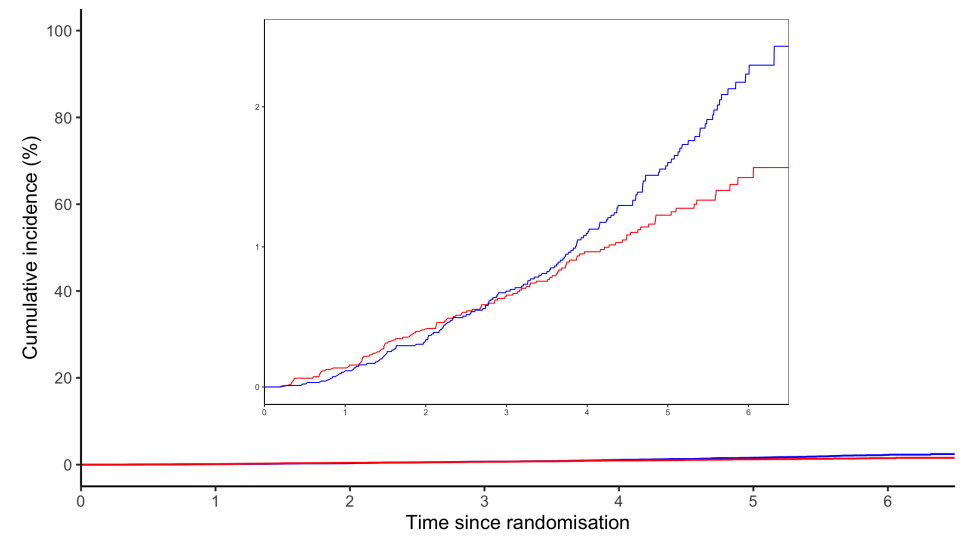


N at risk	0	1	2	3	4	5	6
Aspirin	9525	9481	9408	8286	6291	4016	1495
Placebo	9589	9545	9466	8369	6367	4077	1476

B

Metastatic cancer with subsequent death

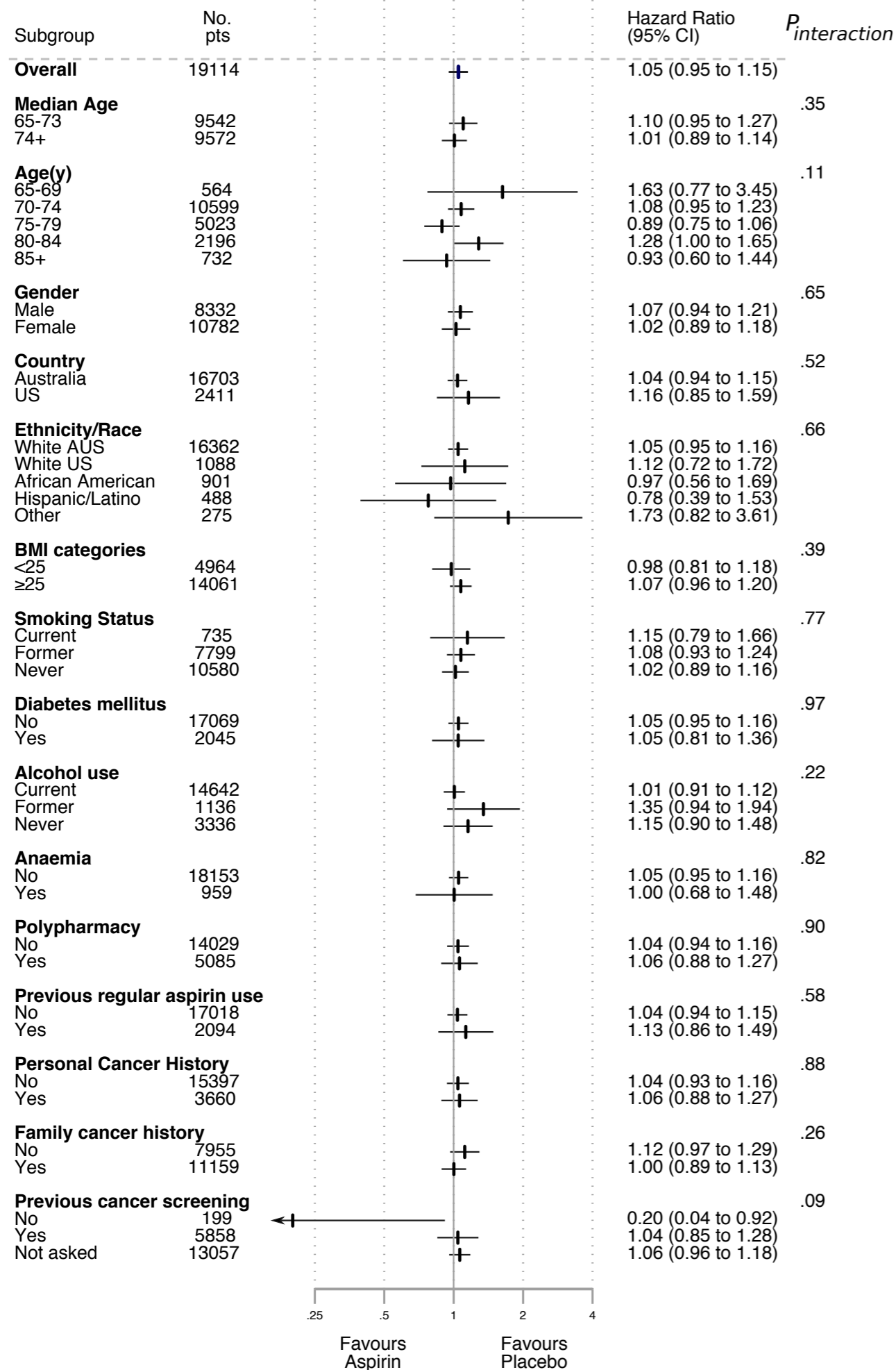
Aspirin Placebo



N at risk	0	1	2	3	4	5	6
Aspirin	9525	9481	9408	8286	6291	4016	1495
Placebo	9589	9545	9466	8369	6367	4077	1476

A

Solid tumor cancer incidence



B

Solid tumor mortality

