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Aspirin and the risk of colorectal cancer according to genetic susceptibility among older individuals

Andrew Bakshi[*,1], **Yin Cao**[*,3], **Suzanne G. Orchard**[1], **Prudence R. Carr**[1], **Amit D. Joshi**[2], **Alisa K Manning**[2], **Daniel D. Buchanan**[4,5,6], **Asad Umar**[9], **Ingrid M Winship**[6,7], **Peter Gibbs**[8], **John R. Zalcberg**[1], **Finlay Macrae**[6,7], **John McNeil**[1], **Paul Lacaze**[#,1], **Andrew T Chan**[#,2]

[1]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, VIC 3004 Melbourne, Australia

[2]Clinical and Translational Epidemiology Unit, MGH Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02108, USA.

[3]Alvin J. Siteman Cancer Center, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St Louis, MO 63110, USA

[4]Colorectal Oncogenomics Group, Department of Clinical Pathology, Melbourne Medical School, The University of Melbourne, Parkville, Australia

[5]University of Melbourne Centre for Cancer Research, The University of Melbourne, Parkville, Australia

[6]Genomic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Australia

[7]Department of Medicine (RMH),The University of Melbourne, Parkville, Australia

[8]Personalised Oncology Division, Walter and Eliza Hall Institute Medical Research, Faculty of Medicine, University of Melbourne, Melbourne, VIC 3052, Australia.

[9]Division of Cancer Prevention, National Cancer Institute, Rockville, MD 20892, USA

Abstract

[*]Corresponding author: Andrew T Chan, MD, MPH, achan@mgh.harvard.edu, Phone: 617 643 0112, Clinical and Translational Epidemiology Unit, MGH Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02108, USA,.

[*]Co-first

[#]Co-senior

Author Contributions

AB: Formal Analysis, Data curation, Conceptualization, Writing - original draft, YC: Conceptualization, Writing - original draft, Methodology, SGO: Data Acquisition, Data curation, Conceptualization, PRC, ADJ, AKM, DDB, AU, IW, PG, JZ, FM: Conceptualization, JJM: Resources, Funding acquisition, Project administration, Supervision, PL: Data Acquisition, Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing - original draft, ATC: Resources, Methodology, Funding acquisition, Project administration, Supervision, Writing - original draft. All authors were involved in writing - review & editing.

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Although aspirin has been considered a promising agent for prevention of colorectal cancer (CRC), recent data suggest a lack of benefit among older individuals. Whether some individuals with higher risk of CRC may benefit from aspirin remains unknown. We used a 95-variant CRC polygenic risk score (PRS) to explore the association between genetic susceptibility to CRC and aspirin use in a prospective study of 12,609 individuals of European descent aged ≥70 years, enrolled in the ASPREE (ASPirin in Reducing Events in the Elderly) double-blinded, placebo-controlled randomized trial (RCT). Cox proportional hazards models were used to assess the association of aspirin use on CRC, as well as the interaction between the PRS and aspirin treatment on CRC. Over a median of 4.7 years follow-up, 143 participants were diagnosed with incident CRC. Aspirin assignment was not associated with incidence of CRC overall (hazard ratio [HR]=0.94, 95% confidence interval (CI) 0.68–1.30) or within strata of PRS (p for interaction=0.97). However, the PRS was associated with an increased risk of CRC (HR=1.28 per standard deviation [SD], 95% CI 1.09–1.51). Individuals in the top quintile of the PRS distribution had an 85% higher risk compared with individuals in the bottom quintile (HR=1.85, 95% CI 1.08–3.15). In a prospective RCT of older individuals, a PRS is associated with incident CRC risk, but aspirin use was not associated with a reduction of incident CRC, regardless of baseline genetic risk.

Introduction

Aspirin has emerged as a promising agent for CRC prevention(1–6). Although the U.S. Preventive Services Task Force (USPSTF) recommended low-dose aspirin for the primary prevention of CRC and cardiovascular disease (CVD) in adults aged 50–59 with ≥10% 10-year CVD risk in 2016, (7) they recently released draft guidelines recommending against using aspirin among adults older than age 60, largely due to concerns about increased risks of gastrointestinal bleeding (GIB) and intracranial hemorrhage (ICH) and uncertainty about aspirin's anti-cancer benefit in older adults(7). However, one limitation of the recommendation was a lack of consideration of baseline CRC risk in weighing the risks and benefits of aspirin.

A key basis for the USPSTF's revised guidelines were data from a recent randomized controlled trial (RCT) of daily low-dose aspirin use in generally healthy older individuals aged ≥70 - the ASPirin in Reducing Events in the Elderly (ASPREE) trial(8), which did not find a reduced risk of CRC among individuals randomized to aspirin treatment during median 4.7 years of follow-up(9). However, since ~50% of CRC occurs among adults over aged 70(10) and screening has not been universally recommended over age 75 years(11), there is an unmet need to identify potential subgroups of older populations who may benefit from aspirin prevention. Thus far, it remains unknown whether older individuals with a higher genetic susceptibility to CRC may potentially have benefits from aspirin that individuals with low CRC risk do not.

Polygenic risk scores (PRS) aggregate the effects of multiple common disease-associated genetic variants identified through genome-wide association studies into a single measure of genetic risk. PRSs have been widely used to capture genetic predispositions, including for different types of cancer (12–14), and have been evaluated as risk prediction tools for

CRC. In a large study based on data from several consortia, a 95 SNP PRS was associated with increased risk of CRC(15). Thus, among participants enrolled in the ASPREE RCT, we examined whether the 95-SNP PRS for CRC(15) was associated with incident CRC risk in individuals 70 years and older, and whether individuals at higher risk of CRC, based on genetic predisposition, might have differentially benefited from aspirin use.

Materials & Methods

Study Population

ASPREE was a randomized, double-blinded placebo-controlled trial in healthy older individuals to determine whether 100mg of daily aspirin improves disability-free survival. The ASPREE trial enrolled 19,114 individuals, of which 13,349 had genotype data available. From that group, we included only individuals with non-Finnish European ancestry, and with a complete covariate dataset, resulting in 12,609 individuals (Supplementary Figure 1). The ASPREE study design(16,17), baseline characteristics(18) and trial results(8,19,20) have been published previously. The ASPREE trial is registered with Clinicaltrials.gov (NCT01038583) and approved by local ethics committees in accordance with the Belmont Report. Participants provided written informed consent for genetic research. Our report of this secondary analysis of a clinical trial follows STROBE guidelines for observational studies.

Genotyping

Genotyping of DNA samples was performed using the Axiom 2.0 Precision Medicine Diversity Research Array (Thermo Fisher Scientific, CA, USA), with alignment to GRCh38. The analysis identified ASPREE participants of non-Finnish European ancestry using principal component analysis (PCA) to compare overlap with the 1000 Genomes Non-Finnish European reference population(21). The TopMED imputation server was used for imputation(22), and variants with imputation quality scores <0.3 were removed, as well as multi-allelic variants.

Endpoint

The study endpoint was invasive CRC, defined as localised (non-metastatic) or metastatic disease, confirmed by an expert panel by histopathology, imaging of metastasis or other strong clinical evidence of metastasis(9). The adjudication process used by ASPREE trial investigators to classify incident CRC diagnoses is described previously(8),(9). We excluded participants with a self-reported prior history of CRC at the time of study enrolment (23).

PRS

The PRS was calculated for genotyped participants using plink (v1.9), based on the sum of the effect sizes for each disease-associated allele found in each participant (Supplementary Figure 2). The PRS was based on 95 CRC-associated SNPs as described previously(15), (24).

Statistical Analysis

The association between the PRS and incident CRC was estimated using a multivariable Cox proportional hazards model, adjusting for age at randomisation, sex, family history of CRC from first-degree relatives, body mass index (BMI), smoking status (current or prior), alcohol consumption (current or not), diabetes (yes/no) and treatment arm (aspirin or placebo). The PRS was assessed first as a continuous variable, then divided by quintiles (q) of the distribution into low (q1), medium (q2–4), and high (q5) risk groups. The c-index was used to determine the discriminative capability of the models tested. We tested for an interaction between the PRS and aspirin treatment for incident CRC risk using the Wald test. Competing risks (death) estimates of the cumulative incidence were visualised using the survfit function from the R survival package, with competing risk of death from other causes adjusted for in plot (25). Statistical analyses were conducted using R v3.6.1(26).

Data Availability

The data underlying this article will be shared on request to the corresponding author or to ASPREE.AMS@monash.edu.

Results

Following quality control, 12,609 participants of European-descent with both genotype data and a complete phenotype data set were identified (Table 1). After excluding participants with a prior history of CRC at enrolment, 143 participants were diagnosed with invasive CRC during the median follow-up time of 4.7 years (77 cases in males, and 66 in females). For calculation of the PRS, 93 of the 95 possible common SNPs in the PRS passed imputation quality control and were available for analysis (listed in Supplementary Table 1). Individuals grouped in the high-risk PRS group (q5) score also had higher rates of family history of CRC than individuals in low (q1) and medium (q2–4) PRS groups.

The PRS was associated with an increased risk of incident CRC (Table 2), with a HR of 1.28 per standard deviation (SD) (95% CI 1.09–1.51, p=0.003), and a c-index of 0.67 (95% CI 0.61–0.73). Compared to individuals in the low-risk PRS group (q1), individuals in the high-risk (q5) PRS group had 85% increased risk of CRC (HR: 1.85; 95% CI 1.08–3.15). After excluding participants with a family history of CRC, the PRS remained associated with incident CRC risk, with a similar HR (HR=1.31 per SD, 95% CI 1.10; 1.5, p=0.002). These findings suggest that the PRS remains associated with risk beyond age 70, even in the absence of a strong clinical risk factor like family history of CRC. The competing risks (adjusted for death) plot shows the differences in cumulative incidence between low, medium and high PRS risk groups (Figure 1).

In the total study population, randomisation to aspirin treatment was not associated with a reduced incidence of CRC (HR 0.94, 95% CI 0.68–1.30, p=0.7) (Table 3). Cumulative incidence competing risk plots further show that there is no significant difference in cumulative incidence between the aspirin or placebo arms when taking into account competing risk (of death) across any of the strata (Figure 2). We did not observe any interaction of aspirin treatment and the PRS in relation to risk of CRC (p

for interaction=0.97). Among individuals within strata defined by PRS, aspirin was not associated with reduced risk of CRC (Table 3) for low (HR 0.76, 95% CI 0.32; 1.81, medium (HR 0.93, 95% CI 0.60; 1.42) or high risk PRS groups (HR 1.12, 95% CI 1.12 (0.59; 2.13).

Discussion

In a population of generally healthy older individuals of European descent aged >70 years, followed for a median of 4.7 years, the 95-SNP PRS continues to identify individuals at higher risk of CRC, including individuals with no family history of CRC. However, we did not observe any evidence of an association of randomized aspirin treatment with risk of incident CRC according to PRS.

Overall, the CRC PRS shows a modest association with incident colorectal cancer risk in older age, though it is not clear the extent to which this might be incorporated into current CRC risk prediction models. Current recommendations propose routine screening be offered between the ages of 45 and 75 (27),(28), with consideration of continuing screening beyond age 75 based on individual health characteristics. A PRS which can identify an increased genetic predisposition to CRC in older age may have utility in further identifying which individuals might benefit from continuing screening into older age (29).

The lack of association between randomization to aspirin and the PRS is consistent with other CRC studies, which have also not observed a significant interaction between aspirin use and PRS(30)(31). Although the USPSTF does not currently recommend prophylactic use of aspirin for the primary prevention of CRC for individuals aged ≥60 years(32), other expert panels have continued to support consideration of its use for those aged <70 (33)(34). Multiple randomized clinical trials (RCT)s (35) have shown aspirin use resulting in a reduction in risk of colorectal adenomas among individuals with history of adenoma or CRC. For example, the CAPP2 RCT showed a reduction in risk of incident CRC among individuals with Lynch syndrome on higher doses of aspirin. However, the effect observed in *CAPP2* was not evident with short-term follow-up (2.5 years of intervention) but only emerged after longer-term follow-up (35). The intervention phase of ASPREE was ceased after a median of 4.7 years of follow up, during which aspirin therapy was found to increase risk of late-stage cancer incidence and cancer mortality. However, longer term follow up, in line with previously reported studies, may reveal a protective effect in older adults. There are numerous other studies also reporting evidence of aspirin reducing incident CRC diagnosis (36) and mortality(37)(38) in younger populations, particularly with longer duration of aspirin use(39,40). In the Nurses' Health Study and Health Professionals Follow-up Study, we recently found that aspirin use was associated with a lower risk of CRC among individuals aged over 70, but only if aspirin use was initiated at a younger age (41).

Indeed, the overall lack of benefit of aspirin observed in the ASPREE trial regardless of baseline genetic risk may also be explained by a differential effect of aspirin when initiated at an older age (the vast majority of ASPREE participants commenced aspirin after age 70) (42,43) or differential metabolism of aspirin at older ages (44) (45). Finally, the ASPREE trial also utilized a relatively low dose of aspirin (100mg) daily, which could account for

some variability in effects compared with other RCTs. However, it is noteworthy that other RCTs, including the Women's Health Study and meta-analyses of RCTs led by Rothwell et. al., observed benefits of aspirin use after long-term follow-up at low doses (46,47).

The strengths of our study are the well-characterised, older population followed prospectively, and the ability to examine aspirin effects alongside PRS in a randomized trial population. All in-trial CRC diagnoses were adjudicated by an expert panel utilising evidentiary documentation. The median age at the end of follow-up in ASPREE was 78 years, making the study well-suited to assessing CRC risk in an older age group where a large proportion of CRC diagnoses occur(10).

This analysis also has several limitations. First, the study had relatively short duration of treatment and follow-up and the vast majority of participants did not initiate aspirin until after age 70. It remains possible that a benefit for aspirin use overall, and potentially by PRS, may emerge with longer treatment duration, longer follow-up, or earlier age of initiation. Second, although the trial cohort was reasonably large, we had a limited number of incident CRC cases, limiting our statistical power, including to examine the effect of aspirin. Third, because this study only examines individuals of non-Finnish European descent, using a PRS derived from a similar ancestral population, it is unclear whether the results would be consistent in populations of more diverse genetic ancestry. Fourth, we did not examine specific genetic variants not captured by the 95 SNP PRS, including rare monogenic variants associated with Lynch syndrome and other CRC-associated syndromes. The literature suggests the possibility that individual genetic variants (distinct from the aggregated effect of many common variants in a PRS) may interact with aspirin treatment for modifying the risk of CRC(48)(49). The majority of these studies have found associations in genes or pathways associated with the development of CRC, such as the WNT pathway(50)(51) the prostaglandin synthesis pathways(52), and the ornithine decarboxylase gene(53). Thus, individual variability in response to aspirin for the primary prevention of CRC according to genetic variation may exist, but independently of the current PRS.

In conclusion, we present an assessment of an established CRC PRS in a group of healthy older individuals participating in an aspirin RCT. Although the PRS was associated with CRC risk among those aged over 70, we found no evidence that aspirin use benefited those at higher genetic risk of CRC according to their PRS. Further studies are needed to assess a potential biological basis for the difference in the association of aspirin with risk of CRC among older adults observed in this trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Prevention Relevance Statement

There is strong evidence to support prophylactic aspirin use for the prevention of colorectal cancer. However recent recommendations suggest the risk of bleeding in older individuals outweighs the benefit. We sought to determine whether some older individuals might still benefit from aspirin based on their genetic susceptibility.

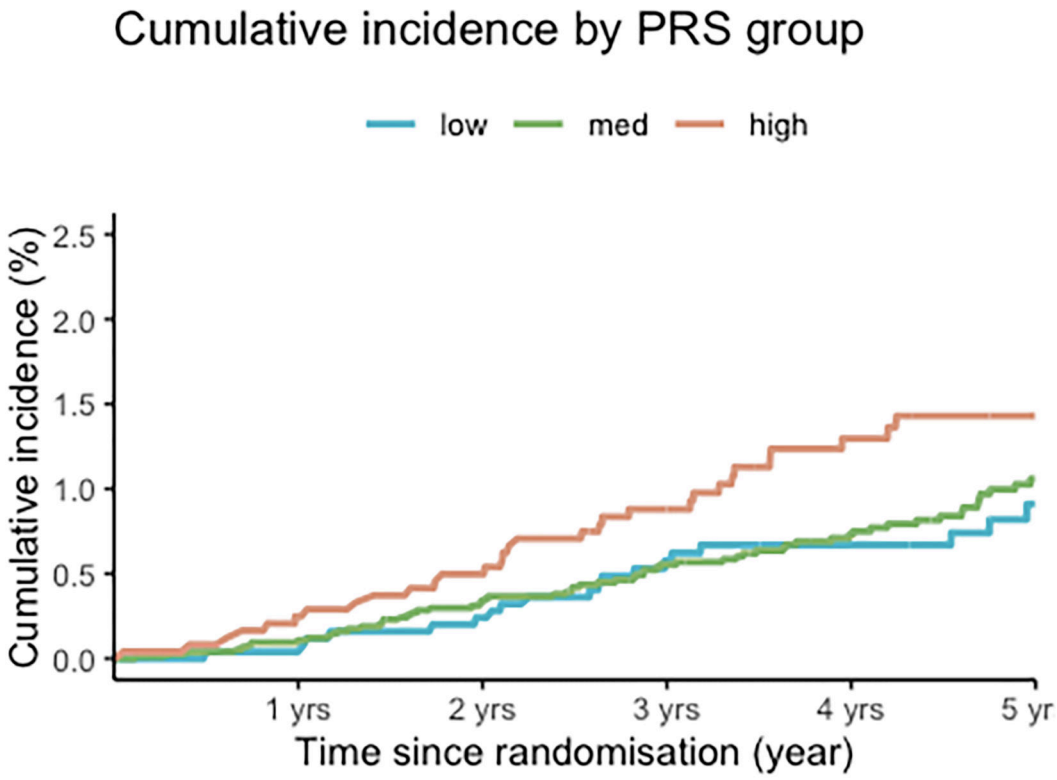

Figure 1 –. Cumulative incidence of colorectal cancer according to PRS groups

Competing risks (death from other causes) plots showing cumulative incidence of colorectal cancer stratified by PRS group (low q1, medium q2-q4 or high q5).

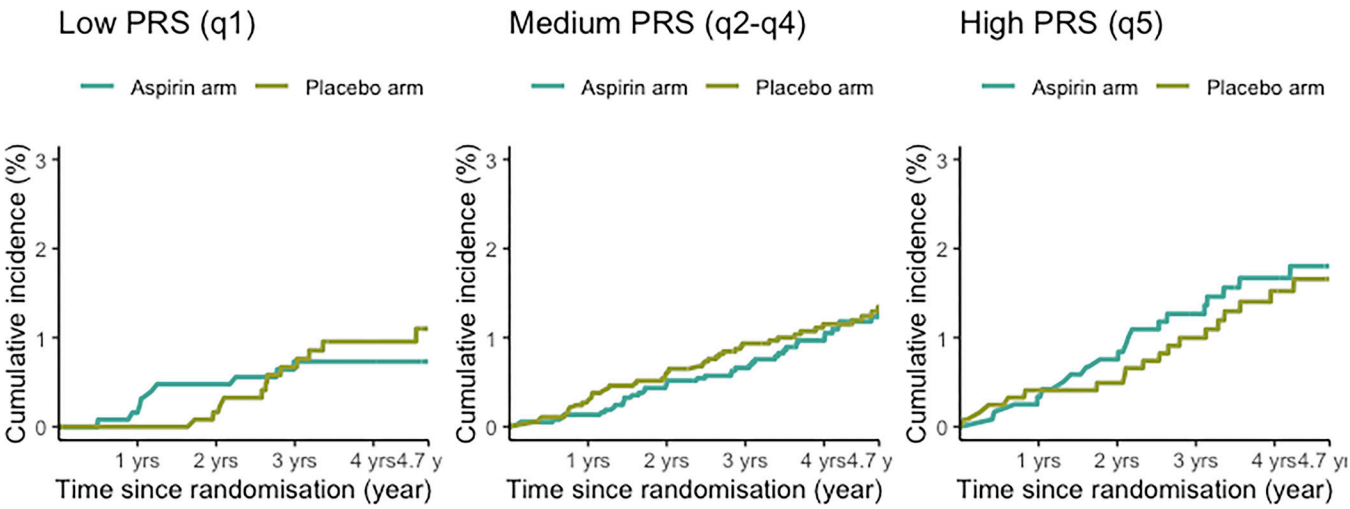

Figure 2 - Cumulative incidence of colorectal cancer by aspirin treatment and PRS groups.

Competing risks (death from other causes) plots showing cumulative incidence of colorectal cancer for low, medium and high PRS risk groups, with each plot stratified by treatment arm (aspirin/placebo).

Table 1.

Baseline characteristics of 12,609 genotyped participants according to PRS group.

Characteristic	Low PRS(q1), No. (%)	Medium PRS (q2-q4), No. (%)	High PRS (q5), No. (%)
No. of participants	2522	7565	2522
PRS, mean (SD)	7.24 (0.21)	7.86 (0.21)	8.49 (0.22)
Family history of colorectal cancer	311 (12.3)	1156 (15.3)	458 (18.2)
Sex, female	1395 (55.3)	4147 (54.8)	1391 (55.2)
Age at randomisation, years, mean (SD)	74.9 (4.1)	75.1 (4.2)	75.0 (4.2)
70–74 years	1562 (61.9)	4563 (60.3)	1534 (60.8)
75–79 years	631 (25.0)	1916 (25.3)	633 (25.1)
80–84 years	261 (10.3)	844 (11.2)	268 (10.6)
85+ years	68 (2.7)	242 (3.2)	87 (3.4)
Smoker - ever	1131 (44.8)	3301 (43.6)	1135 (45.0)
Current alcohol consumption	2028 (80.4)	6031 (79.7)	1994 (79.1)
History of diabetes	223 (8.8)	696 (9.2)	248 (9.8)
Mean body mass index (SD), kg/m^2	28.1 (4.5)	28.0 (4.6)	28.0 (4.5)
Randomized to aspirin	1276 (50.6)	3768 (49.8)	1244 (49.3)

Note: Brackets are for % of the population in that PRS group unless specified.

Table 2.

Association between PRS and risk of colorectal cancer

	Low PRS	Medium PRS	High PRS	per SD
Cases/Person-year	21/11408	84/33598	38/10981	
HR (unadjusted)	Ref	1.36 (0.84–2.19)	1.88 (1.11; 3.21)	1.29 (1.10; 1.52)
HR (adjusted)	Ref	1.32 (0.82; 2.14)	1.85 (1.08; 3.15)	1.28 (1.09; 1.51)

Adjusted model includes covariates for sex, first degree family history of CRC, age at randomisation, smoker (ever), (yes/no), current alcohol intake (yes/no), history of diabetes, BMI and treatment arm. SD=Standard deviation, HR=Hazard ratio, CI=Confidence interval, BMI=Body mass index, PY=Person years.

Table 3.

Interaction between aspirin treatment and PRS with risk of colorectal cancer

	Aspirin (cases/person-year)	Placebo (cases/person-year)	HR for aspirin (vs placebo) (95% CI)
Overall	69/27904	74/28083	0.94 (0.68; 1.30)
Low PRS	9/5769	12/5638	0.76 (0.32; 1.81)
Medium PRS	40/16704	44/16893	0.93 (0.60; 1.42)
High PRS	20/5429	18/5551	1.12 (0.59; 2.13)
Interaction (PRS × Aspirin)	-	-	0.97 (0.70; 1.34)

Adjusted for sex, first degree family history of CRC, age at randomisation, smoking (current or former), alcohol (current/no), history of diabetes, BMI. We tested for an interaction between the PRS and aspirin treatment for incident CRC risk in the coxph model using the Wald test.
SD=Standard deviation, HR=Hazard ratio, CI=Confidence interval, BMI=Body mass index.