Aspirin and the Risk of Colorectal Cancer According to Genetic Susceptibility among Older Individuals

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ABSTRACT

Although aspirin has been considered a promising agent for prevention of colorectal cancer, recent data suggest a lack of benefit among older individuals. Whether some individuals with higher risk of colorectal cancer may benefit from aspirin remains unknown. We used a 95-variant colorectal cancer polygenic risk score (PRS) to explore the association between genetic susceptibility to colorectal cancer and aspirin use in a prospective study of 12,609 individuals of European descent ages ≥70 years, enrolled in the ASPirin in Reducing Events in the Elderly (ASPREE) double-blinded, placebo-controlled randomized trial (randomized controlled trial; RCT). Cox proportional hazards models were used to assess the association of aspirin use on colorectal cancer, as well as the interaction between the PRS and aspirin treatment on colorectal cancer. Over a median of 4.7 years follow-up, 143 participants were diagnosed with incident colorectal cancer. Aspirin assignment was not associated with incidence of colorectal cancer overall [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 colorectal cancer (HR = 1.28 per 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 colorectal cancer risk, but aspirin use was not associated with a reduction of incident colorectal cancer, regardless of baseline genetic risk.

Prevention Relevance: 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.

Introduction

Aspirin has emerged as a promising agent for colorectal cancer prevention (1–6). Although the U.S. Preventive Services Task Force (USPSTF) recommended low-dose aspirin for the primary prevention of colorectal cancer and cardiovascular disease (CVD) in adults, ages 50 to 59 with ≥10% 10-year cardiovascular disease 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 anticancer benefit in older adults (7). However, one limitation of the recommendation was a lack of consideration of baseline colorectal cancer 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, ages ≥70–the ASPirin in Reducing Events in the Elderly (ASPREE) trial (8), which did not find a reduced risk of colorectal cancer among individuals randomized to aspirin treatment during median 4.7 years of follow-up (9). However, since approximately 50% of colorectal cancer occurs among adults over age 70 (10) and screening has not been universally recommended over age 75 years (11), there is an unmet need to identify

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

Materials and Methods

Study population

ASPREE was a randomized, double-blinded placebo-controlled trial in healthy older individuals to determine whether 100 mg 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 Fig. S1). 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 (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational studies.

Genotyping

Genotyping of DNA samples was performed using the Axiom 2.0 Precision Medicine Diversity Research Array (Thermo Fisher Scientific), 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 less than 0.3 were removed, as well as multi-allelic variants.

Endpoint

The study endpoint was invasive colorectal cancer, defined as localized (nonmetastatic) 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 colorectal cancer diagnoses is described previously (8, 9). We excluded participants with a self-reported prior history of colorectal cancer 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 Fig. S2). The PRS was based on 95 colorectal cancer–associated SNPs as described previously (15, 24).

Statistical analysis

The association between the PRS and incident colorectal cancer was estimated using a multivariable Cox proportional hazards model, adjusting for age at randomization, sex, family history of colorectal cancer 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 colorectal cancer risk using the Wald test. Competing risks (death) estimates of the cumulative incidence were visualized 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 colorectal cancer at enrolment, 143 participants were diagnosed with invasive colorectal cancer 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 S1). Individuals grouped in the high-risk PRS group (q5) score also had higher rates of family history of colorectal cancer than individuals in low (q1) and medium (q2–4) PRS groups.

The PRS was associated with an increased risk of incident colorectal cancer (**Table 2**), with an HR of 1.28 per SD [95% confidence interval (CI), 1.09–1.51; $P = 0.003$], and a c-index of

Table 1. Baseline characteristics of 12,609 genotyped participants according to PRS group.

Characteristic	Low PRS (q1), *N* (%)	Medium PRS (q2–q4), *N* (%)	High PRS (q5), *N* (%)
Participants (*N*)	2,522	7,565	2,522
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	1,395 (55.3)	4,147 (54.8)	1,391 (55.2)
Age at randomization, years, mean (SD)	74.9 (4.1)	75.1 (4.2)	75.0 (4.2)
70–74 years	1,562 (61.9)	4,563 (60.3)	1,534 (60.8)
75–79 years	631 (25.0)	1,916 (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	1,131 (44.8)	3,301 (43.6)	1,135 (45.0)
Current alcohol consumption	2,028 (80.4)	6,031 (79.7)	1,994 (79.1)
History of diabetes	223 (8.8)	696 (9.2)	248 (9.8)
Mean BMI (SD), kg/m^2	28.1 (4.5)	28.0 (4.6)	28.0 (4.5)
Randomized to aspirin	1,276 (50.6)	3,768 (49.8)	1,244 (49.3)

Note: Parentheses are for percentage of the population in that PRS group unless specified.

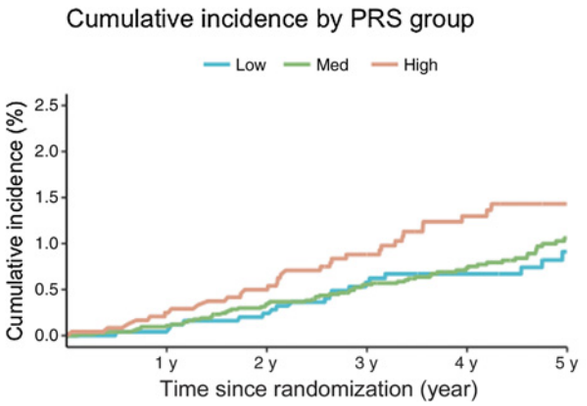

Figure 1.
Cumulative incidence of colorectal cancer according to PRS groups. Competing risks (death from other causes) plots showing cumulative incidence of colorectal cancer stratified by PRS group (low q1, medium q2–q4, or high q5). y, years.

0.67 (95% CI, 0.61–0.73). Compared with individuals in the low-risk PRS group (q1), individuals in the high-risk (q5) PRS group had 85% increased risk of colorectal cancer (HR = 1.85; 95% CI, 1.08–3.15). After excluding participants with a family history of colorectal cancer, the PRS remained associated with incident colorectal cancer 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 colorectal cancer. The competing risks (adjusted for death) plot shows the differences in cumulative incidence between low, medium, and high PRS risk groups (**Fig. 1**).

In the total study population, randomization to aspirin treatment was not associated with a reduced incidence of colorectal cancer (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 (**Fig. 2**). We did not observe any interaction of aspirin treatment and the PRS in relation to risk of colorectal cancer (P for interaction = 0.97). Among individuals within strata defined by PRS, aspirin was not associated with reduced risk of colorectal cancer (**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 more than 70 years, followed for a median of 4.7 years, the 95-SNP PRS continues to identify individuals at higher risk of colorectal cancer, including individuals with no family history of colorectal cancer. However, we did not observe any evidence of an association of randomized aspirin treatment with risk of incident colorectal cancer according to PRS.

Overall, the colorectal cancer 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 colorectal cancer 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 colorectal cancer 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 colorectal cancer studies,

Table 2. Association between PRS and risk of colorectal cancer.

	Low PRS	Medium PRS	High PRS	Per SD
Cases/person-year	21/1,1408	84/3,3598	38/10,981	
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)

Note: Adjusted model includes covariates for sex, first degree family history of colorectal cancer, age at randomization, smoker (ever, yes/no), current alcohol intake (yes/no), history of diabetes, BMI and treatment arm.

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	69/27,904	74/28,083	0.94 (0.68–1.30)
Low PRS	9/5,769	12/5,638	0.76 (0.32–1.81)
Medium PRS	40/16,704	44/16,893	0.93 (0.60; 1.42)
High PRS	20/5,429	18/5,551	1.12 (0.59–2.13)
Interaction (PRS x aspirin)	–	–	0.97 (0.70–1.34)

Note: Adjusted for sex, first degree family history of colorectal cancer, age at randomization, smoking (current or former), alcohol (current/no), history of diabetes, BMI. We tested for an interaction between the PRS and aspirin treatment for incident colorectal cancer risk in the coxph model using the Wald test.

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 colorectal cancer for individuals of ages ≥60 years (32), other expert panels have continued to support consideration of its use for those of ages <70 (33, 34). Multiple randomized clinical trials (35) have shown aspirin use resulting in a reduction in risk of colorectal adenomas among individuals with history of adenoma or colorectal cancer. For example, the CAPP2 RCT showed a reduction in risk of incident colorectal cancer 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 colorectal cancer 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 colorectal cancer 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; refs. 42, 43) or differential metabolism of aspirin at older ages (44, 45). Finally, the ASPREE trial also utilized a relatively low dose of aspirin (100 mg) 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 and colleagues, observed benefits of aspirin use after long-term follow-up at low doses (46, 47).

The strengths of our study are the well-characterized, older population followed prospectively, and the ability to examine aspirin effects alongside PRS in a randomized trial population. All in-trial colorectal cancer diagnoses were adjudicated by an expert panel utilizing evidentiary documentation. The median age at the end of follow-up in ASPREE was 78 years, making the study well-suited to assessing colorectal cancer risk in an older age group where a large proportion of colorectal cancer 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 colorectal cancer cases, limiting our statistical power, including to examine the effect of aspirin. Third,

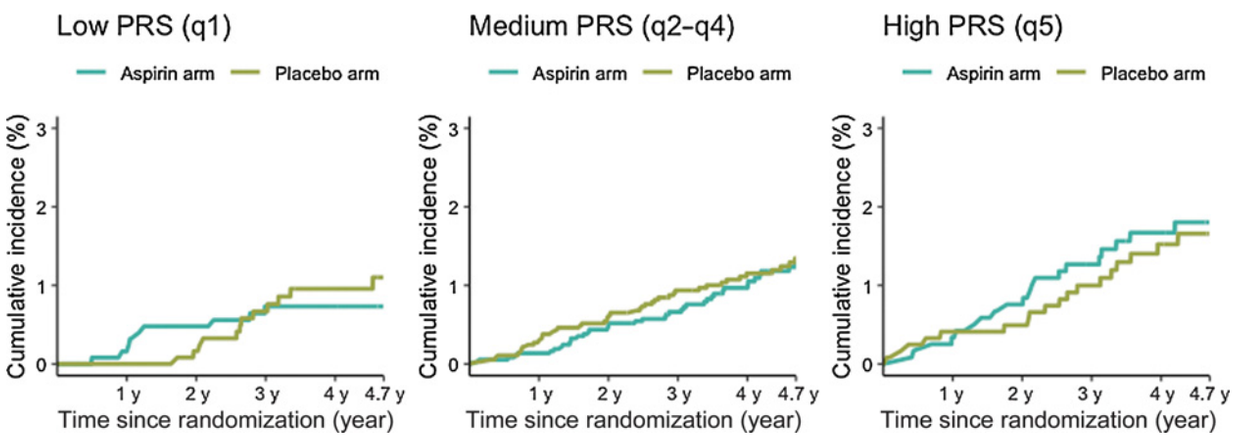

Figure 2.
Cumulative incidence of colorectal cancer by aspirin treatment and PRS groups. Competing risks (death from other causes) plots showing cumulative incidence of colorectal cancer for low, medium, and high PRS risk groups, with each plot stratified by treatment arm (aspirin/placebo). y, years.

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 colorectal cancer–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 colorectal cancer (48, 49). The majority of these studies have found associations in genes or pathways associated with the development of colorectal cancer, 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 colorectal cancer according to genetic variation may exist, but independently of the current PRS.

In conclusion, we present an assessment of an established colorectal cancer PRS in a group of healthy older individuals participating in an aspirin RCT. Although the PRS was associated with colorectal cancer risk among those of ages over 70, we found no evidence that aspirin use benefited those at higher genetic risk of colorectal cancer 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 colorectal cancer among older adults observed in this trial.

Authors' Disclosures

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Authors' Contributions

A. Bakshi: Conceptualization, data curation, formal analysis, methodology, writing–original draft, writing–review and editing. **Y. Cao:** Conceptualization, methodology, writing–original draft, writing–review and editing. **S.G. Orchard:** Resources, data curation, writing–review and editing. **P.R. Carr:** Conceptualization, writing–review and editing. **A.D. Joshi:** Conceptualization, writing–review and editing. **A.K. Manning:** Conceptualization, writing–review and editing. **D.D. Buchanan:** Conceptualization, writing–review and editing. **A. Umar:** Conceptualization, writing–review and editing. **I.M. Winship:** Conceptualization, writing–review and editing. **P. Gibbs:** Conceptualization, writing–review and editing. **J.R. Zalcberg:** Conceptualization, writing–review and editing. **F. Macrae:** Conceptualization, writing–review and editing. **J.J. McNeil:** Resources, supervision, funding acquisition, project administration, writing–review and editing. **P. Lacaze:** Conceptualization, data curation, supervision, funding acquisition, methodology, writing–original draft, writing–review and editing. **A.T. Chan:** Resources, supervision, funding acquisition, methodology, writing–original draft, project administration, writing–review and editing.

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