Original Investigation

Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer

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IMPORTANCE The US Preventive Services Task Force recently recommended the use of aspirin to prevent colorectal cancer and cardiovascular disease among many US adults. However, the association of aspirin use with the risk for other cancer types and the potential population-wide effect of aspirin use on cancer, particularly within the context of screening, remain uncertain.

OBJECTIVES To examine the potential benefits of aspirin use for overall and subtype-specific cancer prevention at a range of doses and durations of use and to estimate the absolute benefit of aspirin in the context of screening.

DESIGN, SETTING, AND PARTICIPANTS Two large US prospective cohort studies, the Nurses' Health Study (1980-2010) and Health Professionals Follow-up Study (1986-2012), followed up 135 965 health care professionals (88 084 women and 47 881 men, respectively) who reported on aspirin use biennially. The women were aged 30 to 55 years at enrollment in 1976; the men, aged 40 to 75 years in 1986. Final follow-up was completed on June 30, 2012, for the Nurses' Health Study cohort and January 31, 2010, for the Health Professionals Follow-up Study cohort, and data were accessed from September 15, 2014, to December 17, 2015.

MAIN OUTCOMES AND MEASURES Relative risks (RRs) for incident cancers and population-attributable risk (PAR).

RESULTS Among the 88 084 women and 47 881 men who underwent follow-up for as long as 32 years, 20 414 cancers among women and 7571 cancers among men were documented. Compared with nonregular use, regular aspirin use was associated with a lower risk for overall cancer (RR, 0.97; 95% CI, 0.94-0.99), which was primarily owing to a lower incidence of gastrointestinal tract cancers (RR, 0.85; 95% CI, 0.80-0.91), especially colorectal cancers (RR, 0.81; 95% CI, 0.75-0.88). The benefit of aspirin on gastrointestinal tract cancers appeared evident with the use of at least 0.5 to 1.5 standard aspirin tablets per week; the minimum duration of regular use associated with a lower risk was 6 years. Among individuals older than 50 years, regular aspirin use could prevent 33 colorectal cancers per 100 000 person-years (PAR, 17.0%) among those who had not undergone a lower endoscopy and 18 colorectal cancers per 100 000 person-years (PAR, 8.5%) among those who had. Regular aspirin use was not associated with the risk for breast, advanced prostate, or lung cancer.

CONCLUSIONS AND RELEVANCE Long-term aspirin use was associated with a modest but significantly reduced risk for overall cancer, especially gastrointestinal tract tumors. Regular aspirin use may prevent a substantial proportion of colorectal cancers and complement the benefits of screening.

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Invited Commentary

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Secondary analysis of randomized clinical trials (RCTs) of aspirin for the prevention of cardiovascular disease (CVD) supports a potential role of aspirin in reducing overall cancer incidence. In 6 trials of daily low-dose aspirin therapy (≥75 mg), aspirin use was associated with a relative risk (RR) of 0.76 (95% CI, 0.66-0.88) for overall cancer after 3 years, with the benefit increasing with longer duration.[1] However, the number of cancers was too limited to reliably establish the effects on specific cancer types, and uncertainties remain in relation to the optimum dose and duration of use. With 10 years of active intervention and another 8 years of posttrial follow-up, the Women's Health Study found no association between alternate-day low-dose (100-mg) aspirin therapy and the overall risk for cancer (RR, 0.97; 95% CI, 0.92-1.03), but found a significant risk reduction for colorectal cancer (CRC) (RR, 0.80; 95% CI, 0.67-0.97).[2]

Prospective data on the association of aspirin with overall cancer within a single, well-characterized population are limited to an analysis of the Cancer Prevention Study II.[3] In that cohort, daily use of adult-strength aspirin for at least 5 years compared with no use was associated with lower overall cancer incidence in men (RR, 0.84; 95% CI, 0.76-0.93) and a nonstatistically significant lower overall cancer incidence in women (RR, 0.86; 95% CI, 0.73-1.03) during 11 years of follow-up.[3] Additional studies have also examined aspirin use and the risk for individual cancers; benefit appears most evident for gastrointestinal tract cancers, including CRC and gastroesophageal cancer.[4-6] However, comparison across these studies is challenging owing to heterogeneities in the definition of aspirin exposure, the doses evaluated, the length of follow-up, and the timing of the assessment.

In 2007, the US Preventive Services Task Force (USPSTF)[7] recommended against the use of aspirin for the prevention of CRC. However, in their 2015 updated draft recommendations,[8,9] the USPSTF reversed this position, acknowledging that supporting evidence had become compelling enough to warrant the inclusion of CRC prevention into their rationale for routine low-dose aspirin use among certain subgroups of adults with specific cardiovascular risk profiles.[10] This recommendation distinguishes aspirin as the first pharmacologic agent to be endorsed by the USPSTF for chemoprevention of a cancer in a population not characterized as high risk.[11] However, the USPSTF[12] and a UK panel[13] have emphasized the need for additional research into the effect of long-term aspirin use, not only on the incidence of CRC but on that of overall cancer, according to a range of doses and by subgroups, including age, sex, baseline cancer risk, or comorbid conditions. It remains unclear what the additional effect of aspirin use on cancer would be in the setting of screening, including lower endoscopy,[11] which is associated with a significantly lower risk for CRC.[14]

To address these critical questions, we examined the association of aspirin with incident cancer among 135 965 women and men enrolled in 2 large prospective US cohort studies. The participants provided detailed and updated information on aspirin use for more than 32 years. Our study setting allowed a more comprehensive assessment of the potential population-wide effect of aspirin at a wide range of doses during long-term follow-up within the context of screening and other medical, reproductive, and lifestyle factors than would be feasible in an RCT.

Key Points

Question What are the potential benefits of aspirin for the prevention of cancer?

Findings In 2 large, prospective cohort studies, regular use of low doses of aspirin for at least 6 years was associated with a significantly lower risk for overall cancer, primarily tumors of the gastrointestinal tract. Although aspirin may prevent colorectal cancers irrespective of screening, substantially more cases appear to be prevented among those who do not undergo screening.

Meaning Long-term aspirin use was associated with a modest but significantly reduced risk for cancer, especially gastrointestinal tract cancer, and may complement the benefits of colorectal cancer screening.

Methods

Study Population

We used data from 2 ongoing prospective studies: the Nurses' Health Study (NHS), a cohort study of 121 700 US female nurses aged 30 to 55 years at enrollment in 1976, and the Health Professionals Follow-up Study (HPFS), a cohort study of 51 529 US male health care professionals aged 40 to 75 years at enrollment in 1986. Participants returned mailed questionnaires at enrollment and every 2 years thereafter to provide data on lifestyle factors, medical history, and disease outcomes and every 4 years to report dietary intake. The follow-up rates in both cohorts have been greater than 90%. The institutional review boards of the Harvard T. H. Chan School of Public Health and Partners Healthcare approved the study protocol, and all patients provided written informed consent for the researchers to access their medical records.

Assessment of Aspirin Use

In the NHS, aspirin use was first assessed in 1980 and every 2 years thereafter except in 1986, and the participants were asked whether they took aspirin most weeks, the number of tablets taken per week, and the duration (in years) of aspirin use. In the HPFS in 1986 and every 2 years thereafter, participants were asked whether they used aspirin 2 or more times per week. Beginning in 1992, the number of tablets taken per week was assessed. For both cohorts, participants were specifically asked about standard-dose (325-mg) aspirin tablets. From 1994 to 1998, participants were also asked to convert intake of 4 baby (81-mg) aspirin to 1 standard aspirin tablet. Since 2000, participants were asked to report separately the regular use of baby or low-dose aspirin and standard-dose aspirin. In this analysis, regular aspirin users were defined as those who reported aspirin use at least 2 times per week, including standard and low-dose aspirin. Nonregular users included those who used aspirin fewer than 2 times per week or used no aspirin. The major reasons for aspirin use were headache, arthritis and other

musculoskeletal pain, and CVD prevention among women[15] and CVD prevention, musculoskeletal pain, CVD, and headache among men.[16]

Ascertainment of Cancer

In each cohort, incident cancers were ascertained by biennial questionnaire reports and the National Death Index.[17,18] Researchers obtained permission from participants or next-of-kin to obtain their medical records and pathologic reports and abstracted the information on anatomic location, stage, and histologic type of the cancer. The confirmed cancers were defined according to the *International Classification of Diseases, Ninth Revision*.

Statistical Analysis

Data were analyzed from September 15, 2014, to December 17, 2015. We analyzed regular aspirin use in relation to the risk for any type of cancer, gastrointestinal tract cancer (colorectum, pancreas, gastroesophagus, and other sites that included the small intestine, anus, liver, biliary tract, and peritoneum) and other non-gastrointestinal tract cancers (breast, advanced prostate, lung, and other non-gastrointestinal tract sites) in the main analyses. We also conducted analysis according to organ site. Person-years accrued from the date of return of the baseline questionnaire (1980 in the NHS and 1986 in the HPFS) until the diagnosis of any type of cancer (excluding nonmelanoma skin or nonadvanced prostate cancers[19]), death, or the end of follow-up (June 30, 2012, for the NHS and January 31, 2010, for the HPFS). At baseline, we excluded participants with cancer or who reported implausible energy intakes.[19]

Cox proportional hazards regression models conditioning on age (months), questionnaire cycle, and sex or cohort (in the combined cohort analysis) were used to compute hazard ratios as estimates for age- and multivariable-adjusted RRs and 95% CIs. We used time-varying aspirin exposure and covariates (when applicable). The covariates included in the multivariable models were established or potential risk factors for major cancers[20,21] (eMethods in the Supplement and **Table 1**). For dose analysis, we calculated the total standard aspirin tablets per week by combining the use of low-dose (converted to standard) and standard aspirin with their corresponding frequency of use within 1 week and updated the information biannually. We also assessed the influence of the duration of regular use (in years), which summed all previous intervals of regular use before each 2-year follow-up. We assessed linear trend using the median of each category as a continuous variable and nonlinearity using restricted cubic splines. We evaluated whether the effects of aspirin differed according to strata defined by the covariates and cardiac risk factors. We tested interactions by likelihood ratio tests.

To estimate the potential population-level effect of aspirin use on reducing the burden of cancer, we calculated the proportion of cancers that were attributable to aspirin use (partial population-attributable risk [PAR]) while controlling for other covariates.[22] We also examined the potential effect of aspirin, including PAR and age- and sex-adjusted absolute incidence and incidence reduction, according to a history of screening for CRC with a lower endoscopy among participants 50 years and older.

As a sensitivity analysis, we evaluated the latency of aspirin dose and the risk for cancer using a lag of 6 to 8 years. We examined the influence of regular aspirin use and duration (former use, ≤10 or >10 years; current use, ≤10 or >10 years) and the time since last regular use among former long-term regular users (>10 years). We also jointly classified aspirin dose and duration to examine whether risk reduction would be achieved with a shorter duration of use at higher doses. All analyses were performed using SAS (version 9.3; SAS Institute Inc) with 2-sided $P < .05$ indicating significance.

Results

During the 32 years of follow-up, we documented 20 414 cancers among 88 084 women and 7571 cancers among 47 881 men (excluding nonmelanoma skin and nonadvanced prostate cancers) during 3 245 734 person-years. Over time, regular aspirin users (≥2 times per week) were more likely to have type 2 diabetes mellitus, to use multivitamins, to have undergone a previous lower endoscopy, and to have consumed more alcohol (eTable 1 in the Supplement). Postmenopausal women who used aspirin regularly were more likely to use menopausal hormone therapy. Men who used aspirin were also more likely to use nonsteroidal anti-inflammatory drugs regularly and to have undergone a previous prostate-specific antigen test.

Compared with nonregular use, regular aspirin use was associated with a lower risk for overall cancer (RR, 0.97; 95% CI, 0.94-0.99), which was primarily owing to a lower incidence of gastrointestinal tract cancers (RR, 0.85; 95% CI, 0.80-0.91), especially CRC (RR, 0.81; 95% CI, 0.75-0.88) (Table 1), with similar estimates in women and men. Regular aspirin use was associated with a nonsignificant reduced risk for gastroesophageal cancer (RR, 0.85; 95% CI, 0.70-1.03). Regular use of aspirin was not associated with the risk for non-gastrointestinal tract cancers (RR, 0.99; 95% CI, 0.97-1.02) (Table 1 and eTable2 in the Supplement). Specifically, we did not observe a significant association between aspirin and breast, advanced prostate, or lung cancer.

The apparent benefit of aspirin on gastrointestinal tract cancers (including CRC) appeared to be dose dependent, emerging at 0.5 to 1.5 standard aspirin tablets per week or the equivalent of a daily dose of low-dose aspirin (**Table 2** and eTable 3 in the Supplement), and no departure from linearity was observed ($P < .001$ for trend). The estimates were similar after applying a 6- to 8-year lag (eTable 4 in the Supplement). For CRC specifically compared with no reported aspirin use, the multivariable RRs were 0.86 (95% CI, 0.76-0.97) for 0.5 to 1.5 standard aspirin tablets per week; 0.84 (95% CI, 0.75-0.93) for 2 to 5 tablets per week; 0.76 (95% CI, 0.68-0.86) for 6 to 14 tablets per week; and 0.61 (95% CI, 0.45-0.81) for at least 15 tablets per week ($P < .001$ for trend).

During the first 5 years of use, we did not observe any significant reduction in the risk for cancer compared with

Table 1. Regular Aspirin Use and Risk for Cancer[a]

Cancer Type	Regular User/Nonregular User		
	Women	Men	All Participants
All[b]			
No. of cases	8962/11 452	3748/3823	12 710/15 275
Person-years	932 102/1 407 535	418 234/487 863	1 350 336/1 895 398
Age-adjusted RR (95% CI)	1.00 (0.98-1.03)	0.95 (0.91-1.00)	0.99 (0.97-1.01)
Multivariable RR (95% CI)[c]	0.98 (0.95-1.01)	0.93 (0.89-0.97)	0.97 (0.94-0.99)
GI tract cancer			
No. of cases	972/1404	889/1028	1861/2432
Age-adjusted RR (95% CI)	0.88 (0.81-0.96)	0.82 (0.75-0.90)	0.85 (0.80-0.91)
Multivariable RR (95% CI)[c]	0.87 (0.80-0.95)	0.82 (0.75-0.90)	0.85 (0.80-0.91)
Colorectal cancer			
No. of cases	688/1040	511/656	1199/1696
Age-adjusted RR (95% CI)	0.84 (0.76-0.92)	0.77 (0.68-0.87)	0.81 (0.75-0.87)
Multivariable RR (95% CI)[c]	0.84 (0.76-0.93)	0.77 (0.68-0.87)	0.81 (0.75-0.88)
Pancreatic cancer			
No. of cases	124/154	162/167	286/321
Age-adjusted RR (95% CI)	1.09 (0.85-1.39)	0.88 (0.70-1.09)	0.97 (0.82-1.14)
Multivariable RR (95% CI)[c]	1.04 (0.81-1.32)	0.87 (0.69-1.09)	0.95 (0.80-1.12)
Gastroesophageal cancer			
No. of cases	61/109	143/138	204/247
Age-adjusted RR (95% CI)	0.72 (0.53-1.00)	0.97 (0.77-1.24)	0.87 (0.72-1.06)
Multivariable RR (95% CI)[c]	0.71 (0.52-0.98)	0.94 (0.74-1.21)	0.85 (0.70-1.03)
Other GI tract cancer			
No. of cases	99/101	73/67	172/168
Age-adjusted RR (95% CI)	1.15 (0.87-1.53)	0.91 (0.65-1.29)	1.05 (0.84-1.30)
Multivariable RR (95% CI)[c]	1.07 (0.80-1.43)	0.93 (0.65-1.31)	1.01 (0.81-1.27)
Non-GI tract cancer			
No. of cases	7990/10 048	2859/2795	10 849/12 843
Age-adjusted RR (95% CI)	1.02 (0.99-1.05)	1.00 (0.95-1.06)	1.02 (0.99-1.04)
Multivariable RR (95% CI)[c]	1.00 (0.97-1.03)	0.97 (0.92-1.02)	0.99 (0.97-1.02)
Breast cancer			
No. of cases	3109/4315	NA	NA
Age-adjusted RR (95% CI)	1.00 (0.96-1.05)	NA	NA
Multivariable RR (95% CI)[c]	0.98 (0.93-1.02)	NA	NA
Prostate cancer[b]			
No. of cases	NA	494/525	NA
Age-adjusted RR (95% CI)	NA	0.98 (0.86-1.11)	NA
Multivariable RR (95% CI)[c]	NA	0.97 (0.85-1.10)	NA
Lung cancer			
No. of cases	745/824	447/414	1192/1238
Age-adjusted RR (95% CI)	1.14 (1.03-1.26)	0.97 (0.85-1.11)	1.08 (0.99-1.17)
Multivariable RR (95% CI)[c]	1.11 (1.00-1.23)	0.96 (0.84-1.11)	1.05 (0.97-1.14)
Other non-GI tract cancer			
No. of cases	4136/4909	1924/1866	6060/6775
Age-adjusted RR (95% CI)	1.01 (0.97-1.06)	1.01 (0.95-1.08)	1.01 (0.98-1.05)
Multivariable RR (95% CI)[c]	1.00 (0.96-1.04)	0.97 (0.90-1.03)	0.99 (0.96-1.03)

Abbreviations: GI, gastrointestinal; NA, not applicable; RR, relative risk.

[a] Data were obtained from the 1980-2012 Nurses' Health Study and the 1986-2010 Health Professionals Follow-up Study.

[b] Advanced prostate cancer cases were defined as regionally invasive or metastatic disease (T3b, N1, or M1 or worse) at diagnosis, as developed metastases, or as death due to prostate cancer during follow-up.

[c] Adjusted for race (white or nonwhite), height (continuous), body mass index (quintile), family history of cancer (yes or no), physical examination in the past 2 years (yes or no), history of colonoscopy or sigmoidoscopy (yes or no), smoking (never, <5, 5-19, 20-39, or ≥40 pack-years), physical activity (quintile), alcohol intake (0, <5, 5-14, 15-29, or ≥30 g/d), current multivitamin use (yes or no), total energy intake (quintile), red and processed meat intake (quintile), folate intake (quintile), calcium intake (quintile), and Alternate Healthy Eating Index 2010 (quintile).[20,21] For men, we also adjusted for the prostate-specific antigen test in the past 2 years (yes or no) and for women, for menopause status (premenopause or postmenopause), menopausal hormone therapy (never, past, or current use), and mammogram in the past 2 years (yes or no). The model was also conditioned on age (months), calendar year of the questionnaire cycle, and sex or cohort.

nonregular users. Beyond 5 years, we observed a progressively greater reduction in the risk for gastrointestinal tract cancers (**Table 3** and eTable 5 in the Supplement) and CRCs ($P < .001$ for trend). Furthermore, the benefit was no longer evident beyond 5 years since the last use among former long-term users; however, power was limited (eTable 6 in the Supplement). A joint analysis of dose and duration suggests that the apparent benefit of aspirin use for gastrointestinal tract cancers (eTable 7 in the Supplement) and CRCs appears with longer duration (>10 years) of use of 0.5 to 1.5 standard aspirin tablets per week compared with people using higher dosages.

Table 2. Dose of Standard Aspirin and Risk for Cancer[a]

Cancer Type	Aspirin Dose, No. of Tablets/wk					P Value for Trend[b]
	0	0.5-1.5	2-5	6-14	≥15	
All[c]						
No. of cases (n = 25 787)	12 320	3666	5421	3651	729	NA
Person-years	1 388 161	456 953	591 278	377 871	91 755	NA
Age-adjusted RR (95% CI)	1 [Reference]	0.96 (0.92-1.00)	0.97 (0.94-1.00)	0.99 (0.95-1.03)	1.02 (0.94-1.10)	.81
Multivariable RR (95% CI)[d]	1 [Reference]	0.97 (0.93-1.00)	0.96 (0.93-0.99)	0.95 (0.91-0.99)	0.97 (0.90-1.05)	.04
GI tract cancer						
No. of cases (n = 3727)	1828	542	740	535	82	NA
Age-adjusted RR (95% CI)	1 [Reference]	0.88 (0.80-0.97)	0.85 (0.78-0.93)	0.86 (0.78-0.95)	0.73 (0.58-0.91)	<.001
Multivariable RR (95% CI)[d]	1 [Reference]	0.89 (0.80-0.98)	0.85 (0.78-0.93)	0.83 (0.75-0.91)	0.69 (0.55-0.86)	<.001
Non-GI tract cancer						
No. of cases (n = 22 060)	10 492	3124	4681	3116	647	NA
Age-adjusted RR (95% CI)	1 [Reference]	0.97 (0.93-1.01)	0.99 (0.96-1.03)	1.01 (0.97-1.06)	1.07 (0.99-1.16)	.09
Multivariable RR (95% CI)[d]	1 [Reference]	0.98 (0.94-1.02)	0.98 (0.95-1.02)	0.97 (0.93-1.01)	1.02 (0.94-1.11)	.65

Abbreviations: GI, gastrointestinal; NA, not applicable; RR, relative risk.

[a] Data were obtained from the 1980-2012 Nurses' Health Study and the 1986-2010 Health Professionals Follow-up Study.

[b] Calculated as tests for trend using the median value of each category as a continuous variable.

[c] For prostate cancer, only advanced cases were included.

[d] Adjusted for race (white or nonwhite), height (continuous), body mass index (quintile), family history of cancer (yes or no), physical examination in the past 2 years (yes or no), history of colonoscopy or sigmoidoscopy (yes or no), smoking (never, <5, 5-19, 20-39, or ≥40 pack-years), physical activity (quintile), alcohol intake (0, <5, 5-14, 15-29, or ≥30 g/d), current multivitamin use (yes or no), total energy intake (quintile), red and processed meat intake (quintile), folate intake (quintile), calcium intake (quintile), and Alternate Healthy Eating Index 2010 (quintile).[20,21] For men, we also adjusted for the prostate-specific antigen test in the past 2 years (yes or no) and for women, for menopause status (premenopause or postmenopause), menopausal hormone therapy (never, past, or current use), and mammogram in the past 2 years (yes or no). The model was also conditioned on age (months), calendar year of the questionnaire cycle, and sex or cohort.

The associations of regular aspirin use with the risk for gastrointestinal tract cancer overall and CRC specifically were similar for women and men (Table 1 and eTables 3 and 5 in the Supplement) and were not modified by age, family history of cancer, history of type 2 diabetes mellitus, cardiac risk factors, body mass index, menopausal status and use of menopausal hormones among women, multivitamin use, regular nonsteroidal anti-inflammatory drug use, smoking history, and history of cancer screening (eFigure in the Supplement). The association of aspirin use with the RR for colorectal (eFigure, B, in the Supplement), breast, and advanced prostate cancers (null associations) did not appear to vary according to a history of endoscopy, mammography, and prostate-specific antigen screening, respectively.

The partial PAR or proportion of incident cancers that would have been prevented with regular use of aspirin was 1.8% for overall cancer, 8.0% for gastrointestinal tract cancer overall, and 10.8% for CRC specifically (eTable 8 in the Supplement). Among individuals older than 50 years, regular aspirin use was estimated to prevent 33 CRCs per 100 000 person-years (128 for nonregular vs 95 for regular users; PAR, 17.0%) among those who did not have a lower endoscopy and 18 CRCs per 100 000 person-years (97 for nonregular vs 79 for regular users; PAR, 8.5%) among those who had a lower endoscopy.

Discussion

In 2 large prospective cohort studies, regular aspirin use was significantly associated with a 3% lower risk for overall cancers, which was primarily owing to a 15% lower risk for gastrointestinal tract cancers and a 19% lower risk for cancers of the colon and rectum. In contrast, regular use of aspirin was not associated with a lower risk for other major types of cancer, such as breast, prostate, or lung. The benefit of aspirin for gastrointestinal tract cancers appeared evident with the use of at least 0.5 to 1.5 standard aspirin tablets per week; the minimum duration of regular use associated with a lower risk was 6 years. Among individuals older than 50 years, regular aspirin use could prevent 33 CRCs per 100 000 person-years (17.0%) among those who did not undergo a lower endoscopy and 18 CRCs per 100 000 person-years (8.5%) among those who underwent lower endoscopy.

Although the relative reduction in overall cancer risk may appear modest, extrapolation of our PAR estimates to US cancer incidence rates in 2015[23] indicates that regular aspirin use could prevent more than 29 800 gastrointestinal tract tumors per year, which account for 25% of cancer-related deaths.[23] Although CRC screening accounted for 50% of the overall decline in CRC incidence during the past 2 decades,[24] uptake

Table 3. Duration of Regular Aspirin Use and Risk for Cancer[a]

Cancer Type	Regular Aspirin Use, y					*P* Value for Trend[b]
	0	1-5	6-10	11-15	≥16	
All cancer[c]						
No. of cases (n = 27 906)	8739	5122	5190	2647	6208	NA
Person-years	1 204 992	598 623	524 570	258 055	641 465	NA
Age-adjusted RR (95% CI)	1 [Reference]	1.02 (0.99-1.06)	1.02 (0.98-1.06)	1.02 (0.97-1.07)	0.98 (0.95-1.02)	.11
Multivariable RR (95% CI)[d]	1 [Reference]	1.00 (0.96-1.03)	0.99 (0.95-1.02)	0.98 (0.94-1.03)	0.94 (0.91-0.98)	.001
GI tract cancer						
No. of cases (n = 4283)	1495	835	815	383	755	NA
Age-adjusted RR (95% CI)	1 [Reference]	0.94 (0.86-1.02)	0.85 (0.78-0.93)	0.79 (0.70-0.89)	0.77 (0.70-0.84)	<.001
Multivariable RR (95% CI)[d]	1 [Reference]	0.94 (0.86-1.02)	0.86 (0.78-0.94)	0.79 (0.70-0.89)	0.76 (0.69-0.84)	<.001
Non-GI tract cancer						
No. of cases (n = 23 623)	7244	4287	4375	2264	5453	NA
Age-adjusted RR (95% CI)	1 [Reference]	1.04 (1.00-1.08)	1.06 (1.02-1.10)	1.07 (1.02-1.12)	1.02 (0.99-1.06)	.57
Multivariable RR (95% CI)[d]	1 [Reference]	1.01 (0.97-1.05)	1.02 (0.98-1.06)	1.02 (0.97-1.07)	0.98 (0.94-1.02)	.15

Abbreviations: GI, gastrointestinal; NA, not applicable; RR, relative risk.

[a] Data were obtained from the 1980-2012 Nurses' Health Study and the 1986-2010 Health Professionals Follow-up Study.

[b] Calculated as tests for trend using the median value of each category as a continuous variable.

[c] For prostate cancer, only advanced cases were included.

[d] Adjusted for race (white or nonwhite), height (continuous), body mass index (quintile), family history of cancer (yes or no), physical examination in the past 2 years (yes or no), history of colonoscopy or sigmoidoscopy (yes or no), smoking (never, <5, 5-19, 20-39, or ≥40 pack-years), physical activity (quintile), alcohol intake (0, <5, 5-14, 15-29, or ≥30 g/d), current multivitamin use (yes or no), total energy intake (quintile), red and processed meat intake (quintile), folate intake (quintile), calcium intake (quintile), and Alternate Healthy Eating Index 2010 (quintile).[20,21] For men, we also adjusted for the prostate-specific antigen test in the past 2 years (yes or no) and for women, for menopause status (premenopause or postmenopause), menopausal hormone therapy (never, past, or current use), and mammogram in the past 2 years (yes or no). The model was also conditioned on age (months), calendar year of the questionnaire cycle, and sex or cohort.

remains suboptimal, with only 58% of the eligible population having undergone an accepted screening option.[25] Our findings suggest that regular aspirin use could prevent about 7400 additional CRCs among the estimated 41.3 million US adults aged 50 to 75 years[26] who undergo CRC screening and 9800 CRCs among the 29.9 million who do not undergo screening.

Besides confirmation of the link between aspirin use and CRC,[3-6,27-30] we observed possible benefits for gastroesophageal cancer, a finding supported by some observational studies.[4-6,30-32] In addition, we found that the apparent benefit of aspirin required at least 6 years of regular use, with a greater benefit observed with increasing duration of use for gastrointestinal tract cancers, and was evident with the use of relatively low-dose equivalents (0.5-1.5 standard tablets per week). These findings are consistent with the secondary analyses of RCTs for the prevention of CVD.[2,30] However, in contrast with the European RCTs,[2] we observed a greater risk reduction among individuals taking higher doses. Nonetheless, few RCTs directly compared different doses.[30,33]

Consistent with RCTs and other observational studies,[6] including previous analyses from our cohorts with shorter follow-up,[34-36] we did not observe any association of aspirin use with the incidence of breast, advanced prostate, and lung cancers. However, accumulating evidence suggests that, compared with cancer incidence, aspirin may have a stronger role in reducing cancer mortality,[1,37,38] particularly for death due to CRC[30,39,40] and possibly for deaths due to gastroesophageal, breast, lung, and prostate cancers.[6,41,42] Thus, for most cancer types, aspirin may act primarily through specific mechanisms (eg, antiplatelet effects)[43] to inhibit progression or metastases.[22] However, our findings suggest that for the gastrointestinal tract, aspirin may influence additional mechanisms critical to early tumorigenesis that may explain the stronger association of aspirin with a lower incidence of gastrointestinal tract cancer. Such mechanisms include modulation of cyclo-oxygenase-2,[43,44] the principal enzyme that produces proinflammatory prostaglandins, including prostaglandin E_2, which increases cellular proliferation, promotes angiogenesis, and increases resistance to apoptosis. Aspirin may also play a role in Wnt signaling,[45] nuclear factor κB signaling, polyamine metabolism, and DNA repair.[46]

To date, few studies have evaluated the potential differential benefits of aspirin in subgroups of population defined by clinical or lifestyle factors. In our analysis, the relative benefits of aspirin did not appear to differ according to age; family history of cancer and cardiac risk factors; comorbid conditions, such as type 2 diabetes mellitus; reproductive factors; and other major lifestyle risk factors for cancer, including cancer screening. Our study also significantly extends prior data by demonstrating that aspirin use, in addition to having a substantial absolute benefit among those individuals who do not

undergo endoscopic screening, may complement the reduction in the risk associated with screening.

The strengths of our study include a large, well-characterized population that included detailed, prospective, and updated assessment of aspirin use for 32 years of follow-up and a large number of cases in which we were able to examine the potential benefits of aspirin on overall and subtype-specific cancer risk at a range of doses and duration of use. In addition, we collected detailed data on potential confounders and were also able to conduct subgroup analysis in the context of important risk factors. Finally, our large population-based cohort allowed us to estimate the potential absolute benefits of aspirin, particularly in the context of endoscopic screening.

Our study has limitations. As an observational study, our results are not as definitive as those of an RCT designed to evaluate the effect of various doses of aspirin on cancer risk. However, such a trial is not likely to be feasible owing to the need for a large number of participants, prolonged follow-up, and likelihood of treatment crossover given the high prevalence of aspirin use in clinical practice. In addition, because total cancer is an end point that reflects the distribution of specific cancer sites in the underlying population, our results with respect to overall cancer risk may not be generalizable to populations in which CRC and breast and prostate cancers do not account for a substantial proportion of overall cancer incidence. Finally, most of our participants are white; additional research among other races or ethnicities is warranted.

Conclusions

Regular aspirin use is associated with modestly reduced incidence of overall cancer, with more substantial benefits observed for gastrointestinal tract cancers, especially colorectal. Aspirin may be a potential low-cost alternative to endoscopic CRC screening in resource-limited settings or a complement in settings in which such programs are already implemented, including the general US population, in whom screening adherence remains suboptimal.[25] Cost-effectiveness analyses balancing the benefits for CVD and cancer; the harms of use, such as gastrointestinal tract bleeding; and the costs of aspirin in the prevention of cancer and CVD are warranted. Continued advances in genetic[47] and molecular biomarkers[48,49] as a basis for a precision medicine–based approach to disease prevention may be helpful in identifying individuals who are most likely to benefit and less likely to be harmed by the long-term use of aspirin.

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