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ARTICLE

Daily Aspirin Use and Cancer Mortality in a Large US Cohort

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Background A recent pooled analysis of randomized trials of daily aspirin for prevention of vascular events found a substantial reduction (relative risk [RR] = 0.63, 95% confidence interval [CI] = 0.49 to 0.82) in overall cancer mortality during follow-up occurring after 5 years on aspirin. However, the magnitude of the effect of daily aspirin use, particularly long-term use, on cancer mortality is uncertain.

Methods We examined the association between daily aspirin use and overall cancer mortality among 100 139 men and women with no history of cancer in the Cancer Prevention Study II Nutrition Cohort. Cox proportional hazards regression models were used to estimate multivariable-adjusted relative risks (RRs) and 95% confidence intervals (CIs).

Results Between 1997 and 2008, 5138 participants died from cancer. Compared with no use, daily aspirin use at baseline was associated with slightly lower cancer mortality, regardless of duration of daily use (for <5 years of use, RR = 0.92, 95% CI = 0.85 to 1.01; for ≥5 years of use, RR = 0.92, 95% CI = 0.83 to 1.02). Associations were slightly stronger in analyses that used updated aspirin information from periodic follow-up questionnaires and included 3373 cancer deaths (for <5 years of use, RR = 0.84, 95% CI = 0.76 to 0.94; for ≥5 years of use, RR = 0.84, 95% CI = 0.75 to 0.95).

Conclusion These results are consistent with an association between recent daily aspirin use and modestly lower cancer mortality but suggest that any reduction in cancer mortality may be smaller than that observed with long-term aspirin use in the pooled trial analysis.

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A recent pooled analysis of randomized trials of daily aspirin for prevention of vascular events by Rothwell et al. (1) reported a statistically significant 15% reduction in overall cancer mortality during an intervention period of up to 10 years. The overall reduction in cancer mortality was mostly attributable to an estimated 37% reduction in cancer mortality during follow-up occurring after 5 years on aspirin (relative risk [RR] = 0.63, 95% confidence interval [CI] = 0.49 to 0.82; 92 cancer deaths in the aspirin group compared with 142 in the control group). Similar effects were observed for lower doses, mostly 75–100 mg/day, and higher doses (≥300 mg/day).

In contrast to the pooled analysis of trials of daily aspirin (1), two very large randomized trials of alternate-day aspirin observed no effect on overall cancer mortality (2,3), raising questions about the frequency of aspirin use needed to reduce cancer risk. The Physicians' Health Study tested 325 mg of aspirin every other day for 5 years and reported a relative risk of 1.16 (95% CI = 0.84 to 1.61, 79 cancer deaths on aspirin compared with 68 on placebo) (2). The Women's Health Study tested a lower dose (100 mg every other day) for 10 years and reported a relative risk of 0.95 (95% CI = 0.81 to 1.11, 284 cancer deaths on aspirin compared with 299 on placebo) (3). Three large observational studies of aspirin use and cancer mortality reported mixed results (4–6), although none of these studies examined aspirin use that was both long term and daily.

Results from the pooled trial analysis (1) potentially have very important implications. If these results are accurate and generalizable, people who begin a long-term regimen of daily low-dose aspirin and continue use for 5 years could reduce their subsequent risk of dying from cancer by more than a third. However, uncertainty remains about the magnitude of the effect of daily aspirin use, particularly long-term use, on cancer mortality. In the pooled trial analysis (1), the relative risk estimate for cancer mortality occurring during follow-up after the first 5 years was based on limited numbers and therefore included a relatively wide confidence interval. In addition, the magnitude of the association with overall cancer mortality is larger than might have been expected, given the absence of apparent effects on cancer mortality in large trials of aspirin taken every other day (2,3) and results from observational studies suggesting that aspirin use does not strongly reduce risk of cancers other than colorectal, esophageal, and stomach cancers (7).

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The purpose of this analysis was to quantify the association between daily aspirin use, particularly long-term use, and overall cancer mortality in the Cancer Prevention Study II (CPS-II) Nutrition Cohort, making use of detailed information on aspirin use collected at multiple time points. Because of the notable 37% reduction in cancer mortality observed in the pooled trial analysis during follow-up occurring after 5 years on daily aspirin (1), we were particularly interested in cancer mortality among individuals in our cohort with a comparable history of aspirin exposure, that is, current daily aspirin users who had used aspirin during the preceding 5 years (referred to as current daily users of ≥5 years).

Methods

Study Population

The men and women in this analysis (n = 184 190) were participants in the CPS-II Nutrition Cohort that was established in 1992 (8). The CPS-II Nutrition Cohort is a subset of the larger CPS-II Cohort established by the American Cancer Society in the year 1982. Informed consent for participation was assumed based on completion and return of study questionnaires. All aspects of the CPS-II Nutrition Cohort study protocol were approved by the Emory University Institutional Review Board.

At enrollment into the CPS-II Nutrition Cohort in 1992 or 1993, participants completed a mailed 10-page self-administered questionnaire that included information on demographic, medical, and behavioral factors. Follow-up questionnaires to update exposure information and ascertain new cancer diagnoses were mailed in 1997 and every 2 years thereafter. The date the 1997 questionnaire was completed was used as the starting point for person-time included in this analysis so that duration of daily aspirin use could be calculated using information from both the 1992 and 1997 questionnaires. A total of 143 792 participants completed the long version of the 1997 follow-up survey that included questions on aspirin use. All analyses excluded participants who had a history of cancer in 1997 (n = 25 722), or missing or uninterpretable information on aspirin use (n = 16 047) or smoking (n = 1884). After exclusion, a total of 100 139 participants (44 360 men and 55 779 women) were included in the analysis.

Assessment of Aspirin Use

Aspirin use was reported at enrollment in the CPS-II Nutrition Cohort in 1992 and 1993, and on follow-up questionnaires completed in 1997 and every 2 years thereafter. The questionnaire completed in 1992 through 1993 (hereafter referred to as the 1992 questionnaire) asked for the average number of days per month aspirin was used during the past year and the average number of pills taken on those days (9). Follow-up questionnaires in 1997 and every 2 years thereafter included similar questions about the number of days per month and number of pills per day but asked separately about use of low-dose (or "baby") aspirin and adult-strength aspirin. Participants reporting use 30 or 31 days per month of either low-dose or adult-strength aspirin were considered daily users.

Mortality Follow-up

Vital status and cause-of-death codes (10,11) were obtained through automated linkage of all cohort participants with the National Death Index (12). Mortality follow-up was completed through December 31, 2008. Death certificates or codes for the cause of death were obtained for 99.3% of known deaths. In addition to overall cancer mortality [International Classification of Diseases-10 (11) codes C00 to C97], we also examined mortality from the 16 cancer sites with the greatest number of deaths (lung cancer, C33 to C34; pancreatic cancer, C25; colorectal cancer, C18 to C20; leukemia, C91 to C95; lymphoma, C82 to C85 and C96; ovarian cancer, C56; prostate cancer, C61; female breast cancer, C50; brain cancer, C71; multiple myeloma, C88 and C90; bladder cancer, C67; liver cancer, C22; esophageal cancer, C15; kidney cancer, C64; melanoma, C43; and stomach cancer, C16). Deaths attributed to liver cancer on the death certificate but known to be gall bladder or extrahepatic bile duct cancers on the basis of information from state cancer registry linkage (n = 12) were not counted as liver cancers. Each of the individual cancer sites examined accounted for at least 90 deaths. No other individual cancer site accounted for more than 50 deaths. We also grouped cancers of the gastrointestinal tract (esophagus, stomach, small intestine, colon, and rectum) and all other cancers, because there is strong evidence that aspirin use lowers the risk of cancers of the gastrointestinal tract, whereas it is less clear if aspirin use is associated with the risk of other cancers.

Statistical Analyses

Two types of analyses were conducted: baseline analyses and updated analyses. In the baseline analyses, aspirin use status was defined at baseline in 1997 and never changed. In the updated analyses, aspirin status was modeled using a time-dependent variable.

Baseline analyses incorporated only information on aspirin use reported on the 1992 and 1997 questionnaires. Participants who reported no use in either the year 1992 or 1997 were categorized as nonusers; those who reported daily use in the year 1997 but not in 1992 were categorized as daily users of less than 5 years duration; and those who reported daily use in both the years 1992 and 1997 were categorized as daily users of 5 or more years duration. All other participants were classified as past or occasional users.

The updated analyses included a time-dependent variable for aspirin use. For follow-up time before January 1, 2004, the approximate midpoint of follow-up, aspirin use was defined as in the baseline analysis. For follow-up time on or after January 1, 2004, the aspirin use variable was updated to incorporate aspirin use reported on the 1999, 2001, and 2003 follow-up questionnaires. Participants who reported no aspirin use on the 1992, 1997, 1999, 2001, and 2003 questionnaires were categorized as nonusers; those who reported daily use in 1999, 2001, and 2003 were categorized as daily users of 5 or more years duration; and those who reported daily use in 2003 but not in both the years 1999 and 2001 were categorized as daily users of less than 5 years duration. All other participants were classified as past or occasional users. Participants who did not provide complete information on aspirin use on each of the three relevant follow-up questionnaires (in the years 1999, 2001, and 2003) (n = 29233) were censored from further follow-up on January 1, 2004 because there was insufficient information to accurately update their aspirin use status. In addition, a, relatively small proportion of participants (n = 6033) did not return their 2003 questionnaire until 2004 or 2005. These participants were

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censored on January 1, 2004 and reentered the analysis on the date their 2003 questionnaire was received.

Diagnosis with a life-threatening cancer may result in individuals quitting daily aspirin use, possibly because protection against heart disease becomes less of a concern or because aspirin use can sometimes be contraindicated during chemotherapy. Analyses of consecutive biennial questionnaires confirmed that daily aspirin users in this cohort who were diagnosed with typically lethal cancers were substantially more likely to quit than other daily aspirin users. Therefore, to avoid biasing results by using information on postdiagnostic aspirin use to predict cancer mortality, participants who had already been diagnosed with cancer at the time they completed their 2003 questionnaire (n = 6300) did not have their aspirin use updated on January 1, 2004, but they were instead censored from further follow-up on that date.

Aspirin use could only be updated once during follow-up because more frequent updating, ie, at the completion of each follow-up questionnaire every 2 years, would have required censoring every 2 years of all participants diagnosed with cancer in order to avoid using information on postdiagnosis aspirin use. This censoring would have resulted in the exclusion of all but a small number of rapidly fatal cancers from the analysis.

Cox proportional hazards regression models (13) were used to estimate relative risks and 95% confidence intervals. Follow-up time for Cox models began on the date of completion of the 1997 questionnaire. All models were adjusted for age [1 year age strata using the stratified Cox procedure (14)], sex (male or female), race (white, black, or other or unknown), education (completed less than high school diploma, high school graduate, some college, college graduate, graduate school, or unknown), smoking (18 categories described below), body mass index (kg/m^2, <22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, ≥30, or unknown), physical activity level (metabolic equivalents per week, <3.5, 3.5 to <4.5, 4.5 to <14, 14 to <24.5, ≥24.5, or unknown), history of heart disease, stroke, diabetes, hypertension, cholesterol-lowering drug use (current), aspirin use in the year 1982 (no use, occasional use, 1 to <15, 15 to <30, ≥30 times per month, or unknown), nonsteroidal anti-inflammatory drug use (none, 1–14, 15–29, 30–59, or ≥60 pills per month), and history of colorectal endoscopy (ever).

Smoking was adjusted for using 18 categories including one category for never smokers, four categories for current smokers based on combinations of duration (<40 years or ≥40 years) and cigarettes per day (<20 or ≥20), 12 categories for former smokers based on combinations of time since quitting (<10 years, 10 to <20 years, 20 to <30 years, 30 to <40 years, ≥40 years, unknown) and cigarettes per day (<20 or ≥20), and one category for those who had never smoked cigarettes but reported ever smoking cigars or pipes on the 1982 questionnaire. Models for prostate and breast cancer were also adjusted for history of prostate-specific antigen testing and history of mammography, respectively. History of prostate-specific antigen testing and history of mammography were categorized as never, in the last 2 years, less than 2 years ago, or unknown.

In both the baseline and updated analyses, we examined whether associations between current daily aspirin use and overall cancer mortality differed by attained age (continuous), sex, smoking status (never, former, current), body mass index (continuous), history of cardiovascular disease (yes or no), and nonsteroidal anti-inflammatory drug use (<15 or ≥15 pills per month in the year 1997). Specifically, we modeled multiplicative interaction terms between current daily aspirin use of any duration and each potential effect measure modifier (coded as noted above) and calculated a P value for interaction ($P_{interaction}$) by comparing the likelihood ratio statistic from models with and without interaction terms (15). Proportionality of hazards was assessed by modeling an interaction term between current daily aspirin use and a linear variable for follow-up time; no statistically significant deviation was observed.

Sex-specific cancer mortality rates were calculated to provide a measure of absolute risk. Cancer mortality rates were standardized to the overall age distribution of person-years contributed by men or women in the baseline analysis. All statistical analyses were performed using SAS version 9.3 (SAS Inc, Cary, NC). All P values were two-sided, and if less than .05, they were considered to be statistically significant.

Results

Participants in this analysis were predominantly white and older than 60 years of age at baseline in the year 1997, regardless of aspirin use (Table 1). Approximately 23.8% of participants reported daily aspirin use at baseline. Among daily aspirin users, 46.0% reported use of low-dose ("baby") aspirin, and 54.0% reported use of adult-strength aspirin. Among daily aspirin users with complete information on the number of pills per day, 85.5% reported use of only one pill per day, likely indicating that the participant used aspirin for cardiovascular disease prevention rather than for pain relief. Patterns of aspirin use appeared consistent for most participants during follow-up. Among participants who were daily aspirin users in the year 1997, 74.5% were still daily aspirin users at the time of completion of the 2003 questionnaire, the approximate midpoint of follow-up. Among participants who did not report use in either the years 1992 or 1997 (the referent group in analyses of baseline aspirin use), 25.2% reported daily aspirin use in 2003.

At baseline in the year 1997, daily aspirin users were slightly more likely than nonusers to be highly educated, former rather than never smokers, obese, and to use nonaspirin nonsteroidal anti-inflammatory drugs regularly (Table 1). Daily aspirin users in 1997 were also more likely than nonusers to report at least occasional aspirin use in the year 1982. As expected, given that cardiovascular risk is an indication for prophylactic aspirin use, daily aspirin users were considerably more likely than nonusers to have had a history of heart disease, stroke, diabetes, or hypertension and to use cholesterol-lowering drugs. Daily aspirin users were also more likely than nonusers to have had a colorectal endoscopy. Among men, daily aspirin users were more likely to report a prostate-specific antigen test within 2 years compared with nonusers (70.9% vs 62.3%, respectively). Among women, daily aspirin users were slightly more likely to report a mammogram within 2 years vs nonusers (90.3% vs 88.0%, respectively).

Daily aspirin use at baseline in the year 1997 was associated with slightly lower overall cancer mortality, compared with nonusers (RR = 0.92, 95% CI = 0.85 to 0.99), and this association did not vary by duration of daily use (Table 2). In time-dependent analyses using updated information from follow-up questionnaires, the inverse association between daily aspirin use and cancer mortality was slightly stronger (RR = 0.84, 95% CI = 0.77 to

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Table 1. Selected potential risk factors by aspirin use in the Cancer Prevention Study II Nutrition Cohort in 1997*

	Men, %				Women, %			
Risk factor	**No use (n=15 043)**	**Past or occasional use (n=14 876)**	**Current daily use for <5 y (n=7835)**	**Current daily use for ≥5 y (n=6606)**	**No use (n=26 248)**	**Past or occasional use (n=20 103)**	**Current daily use for <5 y (n=6225)**	**Current daily use for ≥5 y (n=3203)**
Age, y								
<60	4.9	5.4	3.6	2.3	15.2	15.3	10.5	6.7
60–69	54.6	56.6	54.4	47.0	52.3	55.4	52.8	45.9
70–79	37.4	35.2	39.3	46.6	31.9	28.8	36.0	46.4
≥80	3.1	2.8	2.7	4.0	0.6	0.5	0.7	0.9
Race								
White	97.0	97.9	98.3	98.6	97.1	97.9	98.2	98.5
Black	1.2	0.9	0.5	0.5	1.5	1.1	0.9	0.7
Other or unknown	1.8	1.2	1.1	0.9	1.4	1.0	0.9	0.7
Education								
Less than high school diploma	7.6	6.6	5.1	6.1	4.2	4.1	3.4	2.8
High school graduate	18.8	17.1	16.6	16.8	31.3	29.9	28.7	30.3
Some college	25.2	24.7	24.6	24.4	30.9	32.0	32.1	32.0
College graduate	21.9	23.3	24.7	23.8	19.5	20.5	20.6	19.6
Graduate school	25.9	27.8	28.5	28.4	13.4	13.0	14.6	15.0
Unknown	0.7	0.6	0.5	0.5	0.7	0.5	0.7	0.4
Cigarette smoking status								
Never	36.4	34.0	32.8	29.3	56.4	56.4	53.9	51.9
Current	5.9	5.6	4.8	5.0	5.5	5.3	4.8	7.2
Former	57.7	60.3	62.5	65.7	38.1	38.3	41.3	40.9
Body mass index, kg/m^2								
<22.5	12.3	11.0	10.5	9.6	25.1	24.4	22.2	22.3
22.5 to <25	23.0	22.9	22.9	21.7	21.6	22.1	22.0	20.4
25 to <27.5	28.0	28.7	27.7	28.3	18.4	19.0	19.8	18.9
27.5 to <30	15.6	16.2	16.3	17.5	10.2	10.7	12.1	11.9
≥30	13.6	13.9	14.6	16.3	15.0	14.6	17.1	19.1
Unknown	7.6	7.4	7.9	6.6	9.8	9.2	6.8	7.3
Physical activity, METs/wk								
<3.5	15.3	13.4	11.6	11.9	14.3	12.4	12.0	13.8
3.5 to <4.5	8.8	8.8	8.0	8.1	10.1	10.3	10.5	10.5
4.5 to <14	27.8	29.1	29.2	28.8	32.0	33.4	33.0	32.9
14 to <24.5	29.7	30.9	32.6	34.5	27.6	27.9	29.2	28.8
≥24.5	10.7	10.8	12.2	10.4	8.8	9.2	9.2	7.5
Unknown	7.7	7.0	6.5	6.3	7.2	6.9	6.1	6.5
History of heart disease	7.6	11.9	31.9	51.7	3.3	4.5	14.7	21.8
History of stroke	3.4	4.0	7.1	9.3	1.8	2.2	6.3	8.6
Diabetes	9.0	8.3	11.3	13.1	5.5	5.1	7.6	9.3
Hypertension	34.1	37.7	48.8	53.9	33.5	35.0	45.4	50.7
Cholesterol-lowering drug use (current)	10.7	13.7	27.9	40.2	11.5	12.1	22.1	26.2
Aspirin use 15 y earlier, times/mo in the year 1982								
No use	50.5	26.3	35.4	29.9	39.6	18.3	27.2	23.5
Occasional	30.5	37.7	34.7	32.4	37.6	42.8	39.8	34.5
1 to <15	13.8	26.2	21.5	19.6	15.8	26.7	22.3	19.4
15 to <30	1.3	3.6	2.9	4.2	2.1	5.4	4.5	6.5
≥30	2.0	4.7	3.9	12.1	2.9	5.1	4.8	14.0
Unknown	1.9	1.5	1.6	1.8	2.0	1.6	1.5	2.1
Non-aspirin NSAID use, no. of pills/mo								
None	76.9	68.2	76.3	76.4	64.9	60.7	66.7	68.8
1–14	11.6	18.0	11.0	10.3	18.2	21.6	14.4	11.7
15–29	2.8	4.4	3.3	2.9	4.1	5.5	4.6	4.9
30–59	3.5	4.0	4.4	4.6	5.3	5.9	6.4	6.3
≥60	5.1	5.3	5.0	5.8	7.5	6.3	7.9	8.3
Colorectal endoscopy (ever)	57.4	59.8	62.9	63.1	51.5	52.5	55.6	53.3

* For variables other than age, percentages were adjusted to the age distributions of men and women in the study. NSAID = nonsteroidal anti-inflammatory drug; METs = metabolic equivalents.

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Table 2. Cancer mortality by duration of daily aspirin use, Cancer Prevention Study II Nutrition Cohort, 1997–2008*

	Men				Women				Men and Women		
Aspirin use	**No. of deaths**	**Person-years**	**Rate†**	**RR (95% CI)**	**No. of deaths**	**Person-years**	**Rate†**	**RR (95% CI)**	**No. of deaths**	**Person-years**	**RR (95% CI)**
Baseline aspirin use‡											
No use	1002	149 809	677	1.00 (referent)	1071	276 833	389	1.00 (referent)	2073	426 642	1.00 (referent)
Past or occasional use	952	149 804	661	1.00 (0.91 to 1.09)	755	213 893	366	0.97 (0.88 to 1.07)	1707	363 697	0.99 (0.92 to 1.06)
Current daily use											
Any duration	943	141 986	635	0.91 (0.82 to 1.00)	415	98 276	392	0.96 (0.85 to 1.08)	1358	240 262	0.92 (0.85 to 0.99)
<5 y	488	78 308	617	0.90 (0.80 to 1.01)	265	65 275	388	0.97 (0.84 to 1.11)	753	143 583	0.92 (0.85 to 1.01)
≥5 y	455	63 678	656	0.91 (0.81 to 1.03)	150	33 001	400	0.94 (0.79 to 1.12)	605	96 679	0.92 (0.83 to 1.02)
Updated aspirin use§											
No use	579	106 523	596	1.00 (referent)	627	202 944	337	1.00 (referent)	1206	309 467	1.00 (referent)
Past or occasional use	632	122 567	564	0.95 (0.85 to 1.07)	518	186 777	299	0.93 (0.82 to 1.05)	1150	309 343	0.94 (0.87 to 1.03)
Current daily use											
Any duration	677	136 002	493	0.83 (0.74 to 0.94)	340	110 500	295	0.86 (0.75 to 0.99)	1017	246 502	0.84 (0.77 to 0.92)
<5 y	313	67 797	481	0.83 (0.72 to 0.95)	199	68 190	290	0.87 (0.74 to 1.02)	512	135 986	0.84 (0.76 to 0.94)
≥5 y	364	68 204	504	0.84 (0.73 to 0.97)	141	42 310	304	0.85 (0.70 to 1.03)	505	110 516	0.84 (0.75 to 0.95)

* Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (1-year age strata using the stratified Cox procedure), sex, race (white, black, or other or unknown), education (completed less than high school diploma, high school graduate, some college, college graduate, graduate school, or unknown), smoking (never smoker, never cigarette smoker but ever cigar or pipe smoker, former cigarette smoker subcategorized by combinations of years since quit [<10, 10 to <20, 20 to <30, 30 to <40, ≥40, or unknown] and cigarettes per day [<20 or ≥20], or current cigarette smoker subcategorized by combinations of years smoked [<40 or ≥40] and cigarettes per day [<20 or ≥20]), body mass index (kg/m^2, <22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, ≥30, or unknown), physical activity level (metabolic equivalents per week, <3.5, 3.5 to <4.5, 4.5 to <14, 14 to <24.5, ≥24.5, or unknown]), history of heart disease, stroke, diabetes, hypertension, cholesterol-lowering drug use (current), aspirin use in the year 1982 (no use, occasional use, 1 to <15, 15 to <30, ≥30 times per month, or unknown), nonsteroidal anti-inflammatory drug use (none, 1–14, 15–29, 30–59, or ≥60 pills per month), and history of colorectal endoscopy (ever).

† Cancer mortality rate per 100 000 person-years, standardized to the age distribution of person-years contributed by men or women in the baseline aspirin use analysis.

‡ Aspirin use status at completion of the 1997 questionnaire.

§ Aspirin use status at completion of the 1997 questionnaire for follow-up from 1997 to 2003 and at time of completion of the 2003 questionnaire for follow-up from 2004 to 2008.

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0.92) than in the baseline analysis and results did not differ by duration of daily use.

Age-standardized cancer mortality rates per 100 000 person-years were slightly lower among current daily aspirin users than among nonusers (Table 2). In updated analyses, the difference between cancer mortality rates among nonusers of aspirin and current daily aspirin users was 103 (95% CI = 41 to 165) among men and 42 (95% CI = 1.0 to 83) among women.

The multivariable-adjusted relative risks shown in Table 2 were generally slightly lower (further from the null) than results adjusted only for age and sex. In the baseline analysis, the relative risks adjusted only for age and sex were 0.94 (95% CI = 0.86 to 1.02) for current daily use of less than 5 years and 0.99 (95% CI = 0.90 to 1.08) for current daily use of 5 years or longer. In the updated analysis, the relative risks adjusted only for age and sex were 0.84 (95% CI = 0.76 to 0.93) for current daily use of less than 5 years and 0.88 (95% CI = 0.79 to 0.98) for current daily use of 5 years or longer.

Associations between current daily aspirin use and overall cancer mortality stratified by follow-up interval are shown in Supplementary Table 1 (available online). In the baseline analysis, relative risks for current daily use, compared with nonuse, were similar during the 1997–2003 follow-up interval (RR = 0.90, 95% CI = 0.80 to 1.00) and during the 2004–2008 follow-up interval (RR = 0.94, 95% CI = 0.85 to 1.04). In the updated analysis, the relative risk for current daily use was slightly higher during the 1997–2003 interval (RR = 0.90, 95% CI = 0.80 to 1.00) than during the 2004–2008 interval (RR = 0.76, 95% CI = 0.65 to 0.88).

We also examined associations between current daily aspirin use and cancer mortality by most recent dose, as defined by the dose in the year 1997 in the baseline analyses and by dose either in 1997 or 2003 in the updated analyses. In the baseline analysis, relative risks for current daily use, compared with no use, were similar for low-dose aspirin (RR = 0.95, 95% CI = 0.86 to 1.04) and for adult-strength aspirin (RR = 0.90, 95% CI = 0.82 to 0.99). Relative risks were also similar for low-dose aspirin (RR = 0.87, 95% CI 0.78 to 0.96) and for adult-strength aspirin (RR = 0.82, 95% CI = 0.72 to 0.91) in the updated analysis.

Relative risks for updated current daily aspirin use, compared with no use, were similar among participants with a history of cardiovascular disease, defined as a history of heart disease or stroke at baseline (RR = 0.84, 95% CI = 0.67 to 1.05) and among participants without a history of cardiovascular disease (RR = 0.85, 95% CI = 0.77 to 0.94). Associations between current daily aspirin use and cancer mortality did not statistically significantly differ by age, sex, history of cardiovascular disease, or nonsteroidal anti-inflammatory drug use in either the baseline or updated analyses. However, the association between updated current daily aspirin use, compared with no use, and cancer mortality did differ by smoking status ($P_{interaction}$ = .001; Supplementary Table 2, available online). Current daily aspirin use, compared with no use, was associated with substantially lower cancer mortality among never smokers (RR = 0.68, 95% CI = 0.57 to 0.81) but not among former smokers (RR = 0.92, 95% CI = 0.82 to 1.04) or current smokers (RR = 0.91, 95% CI = 0.70 to 1.19). Because lung cancer accounted for a large proportion of cancer deaths among ever smokers but not among never smokers, we reexamined results after censoring lung cancer deaths. Relative risks remained lower among never smokers (RR = 0.67, 95% CI = 0.56 to 0.81) than among former smokers (RR = 0.85, 95% CI = 0.74 to 0.99) or current smokers (RR = 0.88, 95% CI = 0.59 to 1.31).

Analyses of baseline aspirin use by individual cancer site are shown in Table 3. Daily aspirin use at baseline in the year 1997 was not statistically significantly associated with mortality from any cancer site examined, regardless of duration of use. However, there was some suggestion of lower mortality from cancers of the gastrointestinal tract (RR = 0.82, 95% CI = 0.67 to 1.01).

Analyses of updated aspirin use by individual cancer site are shown in Table 4. Daily aspirin use was associated with lower cancer mortality both from cancers of the gastrointestinal tract and from cancers outside the gastrointestinal tract. Current daily aspirin use was associated with lower risk of fatal colorectal cancer and stomach cancer and also with lower risk of fatal upper gastrointestinal cancer, defined as esophageal and stomach cancer combined (RR = 0.56, 95% CI = 0.37 to 0.86). However, in analyses of individual cancers outside the gastrointestinal tract, statistically significant associations were observed only for liver and bladder cancer.

Because the association between updated aspirin use and cancer mortality differed by smoking status, we examined associations between updated aspirin use and individual cancer sites stratified by smoking status (data not shown). Associations between updated daily aspirin use and mortality from gastrointestinal tract cancers appeared comparable among never smokers (RR = 0.53, 95% CI = 0.32 to 0.89), former smokers (RR = 0.69, 95% CI = 0.50 to 0.95), and current smokers (RR = 0.37, 95% CI = 0.13 to 1.10). In contrast, updated daily aspirin use was associated with lower mortality from nongastrointestinal tract cancers among never smokers (RR = 0.71, 95% CI = 0.59 to 0.85) but not among former smokers (RR = 0.97, 95% CI = 0.85 to 1.10) or current smokers (RR = 1.00, 95% CI = 0.75 to 1.31).

Discussion

In this large prospective study, current daily aspirin use, updated during follow-up, was associated with modestly lower overall cancer mortality. The reduction in overall cancer mortality was driven by both a substantial reduction in mortality from gastrointestinal tract cancers and a small, but statistically significant, reduction in mortality from cancers outside the gastrointestinal tract.

The estimated 16% lower overall cancer mortality associated with 5 or more years of daily aspirin use in our study is considerably smaller than the 37% reduction seen during follow-up after 5 years of randomized aspirin use in the pooled trial analysis (1). It is possible that our study underestimated any reduction in cancer mortality because of confounding by factors associated with both aspirin use and cancer mortality. For example, some confounding by indication could have occurred if participants advised to take aspirin for cardiovascular disease prevention were more likely than other participants to have metabolic factors, such as insulin resistance, that were associated with higher cancer mortality (16,17). Alternatively, the difference between the studies in the strength of the association of long-term daily aspirin use with cancer mortality could be at least partly due to chance variation.

The results of our study of daily aspirin use are difficult to compare with those of three previous large observational studies of aspirin use and cancer mortality (4–6), as none of these studies examined aspirin use that was both long-term and daily. In an analysis of the

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Table 3. Cancer mortality by baseline aspirin use and cancer site, Cancer Prevention Study II Nutrition Cohort, 1997–2008*

	No use		Past or occasional use		Current daily use of any duration		Duration of use among current daily users			
							<5 y		≥5 y	
Cancer type	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)
GI tract†	291	1.00 (referent)	227	0.94 (0.79 to 1.13)	173	0.82 (0.67 to 1.01)	96	0.82 (0.65 to 1.05)	77	0.82 (0.62 to 1.08)
Colorectal	195	1.00 (referent)	162	1.05 (0.84 to 1.30)	108	0.86 (0.66 to 1.11)	61	0.85 (0.63 to 1.15)	47	0.86 (0.61 to 1.22)
Esophagus	46	1.00 (referent)	38	0.90 (0.58 to 1.40)	37	0.93 (0.57 to 1.50)	22	1.01 (0.59 to 1.73)	15	0.81 (0.42 to 1.53)
Stomach	45	1.00 (referent)	23	0.61 (0.36 to 1.02)	23	0.57 (0.33 to 1.01)	12	0.56 (0.29 to 1.09)	11	0.60 (0.28 to 1.24)
Outside GI tract†	1782	1.00 (referent)	1480	1.00 (0.93 to 1.07)	1185	0.94 (0.87 to 1.02)	657	0.94 (0.85 to 1.03)	528	0.94 (0.84 to 1.04)
Lung	492	1.00 (referent)	414	1.00 (0.87 to 1.14)	388	1.03 (0.88 to 1.19)	205	1.01 (0.85 to 1.20)	183	1.04 (0.86 to 1.26)
Pancreas	187	1.00 (referent)	149	0.97 (0.78 to 1.21)	131	1.04 (0.81 to 1.34)	81	1.13 (0.86 to 1.48)	50	0.91 (0.64 to 1.28)
Leukemia	111	1.00 (referent)	106	1.18 (0.90 to 1.55)	77	0.89 (0.64 to 1.22)	42	0.88 (0.61 to 1.28)	35	0.89 (0.59 to 1.36)
Lymphoma	109	1.00 (referent)	95	1.00 (0.75 to 1.33)	67	0.91 (0.66 to 1.28)	33	0.80 (0.53 to 1.19)	34	1.10 (0.72 to 1.69)
Prostate‡	75	1.00 (referent)	65	0.81 (0.58 to 1.15)	68	0.77 (0.53 to 1.12)	39	0.88 (0.59 to 1.33)	29	0.64 (0.39 to 1.03)
Ovary§	94	1.00 (referent)	75	1.06 (0.77 to 1.44)	30	0.83 (0.54 to 1.28)	21	0.89 (0.55 to 1.45)	9	0.70 (0.34 to 1.42)
Breast‖	78	1.00 (referent)	63	1.09 (0.77 to 1.53)	27	0.83 (0.52 to 1.32)	21	1.00 (0.61 to 1.65)	6	0.50 (0.21 to 1.17)
Brain	61	1.00 (referent)	54	1.01 (0.69 to 1.47)	50	1.38 (0.92 to 2.08)	29	1.37 (0.86 to 2.17)	21	1.41 (0.82 to 2.43)
Myeloma	64	1.00 (referent)	45	0.83 (0.56 to 1.23)	44	0.98 (0.64 to 1.49)	23	0.94 (0.57 to 1.54)	21	1.04 (0.60 to 1.80)
Bladder	55	1.00 (referent)	52	1.05 (0.71 to 1.55)	43	0.75 (0.48 to 1.16)	18	0.61 (0.35 to 1.07)	25	0.92 (0.54 to 1.57)
Liver	48	1.00 (referent)	44	1.18 (0.77 to 1.81)	26	0.82 (0.49 to 1.37)	15	0.82 (0.45 to 1.51)	11	0.81 (0.40 to 1.63)
Kidney	47	1.00 (referent)	37	0.99 (0.63 to 1.54)	34	0.90 (0.55 to 1.47)	22	1.05 (0.62 to 1.79)	12	0.68 (0.34 to 1.37)
Melanoma	41	1.00 (referent)	27	0.73 (0.44 to 1.21)	24	0.82 (0.47 to 1.42)	11	0.66 (0.33 to 1.32)	13	1.08 (0.54 to 2.15)
All other	315	1.00 (referent)	250	0.97 (0.82 to 1.16)	174	0.84 (0.69 to 1.03)	96	0.83 (0.66 to 1.05)	78	0.85 (0.65 to 1.12)

* Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (1-year age strata using the stratified Cox procedure), sex, race (white, black, or other or unknown), education (completed less than high school diploma, high school graduate, some college, college graduate, graduate school, or unknown), smoking (never smoker, never cigarette smoker but ever cigar or pipe smoker, former cigarette smoker subcategorized by combinations of years since quit [<10, 10 to <20, 20 to <30, 30 to <40, ≥40, or unknown] and cigarettes per day [<20 or ≥20], or current cigarette smoker subcategorized by combinations of years smoked [<40 or ≥40] and cigarettes per day [<20 or ≥20]), body mass index (kg/m^2, <22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, ≥30, or unknown), physical activity level (metabolic equivalents per week, <3.5, 3.5 to <4.5, 4.5 to <14, 14 to <24.5, ≥24.5, or unknown), history of heart disease, stroke, diabetes, hypertension, cholesterol-lowering drug use (current), aspirin use in the year 1982 (no use, occasional use, 1 to <15, 15 to <30, ≥30 times per month, or unknown), nonsteroidal anti-inflammatory drug use (none, 1–14, 15–29, 30–59, or ≥60 pills per month), and history of colorectal endoscopy (ever).

† Gastrointestinal tract (GI) includes cancers of the esophagus, stomach, small intestine, colon, and rectum.

‡ Men only, additionally adjusted for history of prostate-specific antigen (PSA) testing (in the last 2 years, >2 years ago, or unknown).

§ Only women with intact ovaries were included in the analysis.

‖ Women only, additionally adjusted for history of mammography (in the last 2 years, >2 years ago, or unknown).

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Table 4. Cancer mortality by updated aspirin use and cancer site, Cancer Prevention Study II Nutrition Cohort, 1997–2008*

			Past or occasional use		Current daily use of any duration		Duration of use among current daily users			
							<5 y		≥5 y	
Cancer type	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)
GI tract†	183	1.00 (referent)	148	0.80 (0.64 to 1.00)	116	0.61 (0.47 to 0.78)	57	0.60 (0.44 to 0.82)	59	0.61 (0.44 to 0.84)
Colorectal	116	1.00 (referent)	104	0.94 (0.71 to 1.23)	67	0.63 (0.46 to 0.88)	34	0.62 (0.42 to 0.93)	33	0.64 (0.42 to 0.98)
Esophagus	31	1.00 (referent)	21	0.57 (0.32 to 1.01)	30	0.71 (0.41 to 1.24)	16	0.80 (0.43 to 1.50)	14	0.61 (0.30 to 1.23)
Stomach	32	1.00 (referent)	22	0.69 (0.39 to 1.21)	14	0.38 (0.19 to 0.76)	7	0.40 (0.17 to 0.93)	7	0.36 (0.15 to 0.88)
Outside GI tract†	1023	1.00 (referent)	1002	0.97 (0.89 to 1.06)	901	0.88 (0.80 to 0.97)	455	0.88 (0.79 to 0.99)	446	0.88 (0.78 to 1.00)
Lung	300	1.00 (referent)	279	0.90 (0.76 to 1.07)	314	1.01 (0.85 to 1.20)	152	0.99 (0.80 to 1.21)	162	1.04 (0.84 to 1.29)
Pancreas	126	1.00 (referent)	126	1.03 (0.80 to 1.33)	115	0.95 (0.72 to 1.25)	55	0.89 (0.64 to 1.23)	60	1.03 (0.73 to 1.46)
Leukemia	55	1.00 (referent)	62	1.11 (0.76 to 1.62)	58	0.96 (0.64 to 1.43)	28	0.93 (0.58 to 1.49)	30	0.99 (0.60 to 1.61)
Lymphoma	56	1.00 (referent)	58	0.95 (0.65 to 1.39)	55	1.03 (0.69 to 1.54)	27	0.96 (0.60 to 1.55)	28	1.11 (0.67 to 1.83)
Prostate‡	29	1.00 (referent)	40	1.02 (0.62 to 1.70)	26	0.57 (0.32 to 1.03)	12	0.58 (0.29 to 1.17)	14	0.57 (0.28 to 1.15)
Ovary§	48	1.00 (referent)	47	1.05 (0.69 to 1.60)	25	0.76 (0.46 to 1.27)	16	0.84 (0.47 to 1.51)	9	0.64 (0.30 to 1.35)
Breast‖	30	1.00 (referent)	38	1.45 (0.88 to 2.38)	11	0.63 (0.30 to 1.29)	9	0.84 (0.39 to 1.81)	2	0.28 (0.06 to 1.20)
Brain	40	1.00 (referent)	43	1.02 (0.65 to 1.59)	41	1.13 (0.70 to 1.82)	24	1.25 (0.74 to 2.12)	17	0.96 (0.52 to 1.80)
Myeloma	31	1.00 (referent)	25	0.78 (0.45 to 1.35)	34	1.09 (0.64 to 1.85)	15	0.97 (0.51 to 1.83)	19	1.24 (0.65 to 2.35)
Bladder	28	1.00 (referent)	41	1.30 (0.79 to 2.15)	20	0.52 (0.28 to 0.97)	6	0.35 (0.14 to 0.85)	14	0.70 (0.35 to 1.42)
Liver	37	1.00 (referent)	34	0.88 (0.54 to 1.43)	22	0.52 (0.30 to 0.93)	13	0.62 (0.32 to 1.20)	9	0.42 (0.19 to 0.91)
Kidney	32	1.00 (referent)	28	0.93 (0.55 to 1.58)	27	0.71 (0.40 to 1.25)	14	0.76 (0.40 to 1.47)	13	0.64 (0.31 to 1.32)
Melanoma	21	1.00 (referent)	15	0.71 (0.35 to 1.41)	12	0.55 (0.25 to 1.19)	6	0.53 (0.21 to 1.37)	6	0.56 (0.21 to 1.53)
All other	188	1.00 (referent)	163	0.89 (0.71 to 1.10)	139	0.79 (0.62 to 1.01)	77	0.86 (0.65 to 1.13)	62	0.71 (0.52 to 0.97)

* Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for age (1-year age strata using the stratified Cox procedure), sex, race (white, black, or other or unknown), education (completed less than high school diploma, high school graduate, some college, college graduate, graduate school, or unknown), smoking (never smoker, never cigarette smoker but ever cigar or pipe smoker, former cigarette smoker subcategorized by combinations of years since quit [<10, 10 to <20, 20 to <30, 30 to <40, ≥40, or unknown] and cigarettes per day [<20 or ≥20], or current cigarette smoker subcategorized by combinations of years smoked [<40 or ≥40] and cigarettes per day [<20 or ≥20], body mass index (kg/m^2, <22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, ≥30, or unknown), physical activity level (metabolic equivalents per week, <3.5, 3.5 to <4.5, 4.5 to <14, 14 to <24.5, ≥24.5, or unknown), history of heart disease, stroke, diabetes, hypertension, cholesterol-lowering drug use (current), aspirin use in the year 1982 (no use, occasional use, 1 to <15, 15 to <30, ≥30 times per month, or unknown), nonsteroidal anti-inflammatory drug use (none, 1–14, 15–29, 30–59, or ≥60 pills per month), and history of colorectal endoscopy (ever).

† Gastrointestinal tract (GI) includes cancers of the esophagus, stomach, small intestine, colon, and rectum.

‡ Men only, additionally adjusted for history of prostate-specific antigen (PSA) testing (in the last 2 years, >2 years ago, or unknown).

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first 6 years of follow-up of the CPS-II cohort (1982–1988), aspirin use 16 or more times a month at baseline was not statistically significantly associated with cancer mortality (4), but results for long-duration use were not reported. In the Iowa Women's Health Study, aspirin use at least six times a week at baseline was associated with lower cancer mortality (RR = 0.82, 95% CI = 0.68 to 0.99), but again, results for long-duration use were not reported (5). In the Nurses' Health Study, use of aspirin for 11 or more years was associated with approximately 20% lower overall cancer mortality, with no clear reduction in risk with shorter duration use (6). However, aspirin use was defined as including use as infrequent as once a week.

In our study, the association between daily aspirin use and lower overall cancer mortality was somewhat stronger in analyses of updated aspirin use than in analyses of aspirin use at baseline. Updated aspirin use likely reflects associations with recent aspirin use better than aspirin use at baseline. However, the updated analysis required censoring of participants who were diagnosed with cancer during the first 6 years of follow-up (before aspirin use was updated) but who did not die of cancer until after this time period. If aspirin use is associated with lower risk of rapidly fatal cancer, but not more slowly fatal cancer, then the updated analysis may have overestimated any true long-term reduction in cancer mortality.

Unlike the pooled trial analysis (1), or a previous analysis of daily aspirin use and cancer incidence in the CPS-II Nutrition Cohort (18), we did not observe a larger reduction in risk among long-term daily aspirin users vs shorter term daily users. Several factors could have contributed to the absence of a trend with duration of use. First, current use, even of relatively short duration, could plausibly have some effect on cancer mortality. In the pooled trial analysis (1), there was some suggestion of lower cancer mortality even during the first 3 years of follow-up (RR = 0.90, 95% CI = 0.76 to 1.06). Some recent observational studies reported that postdiagnosis aspirin use was associated with substantially lower cancer mortality among patients with breast cancer (19) and colorectal cancer (20) and with lower risk of biochemical recurrence among patients with prostate cancer (21). Second, many participants who were classified as short-term users (<5 years of daily use) in this analysis are likely to have become long-term users during follow-up. For example, a participant who began daily aspirin in the year 1994 would be classified as a short-term user (<5 years) at baseline in 1997 but would likely have accrued 5 years of daily use by the year 1999. Finally, the confidence intervals around the estimates for longer and shorter term daily aspirin use do not rule out a larger reduction in risk with longer term use.

In this analysis, updated daily aspirin use was associated with lower cancer mortality among never smokers, but no clear association was observed among former and current smokers. Results for the association between aspirin and cancer mortality were not reported by smoking status in the pooled trial analysis (1). However, there was no apparent difference by smoking status in analyses of cancer incidence in six primary prevention trials (1), although numbers were limited. In two large observational studies, the Nurses' Health Study (6) and the Iowa Women's Health Study (5), aspirin use was associated with lower cancer mortality among never and former smokers but not among current smokers. Collectively, the observational data suggest that the association between aspirin use and cancer mortality may be weaker among current smokers. Reasons for differences by smoking status are unclear. One possible explanation is residual confounding by smoking characteristics among smokers. Alternatively, limited evidence suggests that aspirin could cause less complete inhibition of platelet activation among smokers than nonsmokers (22,23). Differences in effects on platelet activation could be relevant for cancer mortality, given the potentially important role of activated platelets in promoting metastasis (24,25). The possibility that aspirin's antiplatelet effects might differ by smoking status is also consistent with results from a meta-analysis of randomized trials of aspirin for prevention of vascular events (26). In that meta-analysis, the association of aspirin (compared with placebo) with risk of vascular events was statistically significantly different by smoking status, with aspirin associated with lower risk only among nonsmokers (26).

In addition to relative risk of cancer mortality, we also calculated cancer mortality rates, a measure of absolute risk. The difference between cancer mortality rates observed among nonusers and daily long-term aspirin users in our updated analysis (approximately 100 per 100 000 person-years in men and approximately 40 per 100 000 person-years in women) would represent an important benefit of aspirin use if it were causal. However, even if causal, differences in absolute rates are likely to differ between our predominantly elderly population and younger populations at much lower risk of cancer mortality.

In analyses of individual cancer sites, updated daily aspirin use was associated with lower mortality from cancers of the gastrointestinal tract, which is generally consistent with previous observational studies (7) and with results of the pooled trial analysis (1). Updated daily aspirin use was associated with slightly lower mortality from cancers outside the gastrointestinal tract. However, statistically significant reductions in risk were observed only for liver and bladder cancer. To our knowledge, previous studies have not reported associations between aspirin use and liver cancer. The association with lower risk of fatal liver cancer should be interpreted cautiously, as it could be due to contraindication of aspirin therapy for individuals with chronic liver disease (27), an important risk factor for liver cancer (28). The association between aspirin use and lower risk of fatal bladder cancer was unexpected, as aspirin has generally not been associated with lower risk of incident bladder cancer (7).

An important limitation of our analysis is that it is an observational study, not a randomized trial. Therefore, we could have underestimated the size of any reduction in cancer mortality from aspirin use because of confounding by factors associated with both daily aspirin use and increased cancer mortality. Alternatively, we could have overestimated any reduction in cancer mortality if daily aspirin use was associated with factors that reduce cancer mortality, for example, promptly seeking medical attention in response to early symptoms of cancer. It should also be noted that there were not enough former long-term daily aspirin users in the study to determine if long-term daily aspirin users might experience lower cancer mortality even after stopping aspirin use, as suggested by long-term postintervention follow-up of three trials (29).

An important strength of this analysis is its large size. Both baseline and updated analyses included over 500 cancer deaths among long-term daily aspirin users, allowing us to obtain relatively precise risk estimates and to examine results separately by sex, smoking status, and cancer site. This study was somewhat larger than the

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pooled trial analysis (1) in which during follow-up after the first 5 years, 92 cancer deaths occurred in the aspirin group and 145 cancer deaths occurred in the control group (1). In addition, this analysis incorporated detailed information on aspirin use collected at several different time points during follow-up.

Our results are consistent with an association between recent daily aspirin use and modestly lower cancer mortality but suggest that any reduction in cancer mortality may be smaller than that observed with long-term daily aspirin use in the pooled trial analysis (1). However, even a relatively modest benefit with respect to overall cancer mortality could still meaningfully influence the balances of risks and benefits of prophylactic aspirin use. Our results provide additional support for a potential benefit of daily aspirin use for cancer mortality, but important questions remain about the size of this potential benefit.

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