

Long-term Aspirin Use and Mortality in Women

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Background: The influence of long-term use of aspirin on total mortality in women remains uncertain.

Methods: We conducted a prospective, nested, case-control study of 79 439 women enrolled in the Nurses' Health Study who had no history of cardiovascular disease or cancer. Women provided data on medication use biennially since 1980. We assessed relative risk (RR) of death according to aspirin use before diagnosis of incident cardiovascular disease or cancer and during the corresponding period for each control subject.

Results: During 24 years, we documented 9477 deaths from all causes. In women who reported current aspirin use, the multivariate RR of death from all causes was 0.75 (95% confidence interval, 0.71-0.81) compared with women who never used aspirin regularly. The risk reduction was more apparent for death from cardiovascular disease (RR, 0.62; 95% confidence interval, 0.55-0.71) than for death from cancer (RR, 0.88; 95% confidence inter-

val, 0.81-0.96). Use of aspirin for 1 to 5 years was associated with significant reductions in cardiovascular mortality (RR, 0.75; 95% confidence interval, 0.61-0.92). In contrast, a significant reduction in risk of cancer deaths was not observed until after 10 years of aspirin use ($P_{\text{linear trend}} = .005$). The benefit associated with aspirin was confined to low and moderate doses and was significantly greater in older participants ($P_{\text{interaction}} < .001$) and those with more cardiac risk factors ($P_{\text{interaction}} = .02$).

Conclusions: In women, low to moderate doses of aspirin are associated with significantly lower risk of all-cause mortality, particularly in older women and those with cardiac risk factors. A significant benefit is evident within 5 years for cardiovascular disease, whereas a modest benefit for cancer is not apparent until after 10 years of use.

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CARDIOVASCULAR DISEASE and cancer are the 2 leading causes of death in women in the United States.¹ Randomized trials have demonstrated a benefit for aspirin therapy in reducing the incidence of cardiovascular events and neoplastic polyps²⁻⁶; however, it remains unclear whether,

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on balance, aspirin therapy significantly influences risk of death, particularly in women. Although considerable evidence suggests that aspirin therapy improves survival in men and women with established cardiovascular disease,⁷ data for women without cardiovascular disease are limited and conflicting. Recently, a randomized trial of almost 40 000 apparently healthy women did not find a significant benefit of low-

dose aspirin therapy on mortality.^{8,9} Nevertheless, the study examined a single dose and included only 1251 total deaths.

We prospectively examined the influence of aspirin therapy on the risk of death from all causes, cardiovascular disease, and cancer in a large cohort of women enrolled in the Nurses' Health Study. During the last 24 years, participants provided detailed updated information on aspirin use and concurrent data on mortality risk factors. This prospective study permitted a more comprehensive examination of long-term aspirin use over a broader range of intake than would be feasible in a placebo-controlled trial. An earlier examination of aspirin use in this cohort did not find a strong relationship with mortality; however, that analysis was limited by the number of deaths (646) and short-term follow-up (6 years).¹⁰ In the present analysis, we offer results that encompass 24 years of follow-up and include 9477 deaths.

STUDY POPULATION

The Nurses' Health Study was established in 1976 when 121 701 married female registered nurses aged 30 to 55 years, residing in the United States, completed a mailed questionnaire. Follow-up questionnaires have been sent biennially since then to ascertain information on risk factors and to identify newly diagnosed cardiovascular events and cancers. In 1980, the questionnaire was expanded to include a validated assessment of diet and medication use.¹¹ The institutional review board at Brigham and Women's Hospital, Boston, Mass, approved this study; questionnaire completion was considered to imply informed consent. For the current analysis, we excluded women who did not return the medication assessment and those who reported cancer (except nonmelanoma skin) or cardiovascular disease (myocardial infarction, stroke, coronary artery bypass grafting or percutaneous coronary intervention, or angina) on or before the 1980 questionnaire.

IDENTIFICATION OF CASE AND CONTROL SUBJECTS

We included deaths that occurred after the 1980 questionnaire and before June 1, 2004. Mortality follow-up using the National Death Index and next of kin was more than 98% complete.^{12,13} For all deaths, we determined cause using death certificates and medical records. We assigned the underlying cause of death according to the *International Classification of Diseases, Eighth Revision (ICD-8)*. Our primary end point was death from any cause, but we also examined death from cardiovascular disease (ICD-8 codes 390-459 and 795), coronary heart disease (ICD-8 codes 410-414), stroke (ICD-8 codes 430-438), any cancer (ICD-8 codes 140-207), lung cancer (ICD-8 code 162), breast cancer (ICD-8 code 174), and colon or rectal cancer (ICD-8 codes 153-154). We documented 9477 deaths among eligible study participants. We established the initial date of diagnosis of these fatal conditions when we confirmed reports of myocardial infarction, stroke, or cancer on the biennial questionnaire using medical records. We have described our methods for confirmation of these end points in detail.^{10,14}

Using previously described methods,¹⁵ for each case subject (women who died), we chose control subjects randomly beginning with the earliest deaths and proceeding systematically through the end of follow-up. We randomly chose 7 control subjects for each of 5854 case subjects and 8 control subjects for each of 3623 case subjects, thus including 100% of all eligible participants (79 439) after baseline exclusions.

ASSESSMENT OF MEDICATION USE

Since 1980, we assessed intake of aspirin biennially except in 1986. We have previously described our aspirin use questionnaire in detail.^{10,16-18} In brief, in 1980, we asked women if they used aspirin "in most weeks," the number of pills or capsules taken each week, and the number of years of use. In subsequent questionnaires, women were asked whether they regularly took aspirin and, if yes, the frequency and number of tablets per week (in categories). Early in the study, most women used standard-dose aspirin tablets; however, to reflect trends in consumption of low-dose aspirin, questionnaires after 1992 asked participants to convert intake of 4 "baby" aspirins to 1 adult tablet. In 2000 and 2002, we inquired specifically about low-dose aspirin. As previously described,¹⁶⁻¹⁸ we examined the duration of use by the number of years of use reported in 1980 with updating of this variable every 2 years.

In a subsample of 200 women who reported taking aspirin in 1990 (91% response rate), we conducted a study to determine indications for use. The major reasons among women taking 1 to 6 aspirins and 7 aspirins or more per week were headache (32% and 18%, respectively), arthritis or other musculoskeletal pain (30% and 50%, respectively), combined headache and musculoskeletal pain (16% and 15%, respectively), cardiovascular disease prevention (9% and 8%, respectively), and other reasons (13% and 9%, respectively).¹⁰ In a separate study of 4238 women who reported using aspirin more than 15 days per month in 1999, the major reasons for use were cardiovascular disease prevention (48%), musculoskeletal or back pain (32%), headache (12%), and other reasons (8%).¹⁹

STATISTICAL ANALYSIS

The standard prospective analysis used for incident diseases in this cohort would have been inappropriate to use for mortality.¹⁸ Because of the need to establish aspirin use at time of diagnosis of fatal disease rather than at death, we would have truncated follow-up for case subjects but not for other subjects in a prospective analysis, thus potentially exaggerating any apparent benefit of aspirin therapy. In our nested case-control analysis, we could end follow-up simultaneously for each case subject and her matched control subjects. This analysis has been used previously in examining mortality in the Nurses' Health Study.¹⁵

For each death, we defined the woman's aspirin use and other covariates according to the most updated information before death or, where relevant, the initial diagnosis of the disease that led to death. In this way, we reduced potential bias caused by initiation or discontinuation of aspirin therapy between the diagnosis of a potentially fatal disease and subsequent death. For 65% of case subjects, we used the last questionnaire completed before death; for 11%, 2 periods before death; for 7%, 3 periods before death; and for the remaining 17%, more than 3 periods before death. In women who did not use aspirin before diagnosis, 28% began using aspirin after diagnosis. We subsequently matched control subjects to case subjects for the period in which exposure data were collected, thereby accounting for the increasing trend to prescribe aspirin during the course of the study and the greater likelihood that a participant would use aspirin with longer follow-up.

We used conditional logistic regression analysis to estimate relative risk (RR) of death associated with aspirin use and the corresponding 95% confidence interval (CI). We obtained similar results using unconditional logistic regression analysis adjusting for period. To increase statistical power, we used unconditional logistic regression analysis for secondary end points.²⁰ Thus, all results presented are from unconditional logistic regression models, controlling for age, period, and mortality risk factors. Based on a previous analysis of this cohort,²¹ we used baseline data on body mass index (calculated as weight in kilograms divided by height in meters squared) to reduce the influence of underlying disease on weight.²² However, additional analyses using updated data on body mass index did not materially alter our results (data not shown). We used odds ratios from these models to approximate RR.²³ We assessed linear trend of categories by assigning the median value of each category and including the term in multivariate models. In our model, we evaluated any curvilinear association by including both linear and quadratic terms (eg, number of aspirin tablets per week and that value squared).^{23,24} We used likelihood ratio tests comparing nested models with and without interaction variables to assess interaction. All *P* values were 2-sided. Significance was set at *P* < .05.

Table 1. Baseline Characteristics of the Study Cohort in 1980^a

Characteristic	No. of 325-mg Aspirin Tablets Consumed per Week				
	None (n = 45 305)	1-2 (n = 11 507)	3-5 (n = 8158)	6-14 (n = 9467)	>14 (n = 5002)
Mean age, y	46.2	46.2	46.0	47.0	48.4
Race/ethnicity ^b					
Nonwhite	3	2	1	1	1
White	97	98	99	99	99
Body mass index, mean ^c	24.0	24.1	24.3	24.6	25.3
Regular vigorous exercise ^d	47	49	47	45	43
Daily intake of saturated fat, mean, g ^e	28.0	28.0	28.1	27.9	28.1
Alcohol consumption, g/d	6.1	6.2	6.6	7.4	6.8
Hypertension	15	13	15	18	21
Diabetes mellitus	2	2	2	2	3
Hypercholesterolemia	5	5	5	6	7
Smoking history					
Past smoker	27	26	28	28	29
Current smoker	28	29	30	30	30
Postmenopausal status ^f	42	42	43	46	50
Past use of hormone therapy	19	18	18	20	22
Current use of hormone therapy	18	20	21	22	24
Current use of a multivitamin	30	40	36	38	41
Parental myocardial infarction at age <60 y	16	17	17	18	19
No. of cardiac risk factors ^g					
0	54	55	51	48	44
1	35	36	37	38	39
2	9	8	9	11	13
≥3	2	2	2	3	4

^aCharacteristics at baseline questionnaire in 1980. Values indicate percentage unless otherwise indicated. All values other than for age have been directly standardized according to the age distribution of the cohort.

^bTo assess the racial/ethnic composition of the cohort, in 1992 we asked participants to self-classify their race using investigator-defined classification options.

^cCalculated as weight in kilograms divided by height in meters squared.

^dLong enough to work up a sweat, at least once a week.

^eMean of energy-adjusted intake.

^fHormones are defined as postmenopausal estrogen or combined estrogen-progesterone preparations. Percentage of past and current use was calculated in postmenopausal women only.

^gIncludes hypertension, hypercholesterolemia, diabetes mellitus, current smoking, body mass index of 30 or more. Total may not sum to 100 because of rounding.

RESULTS

We documented 9477 deaths from any cause that occurred during the 24 years of follow-up; 1991 women died of cardiovascular disease and 4469 died of cancer. Of the deaths from cardiovascular disease, 889 were due to coronary heart disease, 502 to stroke and 600 to other forms of cardiovascular disease (eg, congestive heart failure and others [these were not analyzed separately]). Of the deaths from cancer, 979 were due to lung cancer, 864 to breast cancer, 433 to colorectal cancer, and 2193 to other types of cancer (eg, ovarian and others not analyzed separately). Among the 79 439 participants, women reporting low to moderate use of aspirin were generally similar to nonusers (**Table 1**).

We observed a significantly lower risk of death from all causes among women who reported current regular use of any aspirin compared with women who never used aspirin on a regular basis (multivariate RR, 0.75; 95% CI, 0.71-0.81), even after controlling for a range of risk factors for death (**Table 2**). The magnitude of risk reduction was greatest for death from cardiovascular disease (multivariate RR, 0.62; 95% CI, 0.55-0.71) including coronary heart disease and stroke. We observed only a mod-

est association with death from all cancers (multivariate RR, 0.88; 95% CI, 0.81-0.96). The lower risk of cancer death among current aspirin users was statistically significant for death from colorectal cancer (multivariate RR, 0.72; 95% CI, 0.56-0.92).

We observed a significant linear relationship between increasing duration of aspirin use and decreasing mortality from all causes ($P < .001$; **Table 3**). However, for death from cardiovascular disease, much of the apparent benefit associated with aspirin was achieved within the first 5 years ($P_{\text{linear trend}} = .18$). In contrast, for all cancer-related mortality, a significant benefit was not evident until after at least 10 years of aspirin use ($P_{\text{linear trend}} = .005$). The strongest inverse association of prolonged aspirin use was observed with death from colorectal cancer (multivariate RR, 0.50; 95% CI, 0.33-0.76 for 11-20 years, and multivariate RR, 0.61; 95% CI, 0.41-0.90 for >20 years; $P_{\text{linear trend}} = .02$). Although current aspirin use did not seem to confer an overall significant benefit in death from breast or lung cancer, women who used aspirin for longer than 20 years seemed to have a modest reduction in the risk of death from breast cancer (multivariate RR, 0.68; 95% CI, 0.51-0.89) and lung cancer (multivariate RR, 0.74; 95% CI, 0.57-0.97).

Table 2. Relative Risk of Death From All Causes and From Specific Causes According to Aspirin Use^a

Cause of Death	No. of Cases/Control Subjects	Age-Adjusted RR (95% CI)	Multivariate RR ^b (95% CI)
All causes (n = 9477) ^c			
Never user	2112/14 231	1.0	1.0
Past user	4111/26 169	0.91 (0.86-0.97)	0.97 (0.91-1.04)
Current user	3254/29 562	0.67 (0.63-0.71)	0.75 (0.71-0.81)
Cardiovascular disease (n = 1991) ^d			
Never user	462/14 231	1.0	1.0
Past user	901/26 169	0.93 (0.83-1.05)	0.96 (0.84-1.09)
Current user	628/29 562	0.58 (0.51-0.66)	0.62 (0.55-0.71)
Coronary heart disease (n = 889) ^d			
Never user	229/14 231	1.0	1.0
Past user	362/26 169	0.82 (0.68-0.97)	0.84 (0.69-1.00)
Current user	298/29 562	0.57 (0.48-0.68)	0.62 (0.51-0.75)
Stroke (n = 502) ^d			
Never user	110/14 231	1.0	1.0
Past user	242/26 169	1.01 (0.80-1.29)	1.03 (0.80-1.31)
Current user	150/29 562	0.57 (0.44-0.73)	0.62 (0.48-0.80)
All cancers (n = 4469) ^e			
Never user	1010/14 231	1.0	1.0
Past user	1690/26 169	0.89 (0.82-0.97)	0.95 (0.87-1.03)
Current user	1769/29 562	0.80 (0.74-0.87)	0.88 (0.81-0.96)
Lung cancer (n = 979)			
Never user	204/14 231	1.0	1.0
Past user	404/26 169	0.97 (0.81-1.16)	1.03 (0.86-1.24)
Current user	371/29 562	0.78 (0.65-0.93)	0.88 (0.73-1.05)
Breast cancer (n = 864) ^f			
Never user	230/14 231	1.0	1.0
Past user	263/26 169	0.70 (0.58-0.85)	0.82 (0.68-1.00)
Current user	371/29 562	0.81 (0.68-0.95)	0.95 (0.80-1.13)
Colorectal cancer (n = 433) ^g			
Never user	112/14 231	1.0	1.0
Past user	163/26 169	0.85 (0.66-1.10)	0.91 (0.70-1.18)
Current user	158/29 562	0.66 (0.52-0.85)	0.72 (0.56-0.92)

Abbreviations: CI, confidence interval; RR, relative risk.

^aAspirin never user is defined as a woman who reported no regular aspirin use on all biennial questionnaires before diagnosis of a fatal disease or death. Aspirin past user is defined as a woman who reported no regular aspirin use on the most recent biennial questionnaire before diagnosis of a fatal disease or death but had previously reported regular use. Aspirin current user is defined as a woman who reported regular aspirin use on the most recent biennial questionnaire preceding diagnosis of a fatal disease or death.

^bMultivariate RRs are adjusted for period of death for cases and of matching period for noncases; age (5-y categories); history of hypertension (yes or no); diabetes mellitus (yes or no); history of hypercholesterolemia (yes or no); smoking (never, past, or current smoker); body mass index (quintiles); physical activity (quintiles); postmenopausal hormone use (premenopausal, never, past, or current); current multivitamin use (yes or no); energy-adjusted quintiles of intake of saturated fat and of alcohol (0, 0.1-4.9, 5.0-14.9, and ≥ 15 g/d).

^cModels of death from all causes also include family history of early myocardial infarction (parental age <60 y), breast cancer (mother or sister), and colorectal cancer (parent or sibling).

^dModels of death from cardiovascular disease, coronary heart disease, and stroke also include family history of early myocardial infarction.

^eModels of death from all cancers include family history of breast cancer and colorectal cancer.

^fModels of death from breast cancer include family history of breast cancer.

^gModels of death from colorectal cancer include family history of colorectal cancer.

Compared with women who never used aspirin on a regular basis, current users of low to moderate doses of aspirin had a substantially lower risk of death (multivariate RR, 0.70; 95% CI, 0.64-0.76 for 1-2 standard tablets per week, and RR, 0.67; 95% CI, 0.61-0.74 for 3-5 standard tablets per week; **Table 4**). Use of aspirin at the highest doses was not associated with risk reduction (multivariate RR, 1.10; 95% CI, 0.99-1.19 for >14 standard tablets per week). To assess this nonlinear relationship between aspirin dose and mortality, we performed analyses in which the median value for each category of aspirin tablets was entered into the multivariate model as both a linear and a quadratic term. A significant negative regression coefficient for the linear term ($\beta = -8 \times 10^{-2}$; $P < .001$) and a significant positive coefficient for the quadratic term ($\beta = 5 \times 10^{-3}$; $P < .001$) were

derived, consistent with the observed U-shaped relationship.²⁴ A similar significant U-shaped relationship between risk of death and aspirin dose was observed for death from cardiovascular disease and cancer. Consistent with findings of our previous analysis of aspirin use and incident colorectal cancer, we observed a strong linear relationship between increasing dose and lower risk of death from colorectal cancer when restricting the analysis to women who used aspirin for longer than 10 years ($P_{\text{linear trend}} = .02$).

Based on previous data that suggested a higher incidence of hemorrhagic stroke due to increasing aspirin dose, we also examined the effect of aspirin dose on risk of death from hemorrhagic stroke.¹⁴ Among women who used more than 14 tablets per week, we observed a nonstatistically significant increased risk of death from hem-

Table 3. Relative Risk of Death From All Causes and From Specific Causes According to Duration of Current Aspirin Use^a

Cause of Death	Years of Aspirin Use					<i>P</i> _{linear trend}
	None	1-5	6-10	11-20	>20	
All causes^b						
No. of deaths/controls	2112/14 231	684/5858	838/7228	947/8288	785/8188	
Age-adjusted RR (95% CI)	1.0	0.83 (0.76-0.91)	0.71 (0.65-0.78)	0.60 (0.55-0.65)	0.60 (0.55-0.66)	<.001
Multivariate RR (95% CI)	1.0	0.86 (0.78-0.95)	0.80 (0.73-0.88)	0.70 (0.64-0.77)	0.68 (0.62-0.74)	<.001
Cardiovascular disease^c						
No. of deaths/controls	462/14 231	140/5858	135/7228	204/8288	149/8188	
Age-adjusted RR (95% CI)	1.0	0.76 (0.62-0.92)	0.50 (0.41-0.61)	0.57 (0.48-0.68)	0.52 (0.43-0.63)	.03
Multivariate RR (95% CI)	1.0	0.75 (0.61-0.92)	0.53 (0.43-0.65)	0.65 (0.54-0.78)	0.57 (0.46-0.69)	.18
Coronary heart disease^c						
No. of deaths/controls	229/14 231	80/5858	64/7228	95/8288	59/8188	
Age-adjusted RR (95% CI)	1.0	0.85 (0.65-1.10)	0.48 (0.36-0.63)	0.58 (0.45-0.74)	0.43 (0.32-0.58)	.001
Multivariate RR (95% CI)	1.0	0.83 (0.63-1.09)	0.50 (0.37-0.67)	0.66 (0.50-0.86)	0.48 (0.36-0.65)	.02
Stroke^c						
No. of deaths/controls	110/14 231	35/5858	29/7228	45/8288	41/8188	
Age-adjusted RR (95% CI)	1.0	0.81 (0.55-1.19)	0.47 (0.31-0.70)	0.51 (0.35-0.72)	0.58 (0.40-0.84)	.44
Multivariate RR (95% CI)	1.0	0.81 (0.55-1.20)	0.50 (0.33-0.76)	0.58 (0.40-0.85)	0.63 (0.43-0.92)	.70
All cancers^d						
No. of deaths/controls	1010/14 231	372/5858	488/7228	506/8288	403/8188	<.001
Age-adjusted RR (95% CI)	1.0	0.89 (0.78-1.00)	0.89 (0.79-0.99)	0.75 (0.67-0.84)	0.69 (0.61-0.78)	.003
Multivariate RR (95% CI)	1.0	0.92 (0.81-1.05)	0.98 (0.87-1.10)	0.86 (0.77-0.97)	0.77 (0.68-0.87)	.005
Lung cancer						
No. of deaths/controls	204/14 231	65/5858	99/7228	125/8288	82/8188	
Age-adjusted RR (95% CI)	1.0	0.78 (0.59-1.04)	0.83 (0.65-1.06)	0.80 (0.63-1.01)	0.67 (0.52-0.87)	.49
Multivariate RR (95% CI)	1.0	0.86 (0.64-1.15)	0.95 (0.74-1.23)	0.95 (0.74-1.21)	0.74 (0.57-0.97)	<.001
Breast cancer^e						
No. of deaths/controls	230/14 231	111/5858	100/7228	90/8288	70/8188	
Age-adjusted RR (95% CI)	1.0	1.13 (0.90-1.43)	0.85 (0.67-1.08)	0.73 (0.56-0.94)	0.56 (0.43-0.73)	<.001
Multivariate RR (95% CI)	1.0	1.18 (0.94-1.50)	0.99 (0.77-1.26)	0.92 (0.70-1.19)	0.68 (0.51-0.89)	.005
Colorectal cancer^f						
No. of deaths/controls	112/14 231	42/5858	50/7228	32/8288	34/8188	
Age-adjusted RR (95% CI)	1.0	0.88 (0.62-1.26)	0.82 (0.59-1.15)	0.45 (0.30-0.67)	0.55 (0.37-0.81)	.007
Multivariate RR (95% CI)	1.0	0.88 (0.61-1.27)	0.89 (0.63-1.26)	0.50 (0.33-0.76)	0.61 (0.41-0.90)	.02

Abbreviations: CI, confidence interval; RR, relative risk.

^aDuration is defined as consecutive years of regular aspirin use among current users before diagnosis of a fatal disease or death. Listing of multivariate RRs are adjusted for period of death for cases and of matching period for noncases; age (5-y categories); history of hypertension (yes or no); history of diabetes mellitus (yes or no); history of hypercholesterolemia (yes or no); smoking (never, past, or current smoker); body mass index (quintiles); physical activity (quintiles); postmenopausal hormone use (premenopausal, never, past, or current); current multivitamin use (yes or no); energy-adjusted quintiles of intake of saturated fat and of alcohol (0, 0.1-4.9, 5.0-14.9, ≥15 g/d).

^bModels of death from all causes also include family history of early myocardial infarction (parental age <60 y), breast cancer (mother or sister), and colorectal cancer (parent or sibling).

^cModels of death from cardiovascular disease, coronary heart disease, and stroke also include family history of early myocardial infarction.

^dModels of death from all cancers include family history of breast cancer and colorectal cancer.

^eModels of death from breast cancer include family history of breast cancer.

^fModels of death from colorectal cancer include family history of colorectal cancer.

orrhagic stroke (RR, 1.43; 95% CI, 0.82-2.49) compared with women who never used aspirin.

To evaluate the influence of amount of aspirin used with time, we estimated tablet-years of use by multiplying the number of aspirins used per week by the number of years of use (**Table 5**). We again observed a U-shaped relationship to death, with the greatest reduction in risk seen with a moderate number of tablet-years of use.

We further examined the relationship of aspirin use with mortality within strata defined a priori by risk factors examined in other studies (**Table 6**).^{8,9} The benefit associated with current aspirin use seemed greater with increasing age for total mortality ($P_{\text{interaction}} < .001$), death from cardiovascular disease ($P_{\text{interaction}} = .01$), and death from cancer ($P_{\text{interaction}} = .02$). Smoking did not seem to modify the association of aspirin with death from all causes ($P_{\text{interaction}} = .07$) or cardiovascular disease

($P_{\text{interaction}} = .78$). In contrast, the influence of aspirin on cancer-related mortality seemed to be confined to never and past smokers ($P_{\text{interaction}} = .002$). In addition, the reduction in all-cause mortality associated with current aspirin use seemed greater with an increasing number of cardiac risk factors ($P_{\text{interaction}} = .02$).

During the 24 years of follow-up, aspirin was increasingly used for prevention of cardiac disease. Although we adjusted for time in our analyses, we considered the possibility that the changes in the indication for use with time still may have influenced our results. In 1992, we also began collecting more detailed data on medical follow-up and socioeconomic status.²⁵ Thus, we conducted a secondary analysis in which 1992 was the baseline period and, in addition, controlled for physician visits and years of educational attainment of participants and their spouses. The multivariate risk of death associated

Table 4. Relative Risk of Death From All Causes and From Specific Causes According to Current Aspirin Dose^a

Cause of Death	No. of 325-mg Aspirin Tablets/wk				
	None	1-2	3-5	6-14	>14
All causes^b					
No. of deaths/controls	2112/14 231	1118/12 407	769/7811	856/6490	511/2854
Age-adjusted RR (95% CI)	1.0	0.59 (0.55-0.64)	0.58 (0.53-0.64)	0.74 (0.68-0.81)	1.06 (0.96-1.18)
Multivariate RR (95% CI) ^c	1.0	0.70 (0.64-0.76)	0.67 (0.61-0.74)	0.78 (0.71-0.85)	1.10 (0.99-1.19)
Cardiovascular disease^d					
No. of deaths/controls	462/14 231	160/12 407	130/7811	216/6490	122/2854
Age-adjusted RR (95% CI)	1.0	0.38 (0.32-0.46)	0.44 (0.36-0.54)	0.82 (0.70-0.97)	1.10 (0.90-1.36)
Multivariate RR (95% CI) ^e	1.0	0.45 (0.37-0.54)	0.49 (0.40-0.61)	0.78 (0.65-0.93)	1.10 (0.89-1.37)
Coronary heart disease^d					
No. of deaths/controls	229/14 231	70/12 407	63/7811	107/6490	58/2854
Age-adjusted RR (95% CI)	1.0	0.34 (0.26-0.44)	0.46 (0.35-0.61)	0.87 (0.69-1.11)	1.04 (0.77-1.39)
Multivariate RR (95% CI) ^f	1.0	0.41 (0.31-0.54)	0.53 (0.39-0.71)	0.80 (0.62-1.03)	1.03 (0.75-1.41)
Stroke^d					
No. of deaths/controls	110/14 231	37/12 407	25/7811	57/6490	31/2854
Age-adjusted RR (95% CI)	1.0	0.38 (0.26-0.55)	0.34 (0.22-0.53)	0.88 (0.63-1.22)	1.23 (0.82-1.85)
Multivariate RR (95% CI) ^g	1.0	0.44 (0.30-0.64)	0.38 (0.24-0.60)	0.86 (0.61-1.20)	1.30 (0.86-1.96)
All cancers^h					
No. of deaths/controls	1010/14 231	685/12 407	428/7811	408/6490	248/2854
Age-adjusted RR (95% CI)	1.0	0.77 (0.70-0.85)	0.74 (0.66-0.83)	0.79 (0.70-0.90)	1.07 (0.92-1.24)
Multivariate RR (95% CI) ⁱ	1.0	0.86 (0.78-0.96)	0.83 (0.73-0.93)	0.85 (0.75-0.96)	1.14 (0.98-1.32)
Lung cancer					
No. of deaths/controls	204/14 231	126/12 407	88/7811	91/6490	66/2854
Age-adjusted RR (95% CI)	1.0	0.68 (0.54-0.85)	0.68 (0.53-0.89)	0.78 (0.60-1.00)	1.28 (0.96-1.70)
Multivariate RR (95% CI) ^j	1.0	0.81 (0.64-1.02)	0.79 (0.61-1.03)	0.82 (0.63-1.06)	1.44 (1.08-1.94)
Breast cancer^k					
No. of deaths/controls	230/14 231	155/12 407	82/7811	79/6490	55/2854
Age-adjusted RR (95% CI)	1.0	0.78 (0.64-0.96)	0.71 (0.55-0.91)	0.80 (0.62-1.04)	1.15 (0.86-1.55)
Multivariate RR (95% CI) ^l	1.0	0.91 (0.74-1.12)	0.85 (0.66-1.11)	0.94 (0.72-1.22)	1.31 (0.97-1.77)
Colorectal cancer^m					
No. of deaths/controls	112/14 231	73/12 407	32/7811	31/6490	22/2854
Age-adjusted RR (95% CI)	1.0	0.75 (0.56-1.00)	0.53 (0.35-0.78)	0.57 (0.38-0.85)	0.85 (0.54-1.35)
Multivariate RR (95% CI) ⁿ	1.0	0.82 (0.61-1.12)	0.58 (0.39-0.87)	0.59 (0.39-0.89)	0.89 (0.56-1.43)

Abbreviations: CI, confidence interval; RR, relative risk.

^aAspirin dose is the number of tablets of aspirin used per week among current users before diagnosis of a fatal disease or death. Categories are based on groupings in biennial questionnaires. Tests for trend are based on median value within each category. Multivariate RRs are adjusted for period of death for cases and of matching period for noncases; age (5-y categories); history of hypertension (yes or no); history of diabetes mellitus (yes or no); history of hypercholesterolemia (yes or no); smoking (never, past, or current smoker); body mass index (quintiles); physical activity (quintiles); postmenopausal hormone use (premenopausal, never, past, or current); current multivitamin use (yes or no); energy-adjusted quintiles of intake of saturated fat and of alcohol (0, 0.1-4.9, 5.0-14.9, or ≥ 15 g/d).

^bModels of death from all causes also include family history of early myocardial infarction (parental age <60 y), breast cancer (mother or sister), and colorectal cancer (parent or sibling).

^cMultivariate test for trend: linear parameter estimate, -8×10^{-2} , $P < .001$; quadratic parameter estimate, 5×10^{-3} , $P < .001$.

^dModels of death from cardiovascular disease, coronary heart disease, and stroke also include family history of early myocardial infarction.

^eMultivariate test for trend: linear parameter estimate, -9×10^{-2} , $P < .001$; quadratic parameter estimate, 6×10^{-3} , $P < .001$.

^fMultivariate test for trend: linear parameter estimate, -8×10^{-2} , $P = .005$; quadratic parameter estimate, 6×10^{-3} , $P < .001$.

^gMultivariate test for trend: linear parameter estimate, -9×10^{-2} , $P = .01$; quadratic parameter estimate, 7×10^{-3} , $P < .001$.

^hModels of death from all cancers include family history of breast cancer and colorectal cancer.

ⁱMultivariate test for trend: linear parameter estimate, -5×10^{-2} , $P < .001$; quadratic parameter estimate, 3×10^{-3} , $P < .001$.

^jMultivariate test for trend: linear parameter estimate, -7×10^{-2} , $P = .007$; quadratic parameter estimate, 5×10^{-3} , $P < .001$.

^kModels of death from breast cancer include family history of breast cancer.

^lMultivariate test for trend: linear parameter estimate, -4×10^{-2} , $P = .14$; quadratic parameter estimate, 3×10^{-3} , $P = .04$.

^mModels of death from colorectal cancer include family history of colorectal cancer.

ⁿMultivariate test for trend: linear parameter estimate, -0.13 , $P = .002$; quadratic parameter estimate, 7×10^{-3} , $P = .004$.

with current aspirin use was not materially altered for deaths from all causes (RR, 0.70; 95% CI, 0.64-0.77), cardiovascular disease, (RR, 0.60; 95% CI, 0.49-0.73), and cancer (RR, 0.86; 95% CI, 0.75-0.99). We also found no significant relationship between use of multivitamins and death from all causes (multivariate RR, 1.03; 95% CI, 0.98-1.08), suggesting that our results for aspirin use were not simply related to general behaviors associated with regular use of a medication or supplement. We confirmed that

aspirin use was not significantly associated with death from accidents (multivariate RR, 0.89; 95% CI, 0.67-1.18), for which aspirin does not likely have a biologically plausible role.

COMMENT

In this large prospective study, women who were currently using aspirin had a lower risk of death than did

Table 5. Relative Risk of Death From All Causes and From Specific Causes According to Tablet-Years in Current Aspirin Users^a

Cause of Death	No. of Tablet-Years				
	None	1-15	16-45	46-128	>128
All causes^b					
No. of deaths/controls	2112/14 231	734/7434	740/7360	827/7494	953/7274
Age-adjusted RR (95% CI)	1.0	0.68 (0.62-0.75)	0.62 (0.56-0.67)	0.65 (0.60-0.71)	0.74 (0.68-0.80)
Multivariate RR (95% CI) ^c	1.0	0.78 (0.71-0.86)	0.71 (0.64-0.78)	0.73 (0.67-0.80)	0.80 (0.73-0.87)
Cardiovascular disease^d					
No. of deaths/controls	462/14 231	108/7434	144/7360	144/7494	232/7274
Age-adjusted RR (95% CI)	1.0	0.45 (0.36-0.55)	0.54 (0.44-0.65)	0.51 (0.42-0.62)	0.80 (0.68-0.95)
Multivariate RR (95% CI) ^e	1.0	0.50 (0.40-0.63)	0.61 (0.50-0.74)	0.54 (0.45-0.67)	0.81 (0.68-0.97)
Coronary heart disease^d					
No. of deaths/controls	229/14 231	54/7434	71/7360	71/7494	102/7274
Age-adjusted RR (95% CI)	1.0	0.44 (0.32-0.59)	0.56 (0.42-0.73)	0.53 (0.40-0.70)	0.75 (0.59-0.96)
Multivariate RR (95% CI) ^f	1.0	0.50 (0.36-0.68)	0.63 (0.48-0.84)	0.56 (0.42-0.75)	0.76 (0.58-0.98)
Stroke^d					
No. of deaths/controls	110/14 231	24/7434	35/7360	27/7494	64/7274
Age-adjusted RR (95% CI)	1.0	0.43 (0.28-0.67)	0.54 (0.37-0.80)	0.39 (0.25-0.60)	0.91 (0.66-1.26)
Multivariate RR (95% CI) ^g	1.0	0.48 (0.30-0.75)	0.62 (0.42-0.91)	0.43 (0.28-0.67)	0.94 (0.68-1.32)
All cancers^h					
No. of deaths/controls	1010/14 231	453/7434	411/7360	443/7494	462/7274
Age-adjusted RR (95% CI)	1.0	0.86 (0.77-0.96)	0.75 (0.66-0.84)	0.78 (0.69-0.88)	0.81 (0.72-0.91)
Multivariate RR (95% CI) ⁱ	1.0	0.94 (0.83-1.06)	0.84 (0.74-0.95)	0.86 (0.76-0.97)	0.88 (0.78-0.99)
Lung cancer					
No. of deaths/controls	204/14 231	75/7434	85/7360	102/7494	109/7274
Age-adjusted RR (95% CI)	1.0	0.70 (0.54-0.92)	0.72 (0.55-0.92)	0.82 (0.64-1.04)	0.84 (0.66-1.07)
Multivariate RR (95% CI) ^j	1.0	0.82 (0.62-1.08)	0.86 (0.66-1.10)	0.93 (0.72-1.19)	0.91 (0.71-1.17)
Breast cancer^k					
No. of deaths/controls	230/14 231	117/7434	88/7360	77/7494	89/7274
Age-adjusted RR (95% CI)	1.0	0.95 (0.76-1.19)	0.77 (0.60-0.99)	0.68 (0.52-0.88)	0.81 (0.63-1.03)
Multivariate RR (95% CI) ^l	1.0	1.05 (0.84-1.32)	0.92 (0.71-1.18)	0.80 (0.61-1.05)	0.98 (0.76-1.27)
Colorectal cancer^m					
No. of deaths/controls	112/14 231	53/7434	30/7360	46/7494	29/7274
Age-adjusted RR (95% CI)	1.0	0.89 (0.64-1.24)	0.50 (0.34-0.76)	0.76 (0.54-1.08)	0.48 (0.31-0.72)
Multivariate RR (95% CI) ⁿ	1.0	0.95 (0.68-1.33)	0.55 (0.36-0.83)	0.82 (0.58-1.18)	0.52 (0.34-0.79)

Abbreviations: CI, confidence interval; RR, relative risk.

^aTablet years is computed by multiplying the number of tablets of aspirin used per week in current users before diagnosis of a fatal disease or death with the number of years of use. Categories of tablet-years are based on quartile cut points within current users. Multivariate RRs are adjusted for period of death for cases and of matching period for noncases; age (5-y categories); history of hypertension (yes or no); history of diabetes mellitus (yes or no); history of hypercholesterolemia (yes or no); smoking (never, past, or current smoker); body mass index (quintiles); physical activity (quintiles); postmenopausal hormone use (premenopausal, never, past, or current); current multivitamin use (yes or no); energy-adjusted quintiles of intake of saturated fat and of alcohol (0, 0.1-4.9, 5.0-14.9, or ≥ 15 g/d).

^bModels of death from all causes also include family history of early myocardial infarction (parental age <60 y), breast cancer (mother or sister), and colorectal cancer (parent or sibling).

^cMultivariate test for trend: linear parameter estimate, -7×10^{-3} , $P < .001$; quadratic parameter estimate, 3×10^{-5} , $P < .001$.

^dModels of death from cardiovascular disease, coronary heart disease, and stroke also include family history of early myocardial infarction.

^eMultivariate test for trend: linear parameter estimate, -1×10^{-2} , $P < .001$; quadratic parameter estimate, 5×10^{-5} , $P < .001$.

^fMultivariate test for trend: linear parameter estimate, -1×10^{-2} , $P < .001$; quadratic parameter estimate, 5×10^{-5} , $P < .001$.

^gMultivariate test for trend: linear parameter estimate, -2×10^{-2} , $P < .001$; quadratic parameter estimate, 8×10^{-5} , $P < .001$.

^hModels of death from all cancers include family history of breast cancer and colorectal cancer.

ⁱMultivariate test for trend: linear parameter estimate, -3×10^{-2} , $P = .01$; quadratic parameter estimate, 1×10^{-5} , $P = .03$.

^jMultivariate test for trend: linear parameter estimate, -1×10^{-2} , $P = .68$; quadratic parameter estimate, 4×10^{-6} , $P = .70$.

^kModels of death from breast cancer include family history of breast cancer.

^lMultivariate test for trend: linear parameter estimate, -5×10^{-3} , $P = .07$; quadratic parameter estimate, 2×10^{-5} , $P = .08$.

^mModels of death from colorectal cancer include family history of colorectal cancer.

ⁿMultivariate test for linear trend: $P = .007$.

women who never used aspirin regularly, particularly for death from cardiovascular disease. A modest reduction in cancer-related mortality (principally, colorectal cancer) was also observed, although a significant inverse association was not apparent until after 10 years of aspirin use. Moreover, the apparent benefit associated with aspirin was largely confined to low to moderate doses of aspirin (1-14 standard tablets per week), whereas higher doses (>14 tablets) did not confer any benefit.

Our results seem to be biologically plausible. Aspirin therapy may influence cardiovascular disease and cancer through its effect on common pathogenic pathways such as inflammation,^{26,27} insulin resistance,²⁸ oxidative stress,²⁹ and cyclooxygenase (COX) enzyme activity.³⁰ Specifically, aspirin inhibits the prothrombotic COX-1 isoenzyme in platelets and the tumorigenic COX-2 enzyme in epithelial cells.^{31,32} Because thrombosis and platelet aggregation are relatively acute events,²⁹ it is not

Table 6. Multivariate Relative Risk of Death From All Causes According to Aspirin Use Stratified by Selected Clinical Variables^a

Variable	Multivariate RR (95% CI)		
	Never User	Past User	Current User
Death from all causes^b			
Age, y			
34-54 (n = 1701)	1.0	0.86 (0.75-0.99)	0.84 (0.74-0.94)
55-64 (n = 3404)	1.0	0.96 (0.86-1.06)	0.84 (0.76-0.93)
65-74 (n = 3327)	1.0	0.98 (0.88-1.10)	0.68 (0.60-0.77)
≥75 (n = 1045)	1.0	1.13 (0.89-1.43)	0.51 (0.40-0.67)
P value for interaction			<.001
Smoking status			
Never smoked (n = 3013)	1.0	0.93 (0.84-1.04)	0.73 (0.65-0.81)
Past smoker (n = 3828)	1.0	1.03 (0.93-1.14)	0.75 (0.68-0.83)
Current smoker (n = 2636)	1.0	0.95 (0.84-1.07)	0.80 (0.71-0.90)
P value for interaction			.07
Cardiac risk factors			
None (n = 1973)	1.0	0.96 (0.84-1.08)	0.81 (0.72-0.92)
1 (n = 3235)	1.0	0.94 (0.85-1.04)	0.71 (0.64-0.79)
2 (n = 2575)	1.0	0.90 (0.79-1.02)	0.69 (0.61-0.79)
≥3 (n = 1694)	1.0	0.94 (0.79-1.11)	0.67 (0.56-0.80)
P value for interaction			.02
Death from cardiovascular disease^c			
Age, y			
34-54 (n = 268)	1.0	0.86 (0.61-1.22)	0.76 (0.56-1.02)
55-64 (n = 734)	1.0	0.85 (0.69-1.04)	0.67 (0.55-0.82)
65-74 (n = 732)	1.0	1.03 (0.83-1.29)	0.58 (0.46-0.74)
≥75 (n = 257)	1.0	1.06 (0.69-1.62)	0.50 (0.31-0.80)
P value for interaction			.01
Smoking status			
Never smoked (n = 618)	1.0	0.95 (0.76-1.20)	0.63 (0.50-0.80)
Past smoker (n = 739)	1.0	1.05 (0.84-1.31)	0.66 (0.52-0.82)
Current smoker (n = 634)	1.0	0.90 (0.72-1.12)	0.59 (0.47-0.74)
P value for interaction			.78
Cardiac risk factors			
None (n = 196)	1.0	0.79 (0.55-1.14)	0.62 (0.43-0.90)
1 (n = 584)	1.0	0.85 (0.68-1.06)	0.53 (0.42-0.67)
2 (n = 644)	1.0	0.95 (0.76-1.19)	0.60 (0.47-0.75)
≥3 (n = 567)	1.0	1.02 (0.78-1.33)	0.74 (0.56-0.97)
P value for interaction			.42
Death from all cancers^d			
Age, y			
34-54 (n = 997)	1.0	0.84 (0.69-1.00)	0.96 (0.82-1.11)
55-64 (n = 1726)	1.0	1.01 (0.88-1.16)	0.93 (0.81-1.06)
65-74 (n = 1448)	1.0	0.88 (0.75-1.04)	0.78 (0.66-0.92)
≥75 (n = 298)	1.0	1.32 (0.87-2.02)	0.84 (0.53-1.33)
P value for interaction			.02
Smoking status			
Never smoked (n = 1438)	1.0	0.83 (0.72-0.96)	0.86 (0.74-0.99)
Past smoker (n = 1795)	1.0	1.00 (0.87-1.15)	0.83 (0.73-0.96)
Current smoker (n = 1236)	1.0	1.01 (0.85-1.19)	1.06 (0.85-1.17)
P value for interaction			.002
Cardiac risk factors^e			
None (n = 1200)	1.0	0.87 (0.74-1.02)	0.89 (0.77-1.04)
1 (n = 1640)	1.0	0.97 (0.84-1.12)	0.86 (0.75-0.99)
2 (n = 1078)	1.0	0.90 (0.75-1.09)	0.84 (0.70-1.00)
≥3 (n = 551)	1.0	0.96 (0.73-1.26)	0.78 (0.60-1.04)
P value for interaction			.89

Abbreviations: CI, confidence interval; RR, relative risk.

^aAspirin never user is defined as a woman who reported no regular aspirin use on all biennial questionnaires before diagnosis of a fatal disease or death. Aspirin past user is defined as a woman who reported no regular aspirin use on the most recent biennial questionnaire before diagnosis of a fatal disease or death but had previously reported regular use. Aspirin current user is defined as a woman who reported regular aspirin use on the most recent biennial questionnaire preceding diagnosis of a fatal disease or death. Multivariate RRs are adjusted for age (5-y categories); history of hypertension (yes or no); history of diabetes mellitus (yes or no); history of hypercholesterolemia (yes or no); smoking (never, past, or current smoker); body mass index (quintiles); physical activity (quintiles); postmenopausal hormone use (premenopausal, never, past, or current); current multivitamin use (yes or no); energy-adjusted quintiles of intake of saturated fat and of alcohol (0, 0.1-4.9, 5.0-14.9, or ≥15 g/d). For each stratified analysis, the stratifying variable was omitted from the multivariate models.

^bModels of death from all causes also include family history of early myocardial infarction (parental age <60 y), breast cancer (mother or sister), and colorectal cancer (parent or sibling).

^cModels of death from cardiovascular disease also include family history of early myocardial infarction.

^dModels of death from all cancers include family history of breast cancer and colorectal cancer.

surprising that we observed a benefit of aspirin therapy on vascular disease within 5 years of use. Our finding of a modest benefit against death from cancer only after prolonged use is consistent with our understanding of the slower, stepwise progression of carcinogenesis. The observed U-shaped relationship between aspirin dose and all-cause mortality and death from cardiovascular disease is also consistent with our understanding of the mechanism of aspirin on thrombosis. Low to moderate doses of aspirin inhibit COX-1, which synthesizes the prothrombotic thromboxane A₂. Because this effect of aspirin is cumulative, even very low doses seem to be effective if administered consistently over time.³¹ However, at higher doses, aspirin also inhibits COX-2, which synthesizes antithrombotic prostacyclins, potentially counterbalancing the effect on COX-1.^{30,31}

Considerable data demonstrate a significant benefit of aspirin therapy on all-cause and cardiovascular mortality in men and women with established coronary heart disease,^{7,33-36} with a similar U-shaped dose relationship observed in a meta-analysis of aspirin trials.⁷ Moreover, a trial of high-dose aspirin therapy (1 g/d) in men and women with a previous myocardial infarction showed no benefit for total mortality.³⁷ Similarly, in apparently healthy men, 500 mg/d of aspirin failed to reduce the risk of any cardiovascular end point in men enrolled in the British Doctors Trial,³⁸ whereas low-dose aspirin therapy reduced the risk of nonfatal myocardial infarction in the Physicians' Health Study and the Thrombosis Prevention Trial.^{2,3} However, all of these trials failed to observe a statistically significant benefit of aspirin therapy on all-cause or cardiovascular mortality, likely because of a low event rate and short-term follow-up.^{2,3,38} A subsequent analysis in the Physicians' Health Study that extended follow-up demonstrated that self-selected aspirin use was associated with significantly lower total and cardiovascular mortality³⁹; similarly, another large cohort study with 12 years of follow-up observed a significant reduction in all-cause mortality among male aspirin users.⁴⁰

Previous data including women without a history of cardiovascular disease are limited and conflicting. A recent meta-analysis of 3 primary prevention trials that included women concluded that aspirin therapy had no significant effect on either cardiovascular or total mortality.⁴¹ However, the total analysis included only 364 cardiovascular deaths and 1515 total deaths. Moreover, differences in dosage, treatment duration, length of follow-up, and participant characteristics within each trial also limit the interpretation of these data. The Women's Health Study (WHS), a large, placebo-controlled trial of 100 mg of aspirin every other day, failed to detect a statistically significant reduction in the risk of death from cardiovascular causes.⁸ However, aspirin users in the WHS who were older than 65 years experienced significant benefit across all cardiovascular end points,⁸ consistent with our results demonstrating progressively greater reduction in mortality with increasing age. The Hypertension Optimal Treatment Study also did not find a statistically significant benefit in all-cause or cardiovascular mortality among men and women with hypertension who were randomized to receive 75 mg/d of aspirin. However, this trial, which was primarily designed to assess the effect of blood

pressure lowering, was limited by its small size (589 deaths) and short-term follow-up (median, 3.8 years); among those randomized to receive aspirin, the 95% CI for RR of all-cause mortality encompasses our risk estimate for women who used aspirin for 1 to 5 years.^{42,43}

Consistent with our results, men and women randomized to receive 100 mg/d of aspirin in the Primary Prevention Project experienced an RR of cardiovascular death of 0.56 (95% CI, 0.31-0.99); in women, the RR of cardiovascular death was 0.41 (95% CI, 0.16-1.05) and the RR of total mortality was 0.60 (95% CI, 0.34-1.04). In this trial, all participants had at least 1 cardiovascular risk factor or were older than 65 years.⁴⁴ Similarly, we also found that the effect of aspirin use on mortality was strongest in women with the greatest number of risk factors.

In our study, the inverse association between current aspirin use and cancer-related death was most apparent with colorectal cancer. This is consistent with data on the role of COX-2 in human cancer, which are most compelling for colorectal neoplasia.^{45,46} Consistent with previous findings in our cohort demonstrating a strong inverse dose-response relationship for long-term aspirin use and incident colorectal cancer,¹⁸ we observed a significant reduction in deaths from colorectal cancer in the highest dose category in long-term users of aspirin. Similarly, an American Cancer Society study found a borderline statistically significant reduction in the risk of all fatal cancers in aspirin users, with the greatest reductions in the risk of fatal colorectal and digestive tract cancers, especially in those who reported aspirin use for longer than 10 years. Moreover, the study also observed a U-shaped relationship between aspirin dose and cancer death.^{47,48}

The WHS did not find a benefit for death from all cancers. However, the trial found a risk reduction for death from lung cancer, consistent with results from the British Doctors Trial.^{9,38} Similarly, in women who used aspirin for more than 20 years, we also observed a significantly lower risk of death from lung cancer as well as breast cancer, consistent with findings from the Women's Health Initiative observational study.⁴⁹

Although several of our findings are consistent with those of the WHS, the WHS did not find any overall benefit with aspirin use for death from all causes, cardiovascular disease, or cancers.^{8,9} However, the WHS had shorter follow-up, included fewer participants and end points, and examined only a single regimen of aspirin. Moreover, compared with the WHS, our study population, on average, seemed to have a higher prevalence of mortality risk factors, which is associated in both studies with a greater effect for aspirin use (**Table 7**).

Our study had several strengths. First, we were able to evaluate long-term use across a broader range of intake. Second, we obtained aspirin data prospectively, thus minimizing the influence of errors in recall and biases related to incomplete data collection from participants with fatal diagnoses. Also, to account for changes in participants' patterns of use, we updated aspirin data biennially. Third, we reviewed records to confirm the initial diagnosis of a fatal disease and determine cause of death. This enabled us to evaluate aspirin use before the diagnosis of a fatal disease rather than before death, thereby

Table 7. Characteristics of Nurses' Health Study Cohort and Women's Health Study Cohort

Characteristic	Nurses' Health Study	Women's Health Study ^a
Follow-up duration, y	24 (1980-2004)	10 (1993-2004)
Aspirin dose	1 to \geq 14 tablets/wk	100 mg every other day
No. of participants	79 439	39 876
No. of deaths	9477	1251
Deaths from cardiovascular disease	1991	246
Deaths from cancer	4469	583
Risk characteristics ^b		
Age, mean, y	58	55
Hypertension, %	33	26
Diabetes mellitus, %	5	3
Hypercholesterolemia, %	43	30
Current smoker, %	16	13
Postmenopausal status, %	83	54
Current use of hormones, % ^c	39	55
Cardiac risk factors, % ^d		
0	33	42
1	37	34
2	22	18
\geq 3	8	6

^aData from the Women's Health Study are taken from Ridker et al⁸ and Cook et al.⁹

^bRisk characteristics for the Nurses' Health Study are based on the 1992 questionnaire completed by 77 013 participants. Characteristics for the Women's Health Study are based on a baseline questionnaire completed between 1992 and 1995 by 39 876 participants.

^cHormones are defined as postmenopausal estrogen or combined estrogen-progesterone preparations. Percent of current use was calculated in postmenopausal women only.

^dCardiac risk factors included hypertension, hypercholesterolemia, diabetes mellitus, current smoking, and body mass index of 30 or more.

minimizing any bias related to discontinuation or initiation of use between diagnosis and subsequent death. Moreover, this reduced misclassification inherent in data based entirely on death certifications. Fourth, our control subjects were derived from the same well-defined population as our case subjects, thus reducing potential selection biases. Fifth, our cohort of nurses likely provides more accurate data on actual consumption of over-the-counter aspirin and potential confounding risk factors.

Several limitations of our study merit comment. The study was observational and aspirin use was self-selected. Thus, despite the strong biologic plausibility of our results, it is possible that our findings could be related to the reason for which participants used aspirin.³⁹ However, we categorized participants according to their use of aspirin before diagnosis of subsequently fatal disease, minimizing potential bias related to changes in aspirin intake because of illness. Nevertheless, we cannot completely exclude residual confounding, and our findings cannot assign causality. Although intervention trials of aspirin therapy potentially would be more definitive, our data highlight the need to examine prolonged use of a wider range of doses. Such intervention trials may not be feasible given the need for a large number of participants and prolonged follow-up.

Because our study design matched cases of death with noncases, we were only able to assess the effect of aspirin on fatal outcomes. Specifically, we documented only 41 deaths related primarily to gastrointestinal tract bleeding and, therefore, could not reliably estimate the effect of aspirin use on this end point. However, in this cohort, we previously observed a dose-dependent increase in reported serious episodes of gastrointestinal tract bleeding.¹⁸ Moreover, the limited number of deaths related to this potential complication of aspirin use is of interest in itself.

In summary, our results suggest that, among women, aspirin use at low to moderate doses is associated with a reduced risk of all-cause mortality, largely due to death from cardiovascular disease. Although aspirin therapy seemed to have a benefit against death from cancer, the effect was relatively modest, requiring prolonged use. However, because our study was observational, these results should be interpreted cautiously and are insufficient evidence to alter current clinical recommendations. Nevertheless, these data support a need for continued investigation of the use of aspirin for chronic disease prevention.

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