

# Low-Dose Aspirin in the Primary Prevention of Cancer

## The Women's Health Study: A Randomized Controlled Trial

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**A** GROWING BODY OF LITERATURE supports a protective effect of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) on the development of cancer. In experimental animal models, NSAIDs have been shown to suppress tumor growth.<sup>1,2</sup> Observational epidemiological investigations suggest a strong inverse association, with risk reductions as high as 20% to 50% for various cancer sites,<sup>3</sup> including but not limited to colorectal cancer,<sup>4,5</sup> breast cancer,<sup>6</sup> and gastric cancer.<sup>3</sup> In addition, polyp prevention trials have consistently demonstrated a beneficial effect of aspirin and other NSAIDs on recurrence of colorectal adenomas.<sup>5</sup>

Aspirin is thought to influence cancer risk primarily through its effect on cyclooxygenase (COX) activity. Aspirin, as well as other NSAIDs, inhibits the COX enzymes, which convert arachidonic acid into prostaglandins.<sup>7</sup> The proposed mechanism for aspirin's effect

See also pp 56 and 105.

**Context** Basic research and observational evidence as well as results from trials of colon polyp recurrence suggest a role for aspirin in the chemoprevention of cancer.

**Objective** To examine the effect of aspirin on the risk of cancer among healthy women.

**Design, Setting, and Participants** In the Women's Health Study, a randomized 2 × 2 factorial trial of aspirin and vitamin E conducted between September 1992 and March 2004, 39 876 US women aged at least 45 years and initially without previous history of cancer, cardiovascular disease, or other major chronic illness were randomly assigned to receive either aspirin or aspirin placebo and followed up for an average of 10.1 years.

**Intervention** A dose of 100 mg of aspirin (n=19 934) or aspirin placebo (n=19 942) administered every other day.

**Main Outcome Measures** Confirmed newly diagnosed invasive cancer at any site, except for nonmelanoma skin cancer. Incidence of breast, colorectal, and lung cancer were secondary end points.

**Results** No effect of aspirin was observed on total cancer (n=2865; relative risk [RR], 1.01; 95% confidence interval [CI], 0.94-1.08; P=.87), breast cancer (n=1230; RR, 0.98; 95% CI, 0.87-1.09; P=.68), colorectal cancer (n=269; RR, 0.97; 95% CI, 0.77-1.24; P=.83), or cancer of any other site, with the exception of lung cancer for which there was a trend toward reduction in risk (n=205; RR, 0.78; 95% CI, 0.59-1.03; P=.08). There was also no reduction in cancer mortality either overall (n=583; RR, 0.95; 95% CI, 0.81-1.11; P=.51) or by site, except for lung cancer mortality (n=140; RR, 0.70; 95% CI, 0.50-0.99; P=.04). No evidence of differential effects of aspirin by follow-up time or interaction with vitamin E was found.

**Conclusions** Results from this large-scale, long-term trial suggest that alternate day use of low-dose aspirin (100 mg) for an average 10 years of treatment does not lower risk of total, breast, colorectal, or other site-specific cancers. A protective effect on lung cancer or a benefit of higher doses of aspirin cannot be ruled out.

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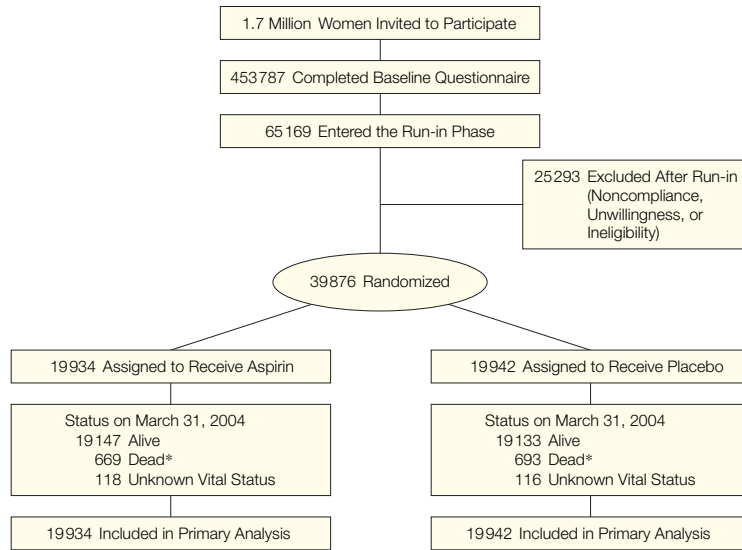
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**Figure 1.** Flow Diagram of the Aspirin Component of the Women’s Health Study (WHS)



\*The numbers of deaths are higher than those in Table 2 because this figure includes all reported deaths in the WHS, whereas the deaths in Table 2 include only reported deaths confirmed by the Endpoints Committee or by a death certificate.

on cancer lies with its effect on the cyclooxygenase 2 (COX-2) enzyme, which is linked to inflammation and related to tumor growth through its effect on apoptosis, cell migration, and angiogenesis.<sup>1,8</sup> Aspirin may also have an effect through its potential role as an antioxidant,<sup>7</sup> or through modulation of estrogen biosynthesis.<sup>9</sup>

In contrast with the observational evidence on cancer incidence, data from randomized trials, which provide more definitive results due to their ability to minimize bias and confounding, have been far more limited.<sup>10,11</sup> The Physicians’ Health Study (PHS) found no effect on colorectal cancer of 325 mg of aspirin administered every other day over a 5-year randomized period<sup>11</sup> or in posttrial follow-up.<sup>12</sup> In addition, no randomized trial has yet assessed the impact of aspirin on the development of breast cancer.

The Women’s Health Study (WHS) was a randomized, double-blind, placebo-controlled, 2 × 2 factorial trial evaluating the balance of benefits and risks of 100 mg of aspirin every other day and 600 IU of vitamin E every other day (see accompanying article on page

56), in the primary prevention of cardiovascular disease<sup>13</sup> and cancer in a cohort of 39 876 healthy female health care professionals over an average duration of 10.1 years. This article reports the findings for the aspirin component with regard to cancer risk.

**METHODS**

**Study Design and Participants**

The WHS is a randomized 2 × 2 factorial trial evaluating the effects of low-dose aspirin (100 mg every other day, provided by Bayer HealthCare) and vitamin E (600 IU every other day, provided by the Natural Source Vitamin E Association) in the primary prevention of cardiovascular disease and cancer. The trial initially contained a beta carotene component, which was terminated January 18, 1996, after an average of 2 years of follow-up.<sup>14</sup> Written informed consent was obtained from all participants. The trial was approved by the institutional review board of Brigham and Women’s Hospital, Boston, Mass, and monitored by an external data and safety monitoring board.

Detailed methods of the design have been described previously.<sup>13,15</sup> In brief,

from September 1992 to May 1995, letters of invitation to participate in the trial and baseline health questionnaires were mailed to more than 1.7 million female health care professionals throughout the United States (FIGURE 1). Women were eligible if they were aged at least 45 years without previous history of cancer (except nonmelanoma skin cancer), cardiovascular disease, or other major chronic illness; no history of adverse effects to aspirin; not taking aspirin or NSAIDs more than once a week (or willing to forgo their use during the trial); not taking anticoagulants or corticosteroids; and not taking individual supplements of vitamin A, vitamin E, or beta carotene more than once a week. The 65 169 women who were willing and eligible entered a 3-month run-in period using both placebo aspirin and placebo vitamin E to identify likely long-term compliers to pill taking. A total of 39 876 women remained willing and eligible, were compliant during run-in, and were randomized into the trial (19 934 to aspirin and 19 942 to placebo). Randomization used blocks of size 16 within 5-year age strata and took place from April 30, 1993, through January 24, 1996.

Participants were sent an annual supply of monthly calendar packs containing active agents or placebo. Every 6 months for the first year, then every 12 months subsequently, participants were sent questionnaires seeking information on compliance, adverse effects, occurrence of relevant clinical end points, and risk factors. Study medications and end point ascertainment were continued in blinded fashion through the scheduled end of the trial on March 31, 2004. Follow-up and validation of reported end points were completed in February 2005. Morbidity and mortality follow-up were 97.2% and 99.4% complete, respectively.

Compliance, defined as taking at least two thirds of the study aspirin or aspirin placebo, was 76% at 5 years and 67% at 10 years, with an average of 73% throughout the trial. Compliance was slightly but statistically significantly lower in the active aspirin group, with

proportions averaging about 1% lower from 24 months onward. Use of outside aspirin for 4 or more days per month averaged 12% during the follow-up, with no statistically significant difference by aspirin assignment.

### End Point Definition

All participants were followed up for the occurrence of cancer or cardiovascular events. Following a report of cancer by questionnaire or death certificate, written consent for medical record review was requested from the participant, or next of kin if deceased, and medical records were obtained from hospitals or treating physicians. All relevant information was reviewed by the WHS Endpoints Committee composed of physicians blinded to treatment assignment. Reports of cancer were confirmed on the basis of pathology or cytology reports (96.8%) or, rarely, based on strong clinical and radiological or laboratory marker evidence (eg, elevated CA-125) when a pathology or cytology review was not conducted. The primary cancer end point for the WHS was any invasive cancer, excluding nonmelanoma skin cancer. The incidence of breast, colorectal, and lung cancer were secondary end points for the aspirin component of the trial. Only confirmed cancer end points were included in these analyses.

In addition, a total of 5088 women self-reported a diagnosis of colon polyp occurring following randomization. Medical records were obtained and reviewed for a random subset of these women. Of 558 postrandomization polyp reports reviewed, 295 were confirmed for a total confirmation rate of 53% (55% in the aspirin group and 51% in the placebo group). Because confirmation of these reports is incomplete, preliminary data on self-reported colon polyps only are presented. The use of colonoscopy or sigmoidoscopy for screening purposes during the past year, as reported on the 12-month questionnaire among women without cancer, was similar by aspirin assignment (5.1% vs 5.2% in active vs placebo, respectively). As reported on the final ques-

tionnaire, the use of colonoscopy for screening purposes from the beginning of the trial was similar by aspirin assignment (41.0% vs 41.7% in active vs placebo, respectively), as was use of sigmoidoscopy (22.5% vs 23.6%, respectively).

### Statistical Analysis

Primary analyses were based on the intent-to-treat principle, including all randomized women, as randomized. Kaplan-Meier survival curves were used to estimate incidence over time, and the log-rank test was computed to compare curves. Cox proportional hazards regression models<sup>16</sup> were used to estimate the relative risks (RRs) and 95% confidence intervals (CIs) comparing women randomized to active aspirin vs aspirin placebo, adjusting for age and randomized vitamin E and beta carotene assignments. Tests of proportionality used an interaction term for aspirin  $\times$  the logarithm of follow-up time. The RR by 2-year follow-up periods was used to investigate patterns in the effect over time. All analyses were conducted with SAS version 8.2 (SAS Institute, Cary, NC), and a 2-sided significance level of  $\alpha=.05$  was used ( $P\leq .05$ ).

Analyses were conducted for the primary end point of total invasive cancer as well as for site-specific cancers. If a woman developed more than 1 primary cancer (excluding nonmelanoma skin cancer), the first following randomization was used in these analyses. In secondary analyses, the effects of aspirin on the combination of invasive and in situ cancers, estrogen- and progesterone-receptor positive breast cancer, colon cancer site and stage (Dukes classification<sup>17</sup>), and small cell and non-small cell lung cancer were examined.

Additional analyses examined the effect of aspirin on cancer risk according to known risk factors for cancer at baseline, including age, body mass index (calculated as weight in kilograms divided by the square of height in meters), smoking (current, past, or never), alcohol use ( $<1$  or  $\geq 1$  drinks per week),

and family history of cancer (history of breast, colorectal, or ovarian cancer in a parent or sibling). Participants were asked at baseline if they ever smoked 100 or more cigarettes in their lifetime. Responses included yes, currently smoke (current); yes, smoked in the past but quit (past); or no (never). Subgroups defined by physical activity (estimated energy expenditure per week from leisure activities of  $<1000$  or  $\geq 1000$  kcal per week), menopausal status and hormone therapy (premenopausal, postmenopausal with or without hormone therapy, or uncertain menopausal status), and other randomized assignments were also examined. Tests for effect modification used a 1-degree interaction term in the Cox proportional hazards regression model in the case of ordinal subgroups, or a multidegree of freedom test for unordered categories.

To examine the effect of actual as opposed to assigned aspirin use, separate sensitivity analyses according to compliance were conducted. Women were censored if and when they stopped taking at least two thirds of their study medication, whether active aspirin or aspirin placebo. To allow for a lag in effect, additional analyses censored women 2 years after they limited compliance. The effect of aspirin among those women who consistently reported good compliance during the first 2 years or 5 years of the trial on cancers occurring following these periods was also examined.

## RESULTS

No statistically significant differences in baseline characteristics were observed between the aspirin and placebo groups (TABLE 1).<sup>13,15</sup> Mean (SD) age at trial entry was 54.6 (7.0) years, 5235 women (13%) were current smokers, 14 265 women (36%) were past smokers, and 20 340 women (51%) were never smokers. Mean (SD) body mass index was 26.0 (5.1), and 21 682 women (54%) were postmenopausal of whom 11 948 (55%) were current, 2745 (13%) were past, and 6959 (32%) were never users of hormone therapy, with 30 women missing hormone informa-

tion. A total of 7046 women (18%) reported a family history of breast, colorectal, or ovarian cancer in a parent or sibling.

During an average 10.1 years of follow-up, 2865 cases of invasive cancer, excluding nonmelanoma skin cancer, were confirmed by the study end points committee (741 events per 100 000 person-years) (TABLE 2). Of these cases, 1230 (43%) were breast cancer, 269 (9%) were colorectal cancer, and 205 (7%) were lung cancer. There was no effect of aspirin on incidence of the primary end point of total cancer (RR, 1.01; 95% CI, 0.94-1.08; *P* = .87) or of

cancer at other sites, including breast (RR, 0.98; 95% CI, 0.87-1.09; *P* = .68) or colorectal cancer (RR, 0.97; 95% CI, 0.77-1.24; *P* = .83), although there was a trend toward reduction in lung cancer in the active aspirin group that was not statistically significant (RR, 0.78; 95% CI, 0.59-1.03; *P* = .08). There were no statistically significant effects on other cancer sites considered. In addition to those cases listed, there were 11 cases of Hodgkin lymphoma (7 vs 4 in aspirin vs placebo groups) and 122 cases of non-Hodgkin lymphoma (RR, 0.97; 95% CI, 0.68-1.38; *P* = .85). There were 7 confirmed cases of esophageal

cancer (2 in aspirin and 5 in placebo groups), and 151 confirmed cases of cancer occurring at other sites not listed in Table 2 (78 vs 73 in aspirin vs placebo groups, respectively).

No difference was observed by aspirin assignment when cases of carcinoma in situ were considered in addition to invasive cancer, with a total of 3241 confirmed invasive or in situ cancers (RR, 1.00; 95% CI, 0.94-1.07; *P* = .94). When these cancers were further divided by site, there were 1535 cases in the breast (RR, 0.98; 95% CI, 0.89-1.08; *P* = .69) and 298 cases in the colon or rectum (RR, 0.97; 95% CI, 0.77-1.22).

Of the invasive breast cancer cases, 820 were estrogen-receptor positive and progesterone-receptor positive, 125 were estrogen-receptor positive and progesterone-receptor negative, and 25 were estrogen-receptor negative and progesterone-receptor positive. None of these subtypes was statistically significantly affected by aspirin assignment (RR, 0.98; 95% CI, 0.85-1.12; *P* = .77 for estrogen-receptor positive/progesterone-receptor positive; RR, 0.81; 95% CI, 0.57-1.15; *P* = .24 for estrogen-receptor positive/progesterone-receptor negative; and RR, 0.79; 95% CI, 0.36-1.73; *P* = .55 for estrogen-receptor negative/progesterone-receptor positive). There was no statistically significant effect of aspirin by site of colon cancer, including 112 proximal cancers (RR, 0.86; 95% CI, 0.60-1.25; *P* = .44) or 95 distal cancers (RR, 0.94; 95% CI, 0.63-1.40; *P* = .75), or colorectal cancer stage, including 89 cases of Dukes stage A (RR, 0.93; 95% CI, 0.62-1.41; *P* = .74), 66 cases of Dukes stage B (RR, 0.94; 95% CI, 0.58-1.52; *P* = .79), and 113 cases of Dukes stage C (RR, 1.05; 95% CI, 0.73-1.52; *P* = .79). In addition, there were 2510 self-reports of colon polyps in the aspirin group and 2578 in the placebo group, leading to an RR of 0.97 (95% CI, 0.92-1.02; *P* = .27). When lung cancer cases were classified by cell type, there was no statistically significant effect on non-small cell cancer (RR, 0.85; 95% CI, 0.61-1.19; *P* = .35), with a marginally statistically significant reduction in small

**Table 1.** Baseline Characteristics of Women by Randomized Aspirin Assignment\*

Characteristics	Aspirin (n = 19 934)	Placebo (n = 19 942)	Total (N = 39 876)	P Value
Age, y				
Mean (SD)	54.6 (7.0)	54.6 (7.0)	54.6 (7.0)	.80
45-54	12 010 (60.2)	12 015 (60.2)	24 025 (60.2)	]. >.99
55-64	5876 (29.5)	5878 (29.5)	11 754 (29.5)	
≥65	2048 (10.3)	2049 (10.3)	4097 (10.3)	
BMI				
Mean (SD)	26.1 (5.1)	26.0 (5.0)	26.0 (5.1)	.30
<25	9912 (50.8)	9937 (50.8)	19 849 (50.8)	]. .79
25 to <30	6027 (30.9)	6054 (31.0)	12 081 (30.9)	
≥30	3575 (18.3)	3551 (18.2)	7126 (18.2)	
Smoking status				
Current	2580 (13.0)	2655 (13.3)	5235 (13.1)	]. .58
Past	7167 (36.0)	7098 (35.6)	14 265 (35.8)	
Never	10 171 (51.1)	10 169 (51.0)	20 340 (51.1)	
Alcohol use, drinks/wk				
<1	11 627 (58.3)	11 599 (58.2)	23 226 (58.3)	]. .74
≥1	8302 (41.7)	8338 (41.8)	16 640 (41.7)	
Physical activity, kcal/wk				
<1000	12 923 (65.7)	13 071 (66.3)	25 994 (66.0)	]. .17
≥1000	6751 (34.3)	6632 (33.7)	13 383 (34.0)	
Menopausal status and use of HT				
Premenopausal	5478 (27.5)	5495 (27.6)	10 973 (27.6)	]. .40
Uncertain	3521 (17.7)	3628 (18.2)	7149 (18.0)	
Postmenopausal and current HT	6037 (30.4)	5911 (29.7)	11 948 (30.0)	
Postmenopausal and no HT	4850 (24.4)	4854 (24.4)	9704 (24.4)	
Family history of cancer†				
Yes	3529 (17.7)	3517 (17.6)	7046 (17.7)	]. .86
No	16 405 (82.3)	16 425 (82.4)	32 830 (82.3)	
Randomized to receive vitamin E				
Yes	9966 (50.0)	9971 (50.0)	19 937 (50.0)	]. .99
No	9968 (50.0)	9971 (50.0)	19 939 (50.0)	
Randomized to receive beta carotene				
Yes	9967 (50.0)	9972 (50.0)	19 939 (50.0)	]. .99
No	9967 (50.0)	9970 (50.0)	19 937 (50.0)	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; HT, hormone therapy.

\*Data are presented as No. (%) unless otherwise indicated. Because of rounding, percentages may not all total 100.

See "Methods" section of the text for descriptions of smoking status, alcohol use, and physical activity.

†History of breast, colorectal, or ovarian cancer in a parent or sibling.

cell cancers (12 vs 22; RR, 0.54; 95% CI, 0.27-1.10;  $P = .09$ ).

No difference was observed by aspirin assignment in overall cancer mortality during the trial (RR, 0.95; 95% CI, 0.81-1.11;  $P = .51$ ), with 583 such deaths confirmed (Table 2). There was also no difference in deaths due to breast cancer ( $n = 63$ ) or colorectal cancer ( $n = 65$ ). Among the 140 deaths due to lung cancer, however, there was a statistically significant reduction among those women assigned to active aspirin vs placebo (58 vs 82; RR, 0.70; 95% CI, 0.50-0.99;  $P = .04$ ). There were no other differences by aspirin assignment in confirmed deaths at other cancer sites considered. In addition, there was no difference in total mortality.

Cumulative incidence curves (FIGURE 2) suggested no variation in the effect of randomized aspirin over time on total cancer (log-rank  $P = .83$ ). In addition, plots of the RR by 2-year follow-up intervals (FIGURE 3) did not suggest an increasing effect with duration of use for total, breast, colorectal, or lung cancer. Tests for proportionality of the hazard ratio over time indicated no statistically significant trend over time for total cancer ( $P = .16$ ), breast cancer ( $P = .87$ ), colorectal cancer ( $P = .69$ ), lung cancer ( $P = .94$ ), or cancer death ( $P = .24$ ). There were no effects on total cancer after excluding the first 2 years (RR, 1.00; 95% CI, 0.92-1.08;  $P = .97$ ) or first 5 years (RR, 0.98; 95% CI, 0.89-1.09;  $P = .73$ ) of follow-up. For breast cancer, the RR after excluding the first 2 years was 0.98 (95% CI, 0.87-1.11;  $P = .74$ ), and the RR after excluding the first 5 years was 0.96 (95% CI, 0.83-1.12;  $P = .63$ ); for colorectal cancer, the RR was 0.97 (95% CI, 0.75-1.26;  $P = .82$ ) after 2 years and 1.13 (95% CI, 0.81-1.58;  $P = .46$ ) after 5 years; and for cancer mortality, the RR was 0.94 (95% CI, 0.79-1.11;  $P = .45$ ) after 2 years and 0.96 (95% CI, 0.78-1.18;  $P = .70$ ) after 5 years. For lung cancer, the RR after excluding the first 2 years was 0.76 (95% CI, 0.56-1.03;  $P = .07$ ) and the RR after excluding the first 5 years was 0.79 (95% CI, 0.54-1.16;  $P = .23$ ); and for lung cancer mor-

tality, the RR was 0.71 (95% CI, 0.50-1.02;  $P = .06$ ) after 2 years and 0.68 (95% CI, 0.45-1.05;  $P = .08$ ) after 5 years.

When effect modification of the impact of aspirin on total cancer by baseline risk factors was considered (TABLE 3), there was no statistically significant difference in effect by age, body

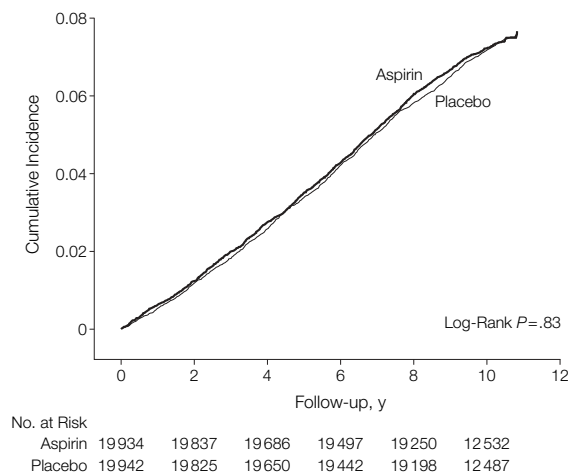
mass index, alcohol use, physical activity, menopausal status and hormone therapy, family history of cancer, or by the other randomized interventions, vitamin E or beta carotene. There was, however, a statistically significant difference in the aspirin effect by smoking status, but in an unexpected direc-

**Table 2.** Confirmed Invasive Cancer Cases by Randomized Aspirin Assignment

Cancer Site	No. of Events		Relative Risk (95% Confidence Interval)	P Value
	Aspirin (n = 19934)	Placebo (n = 19942)		
Total*	1438	1427	1.01 (0.94-1.08)	.87
Breast	608	622	0.98 (0.87-1.09)	.68
Colorectal	133	136	0.97 (0.77-1.24)	.83
Colon	103	111	0.92 (0.71-1.21)	.57
Rectal	30	25	1.20 (0.70-2.04)	.50
Lung	90	115	0.78 (0.59-1.03)	.08
Stomach	10	10	1.00 (0.42-2.40)	>.99
Pancreas	30	21	1.42 (0.81-2.49)	.21
Uterine	123	101	1.22 (0.94-1.58)	.14
Ovary	63	66	0.95 (0.68-1.35)	.79
Kidney	26	35	0.74 (0.45-1.23)	.25
Bladder	27	24	1.12 (0.65-1.94)	.69
Melanoma	68	70	0.97 (0.70-1.36)	.87
Thyroid	35	25	1.40 (0.84-2.34)	.20
Brain	17	14	1.21 (0.60-2.46)	.59
Leukemia/lymphoma	104	90	1.15 (0.87-1.53)	.32
Leukemia	37	24	1.54 (0.92-2.57)	.10
Lymphoma	67	66	1.01 (0.72-1.42)	.94
Multiple myeloma	18	12	1.50 (0.72-3.11)	.28
Any cancer death	284	299	0.95 (0.81-1.11)	.51
Any death	609	642	0.95 (0.85-1.06)	.32

\*Excluding nonmelanoma skin cancer.

**Figure 2.** Cumulative Incidence of Total Invasive Cancer (Excluding Nonmelanoma Skin Cancer) by Randomized Aspirin Assignment



tion. Never smokers at baseline had a significant increase in risk among those participants assigned to aspirin, although past smokers had a marginally significant decrease in risk, with no effect among current smokers, leading to a statistically significant interaction by smoking ( $P=.02$ ). This effect was primarily observed for breast cancer, where the interaction was marginal ( $P=.09$ ); among never smokers, women assigned to aspirin had an increased risk (RR, 1.11; 95% CI, 0.94-1.30;  $P=.21$ ), but among past smokers they had a decreased risk (RR, 0.84; 95% CI, 0.70-1.01;  $P=.07$ ), with no effect among current smokers (RR, 0.93; 95% CI, 0.69-1.25;  $P=.63$ ). No statistically significant effect modification by smoking was observed for colorectal or lung cancer. In particular, for lung cancer, the RRs were 0.83 (95% CI, 0.57-1.19;  $P=.30$ ) with 117 cases among current smokers, 0.69 (95% CI, 0.43-1.11;  $P=.13$ ) with 70 cases among past smokers, and 1.00 (95% CI, 0.39-2.51;  $P=.99$ ) with 18 cases among never smokers.

In sensitivity analyses by compliance, there were no effects on total can-

cer in analyses censoring women at the time they stopped taking at least two thirds of their study pills (RR, 1.03; 95% CI, 0.94-1.12;  $P=.55$ ) or in an analysis censoring women 2 years after they stopped taking their study pills (RR, 1.02; 95% CI, 0.94-1.11;  $P=.56$ ). Results for breast, colorectal, or lung cancer also did not show any significance. Among women who consistently took at least two thirds of their study aspirin or aspirin placebo during the first 2 years of the trial, there was no effect on total (RR, 1.02; 95% CI, 0.93-1.11;  $P=.69$ ), breast (RR, 0.99; 95% CI, 0.87-1.13;  $P=.88$ ), colorectal (RR, 1.07; 95% CI, 0.80-1.43;  $P=.63$ ), or lung (RR, 0.83; 95% CI, 0.59-1.16;  $P=.27$ ) cancers occurring after 2 years of follow-up. The same was true among women who complied with study medication use during the first 5 years of intervention.

**COMMENT**

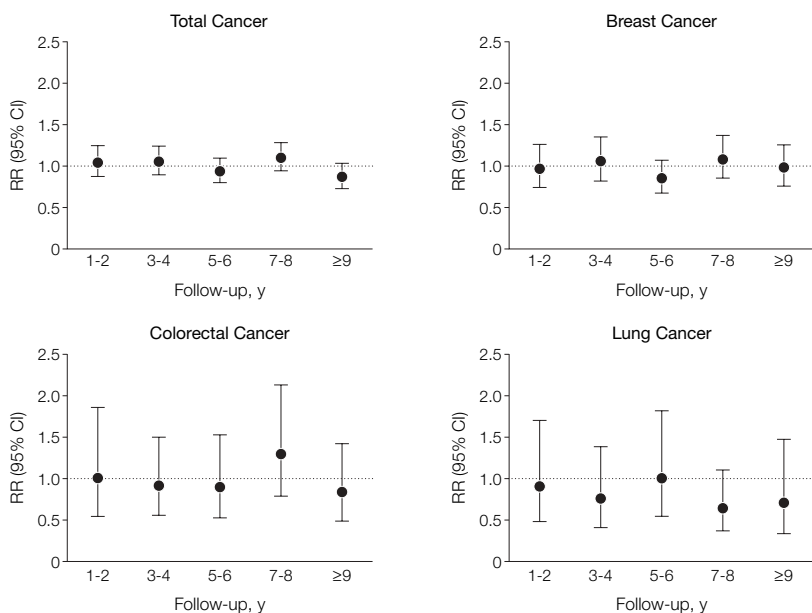
No overall effect of aspirin administered at a dose of 100 mg every other day on total cancer was found among nearly 40 000 women randomized to aspirin or aspirin placebo and followed

up for an average of 10 years. This was true for several cancer sites considered, including breast cancer, by far the most common cancer type in this cohort, and colorectal cancer. A marginally statistically significant protective effect on lung cancer was observed, which was significant for lung cancer deaths. No apparent effect modification by duration of aspirin use was found, and estimates were virtually identical after excluding the first 2 or 5 years of follow-up.

The strongest evidence of an aspirin benefit from observational studies has emerged for breast and colorectal cancer. Although no randomized trials have previously examined the effect of aspirin on breast cancer, a meta-analysis estimated an RR for aspirin of 0.70 among 4 case-control studies, and an RR of 0.79 among 6 cohort studies, the latter with considerable heterogeneity.<sup>6</sup> Results by dose or duration of use were inconsistent across these studies. In a nested case-control study,<sup>18</sup> the largest reduction in breast cancer occurred among those women using the lowest dose of 75 mg. In contrast, data from the Women's Health Initiative cohort study<sup>19</sup> found no reduction among women taking 81 mg of aspirin daily, but did find reductions with higher doses, other NSAIDs, and a trend with longer duration. Finally, in a population-based case-control study, larger decreases in risk were found among regular users and those participants taking aspirin at least 7 times a week.<sup>9</sup> In that study, reductions were restricted to hormone-receptor-positive breast cancer, a finding that was not replicated in the WHS.

Of the 2 randomized trials assessing colorectal cancer incidence,<sup>11,20</sup> no reduced risk was found. The PHS demonstrated no effect of 325 mg of aspirin every other day on colorectal cancer among 22 071 male physicians initially free of cancer either during the 5-year trial period<sup>11</sup> or in longer-term observational follow-up.<sup>12</sup> The Aspirin/Folate Polyp Prevention Study<sup>20</sup> was designed to examine colorectal adenomas but reported 6 cases of colorectal cancer, 1 in the placebo group, 2 in the

**Figure 3.** Relative Risks (RRs) and 95% Confidence Intervals (CIs) Comparing Active vs Placebo Aspirin Assignment for Total, Breast, Colorectal, and Lung Cancer by 2-Year Follow-up Intervals



low-dose aspirin group, and 3 in the high-dose aspirin group. In a meta-analysis of 14 mostly observational studies of cancer incidence, all but 2 found a beneficial association with aspirin, with a summary RR of 0.71.<sup>4</sup>

A protective effect is supported by trials of recurrent colorectal adenoma,<sup>20-22</sup> with a summary RR estimate of 0.77.<sup>5</sup> It has been suggested that the lack of effect on colorectal cancer observed in the 2 trials could be due to the natural history of disease requiring a longer duration.<sup>5</sup> Among male health care professionals, the reduction in risk became stronger with longer and more consistent use of aspirin.<sup>23</sup> In the Nurses' Health Study, there was a strong gradient in risk reduction with increasing years of aspirin use, with the largest benefit observed among those participants using aspirin for at least 20 years.<sup>24</sup> Among those participants using aspirin for 10 to 19 years, comparable in length with the WHS, the RR was 0.70, but not statistically significant. A duration effect, however, is not supported by the 10-year follow-up in the WHS or the observational posttrial follow-up in the PHS.<sup>12</sup>

Only 1 other randomized trial of aspirin has examined the impact on cancer incidence. In a British open-labeled trial<sup>10</sup> of 500 mg of aspirin daily among 5139 male physicians followed up for 6 years with two thirds randomized to daily aspirin, the overall risk of death due to cancer was decreased by 18%, with no difference in the incidence of nonfatal malignant neoplasms. Lung cancer deaths, however, were reduced by 36%, an observation that was deemed unanticipated and likely due to data fluctuations.<sup>10</sup> Although the PHS found no effect on colorectal cancer,<sup>11</sup> unpublished data on lung cancer deaths, which were based on small numbers, were compatible with those found in the WHS and the British trial.<sup>10</sup> In the PHS, there was a nonsignificant 22% reduction in lung cancer mortality in the active aspirin group during the trial period (14 vs 18,  $P = .48$ ; J. M. Gaziano, written communication, 2005). There was also a 13% reduction in lung cancer incidence (25

vs 29,  $P = .61$ ), with no reduction in total cancer incidence or mortality. Observational evidence for an effect of aspirin on lung cancer has been mixed. A meta-analysis of 5 studies, including 2 case-control and 3 cohort studies, found an RR of 0.84 (95% CI, 0.66-1.07) for aspirin and lung cancer, but with statistically significant heterogeneity across studies.<sup>3</sup> Several large cohort studies<sup>8,25-28</sup> have found differen-

tial but inconsistent results by sex. Although some studies found a stronger association for non-small cell lung cancer,<sup>27</sup> this was also inconsistent.<sup>28</sup> Thus, although results from the British trial,<sup>10</sup> the PHS, and the WHS are compatible with a reduction in risk of lung cancer, particularly lung cancer mortality, evidence for such an effect remains uncertain and may simply reflect the play of chance.

**Table 3.** Effect of Randomized Aspirin Assignment on Confirmed Total Cancer by Subgroups

Characteristics	No. of Events		Relative Risk (95% Confidence Interval)	P Value	P for Interaction
	Aspirin (n = 19 934)	Placebo (n = 19 942)			
Age, y					.32
45-54	671	647	1.04 (0.93-1.16)	.49	
55-64	515	512	1.00 (0.89-1.14)	.94	
≥65	252	268	0.93 (0.78-1.11)	.42	
BMI					.15
<25	699	738	0.95 (0.86-1.05)	.32	
25 to <30	426	406	1.05 (0.91-1.20)	.52	
≥30	281	260	1.08 (0.91-1.28)	.37	
Smoking*					.02
Current	226	240	0.98 (0.82-1.17)	.81	
Past	506	559	0.89 (0.79-1.00)	.06	
Never	705	628	1.12 (1.01-1.25)	.03	
Alcohol use, drinks/wk*					.71
<1	821	800	1.02 (0.92-1.12)	.71	
≥1	617	627	0.99 (0.89-1.11)	.87	
Physical activity, kcal/wk*					.98
<1000	959	957	1.00 (0.92-1.10)	.92	
≥1000	461	457	1.00 (0.88-1.14)	.97	
Menopausal status and use of HT					.90
Premenopausal	291	303	0.96 (0.82-1.13)	.66	
Uncertain	195	189	1.06 (0.87-1.30)	.55	
Postmenopausal and current HT	490	478	1.00 (0.88-1.14)	.96	
Postmenopausal and no HT	458	455	1.01 (0.88-1.14)	.93	
Family history of cancer†					.37
Yes	264	280	0.94 (0.79-1.11)	.46	
No	1174	1147	1.02 (0.94-1.11)	.59	
Randomized to receive vitamin E					.67
Yes	716	721	0.99 (0.89-1.10)	.85	
No	722	706	1.02 (0.92-1.13)	.67	
Randomized to receive beta carotene					.08
Yes	744	692	1.07 (0.97-1.19)	.18	
No	694	735	0.94 (0.85-1.05)	.26	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; HT, hormone therapy.  
 \*See "Methods" section of the text for descriptions of smoking status, alcohol use, and physical activity.  
 †History of breast, colorectal, or ovarian cancer in a parent or sibling.

In subgroup analyses, no difference in effects by a number of cancer risk factors, including age, body mass index, or family history of cancer, was observed. For smoking, there was an increased risk of total cancer with active aspirin among never smokers, a protective effect among past smokers, and no effect among current smokers, an interaction largely due to modification of the effect on breast cancer. This result was unanticipated and could be due to chance, particularly given the number of comparisons made. Proinflammatory tobacco carcinogens, however, could potentially increase aspirin's effectiveness in cancer chemoprevention.<sup>29</sup> Although at least 1 previous study has suggested larger effects of aspirin on lung cancer among smokers,<sup>30</sup> this has not been consistent.<sup>28</sup> Modification of aspirin's effect on breast cancer by smoking has not previously been reported to our knowledge.

The issue of adequate dose remains an unanswered question. Low-dose aspirin has been shown to permanently inhibit platelet aggregation,<sup>31</sup> and the dose used in the WHS, 100 mg every other day, has been found to substantially reduce levels of both thromboxane and prostacyclin in men and women.<sup>32</sup> Aspirin, however, has been found to be a more potent inhibitor of platelet COX-1 than of COX-2 activity in other cells,<sup>7,31</sup> which may be influenced by dose. Low-dose aspirin appears relatively specific for COX-1, although higher doses ( $\geq 1$  g/d) inhibit both COX-1 and COX-2 and may have a stronger anti-inflammatory effect.<sup>8</sup> In addition, the required dosing interval for COX-2 inhibition may be shorter, due to the rapid resynthesis of the enzyme.<sup>31</sup> COX-2 expression has been found to be increased in colorectal neoplasia,<sup>8</sup> as well as in breast tumor cell tissue,<sup>33</sup> suggesting that higher and/or more frequent doses of aspirin may be more effective in cancer prevention. It is thus possible that the low every-other-day dose of 100 mg used in this trial could have limited aspirin's effect on COX-2 activity and cancer chemoprevention.

In general, the effects of aspirin observed in studies of colon polyps appear to strengthen with increasing dose, and a meta-analysis found a lower risk of adenomatous polyps only at higher doses of aspirin and other NSAIDs.<sup>34</sup> However, the dose-response effect has not been consistent. Although some studies have found a reduction in risk of colorectal adenoma or cancer only with higher doses,<sup>4,34-36</sup> in the Aspirin/Folate Polyp Prevention Study,<sup>20</sup> effects on colorectal adenomas were observed for low-dose (81 mg daily) but not for higher-dose (325 mg daily) aspirin. In addition, in studies among healthy subjects using colorectal mucosal prostaglandin E<sub>2</sub> levels as a biomarker, a daily dose of 81 mg of aspirin was sufficient to suppress these levels after a 28-day period,<sup>37,38</sup> and the extent of reduction of prostaglandin E<sub>2</sub> was not greater at higher doses.<sup>38</sup> Although the low alternate-day dose of aspirin used in the WHS could possibly explain the lack of effect on cancer, evidence for a dose-response effect remains inconsistent.

The strength of the WHS and other randomized trials is a reduction in possible biases that remain in observational studies. Case-control studies, in particular, could have protopathic bias, in which, for example, early and undiagnosed symptoms of the disease affect the use of aspirin. In general, however, findings for breast and colorectal cancer from case-control and cohort studies tend to be consistent.<sup>3,4,6</sup> Confounding by indication is also reduced in intent-to-treat analyses. Conditions that lead to self-selected use of aspirin could be related to the subsequent development of cancer.<sup>39</sup> In the PHS, post-trial self-selected use of aspirin was associated with several risk factors for both cancer and cardiovascular disease as well as gastrointestinal symptoms.<sup>12,40</sup> Randomized trials reduce the possibility of bias by uncontrolled or unmeasured confounders.

The findings from the WHS suggest that aspirin at a dose of 100 mg every other day is not effective in reducing risk of cancer in healthy women, although a beneficial effect on lung can-

cer cannot be ruled out. This large study of almost 40 000 women had a duration of 10 years of treatment and follow-up, which was the longest of any trial completed to date, and should be sufficient to detect long-term effects. To determine whether higher doses of aspirin taken daily would be effective in cancer prevention requires direct randomized trial data. Such data would need to be considered in the context of risk of gastrointestinal adverse effects<sup>13</sup> before recommending higher-dose aspirin for cancer chemoprevention among low-risk individuals.

**Author Contributions:** Dr Cook had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition of data:** Lee, Gaziano, Gordon, Hennekens, Buring.

**Analysis and interpretation of data:** Cook, Lee, Gaziano, Ridker, Manson, Hennekens, Buring.

**Drafting of the manuscript:** Cook.

**Critical revision of the manuscript for important intellectual content:** Cook, Lee, Gaziano, Gordon, Ridker, Manson, Hennekens, Buring.

**Statistical analysis:** Cook.

**Obtained funding:** Hennekens, Buring.

**Administrative, technical, or material support:** Lee, Gaziano, Gordon, Ridker, Manson, Hennekens, Buring.

**Study supervision:** Cook, Lee, Gaziano, Gordon, Ridker, Manson, Hennekens, Buring.

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