

Supplementary Materials

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Timing of aspirin use in colorectal cancer chemoprevention: a prospective cohort study

Supplementary Methods. Study population, assessment of aspirin use, ascertainment of timeline of analyses, ascertainment of CRC cases and participant deaths, ascertainment of covariates, and construction of multivariable models

Supplementary References.

Supplementary Table 1. Age-standardized participant characteristics according to remote period status of aspirin use in the NHS

Supplementary Table 2. Age-standardized participant characteristics according to remote period status of aspirin use in the HPFS

Supplementary Table 3. Age-standardized participant characteristics according to recent period status of aspirin use in the NHS

Supplementary Table 4. Age-standardized participant characteristics according to recent period status of aspirin use in the HPFS

Supplementary Table 5. Remote period duration of aspirin use, recent period duration of aspirin use and colorectal cancer risk in the NHS

Supplementary Table 6. Remote period duration of aspirin use, recent period duration of aspirin use and colorectal cancer risk in the HPFS

Supplementary Table 7. Remote period dose of aspirin use, recent period dose of aspirin use and colorectal cancer risk in the pooled NHS and HPFS (sensitivity analyses 1)

Supplementary Table 8. Remote period dose of aspirin use, recent period dose of aspirin use and colorectal cancer risk in the pooled NHS and HPFS (sensitivity analyses 2)

Supplementary Table 9. Remote period dose of aspirin use, recent period dose of aspirin use and colorectal cancer risk in the NHS

Supplementary Table 10. Remote period dose of aspirin use, recent period dose of aspirin use and colorectal cancer risk in the HPFS

Supplementary Table 11. Joint associations of remote period duration/dose of aspirin use, and recent period duration/dose of aspirin use (low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent, accordingly to duration and dose respectively) with colorectal cancer risk in the NHS

Supplementary Table 12. Joint associations of remote period duration/dose of aspirin use, and recent period duration/dose of aspirin use (low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent, accordingly to duration and dose respectively) with colorectal cancer risk in the HPFS

Supplementary Table 13. Joint associations of remote period duration and dose of aspirin use (low duration and low dose, low duration and high dose, high duration and low dose, and high duration and high dose) with colorectal cancer risk in the NHS and HPFS

Supplementary Table 14. Joint associations of recent period duration and dose of aspirin use (low duration and low dose, low duration and high dose, high duration and low dose, and high duration and high dose) with colorectal cancer risk in the NHS and HPFS

Supplementary Table 15. Joint associations of overall status (combined duration and dose) and timing of aspirin use with colorectal cancer risk in the NHS and HPFS

This supplementary material has been provided by the authors to give readers additional information about this work.

Supplementary Methods

Study Population

This study was conducted using data from two ongoing US large cohort studies: the NHS and HPFS. The details of these cohorts have been described previously.[1, 2] The NHS was initiated in 1976,[2] when 121,700 female registered nurses aged 30 to 55 years were enrolled. HPFS began in 1986,[1] enrolling 51,529 male health professionals between 40 and 75 years. In both cohorts, demographics were collected at enrollment. Anthropometric data and information on lifestyles, dietary factors, medical history, family history, menstrual and reproductive history (women only), medications, disease diagnoses and disease outcomes were biennially or quadrennially updated thereafter throughout follow-up via self-administered questionnaires. A response rate exceeding 90% of potential person-time have been achieved. The NHS and HPFS protocols were approved by the Institutional Review Board of the Brigham and Women's Hospital (Boston, MA), the Harvard T. H. Chan School of Public Health (Boston, MA), and those of participating registries as required. Informed consent for cohort participation was indicated by the completion and return of the questionnaires from participants. Written informed consent was required to retrieve medical records. Participants who were alive and free of cancer at the time when information on their aspirin use was first assessed were eligible for inclusion. Participants who reported any cancer (except nonmelanoma skin cancer), or who reported colorectal adenoma removal were excluded from subsequent follow-up.

Assessment of Aspirin Use

Duration and dose of aspirin use was first assessed in the NHS in 1980, with biennial updates thereafter except for 1986. Participants reported "whether they took aspirin most weeks", "the duration of aspirin use in years" and "the number of standard-dose (325mg equivalent) tablets taken per week". In HPFS, participants were first queried on duration and dose of aspirin use in 1986 and 1992, respectively, and with regular updates every 2 years. Participants reported "whether they used aspirin 2 or more times per week" and "the number of standard-dose tablets taken per week". Between 1994 and 1998, participants were asked to convert intake of 4 low-dose (81mg equivalent) aspirin tablets to 1 standard-dose tablet. Since 2000, participants reported their use of low-dose and standard-dose aspirin separately in questionnaires. We calculated total duration of use by summing all previous intervals of regular aspirin use before each 2-year follow-up. The most common reasons for aspirin use in the NHS and HPFS included headache, arthritis and musculoskeletal pain, and cardiovascular disease prevention, etc.[3, 4]

Ascertainment of Timeline of Analyses

The "remote periods" were defined as that >10 years before follow-up periods, and the "subsequent 10-year periods" were defined as in the immediate 10 years before follow-up periods. To be specific, the "remote period" began from the year aspirin use were first assessed (i.e. duration of use: 1980 in the NHS and 1986 in HPFS; dose of use: 1980 in the NHS and 1992 in HPFS), and it was then extended by every subsequent 2-year interval at a time in each model, until 2002. The "subsequent 10-year period" began from the end of "remote period", and was then moved forward by every subsequent 2-year interval at a time in each model, until 2012. The follow-up in each model began from the end of the first "subsequent 10-year period" to 2014. Timelines of our analyses in both cohorts were illustrated in Figure 1 (duration of aspirin use) and Figure 2 (dose of aspirin use), respectively.

Ascertainment of CRC Cases and Participant Deaths

Physician-diagnosed incident cancer events were reported by participants biennially via questionnaires. Medical records and pathology reports were then accessed with their permission to ascertain cancer diagnoses. Cohort investigators referred to state cancer registries if medical records were unavailable. We specifically considered incident CRC cases in this study. Through the National Death Index and next-of-kin or postal authorities, death events were ascertained with an identifying rate exceeding 96%. Cohort investigators reviewed death certificates, and requested permission from next of kin of dead participants to further review medical records. Cancer diagnoses and causes of death were assigned according to the International Classification of Diseases, 8th Revision (ICD-8).

Ascertainment of Covariates

We considered age, sex, race, pack-years of smoking, physical activity, cumulative average body mass index (BMI), alcohol consumption, Alternate Healthy Eating Index (AHEI), regular use of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), family history of CRC, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy, menopausal status, multivitamin use, and intake of total calorie, red or processed meat, fiber, folate, calcium, and vitamin D as potential confounders in multivariable analyses. Specifically, throughout follow-up in both the NHS and HPFS, participants biannually reported smoking behavior (pack-years of smoking), physical activities (metabolic equivalent of tasks (MET) scores were assigned to every specific type of physical activity, and total physical activity in MET-hours/week was calculated), bodyweight (which we used to calculate participants' BMI, kg/m²), menopausal status (including postmenopausal hormone use, women only), history of non-aspirin NSAIDs and multivitamin use, and history of diabetes mellitus and screening colonoscopy or sigmoidoscopy. Dietary data (including information on intake of total calories, alcohol, red or processed meat, fiber, folate, calcium, and vitamin D) and family history of CRC were updated quadrennially. AHEI was then calculated based on food frequency questionnaire data to measure overall dietary quality.[5] Except for the above-mentioned time-varying covariates, height, sex, and race were assessed once in both cohorts. The

validity and reproducibility of information on anthropometrics, lifestyle and dietary data, and disease outcomes in both cohorts have previously been described.[5-9]

Construction of Multivariable Models

We controlled for age (continuous, months) and follow-up cycle (each 2-year interval) in age-adjusted models. We additionally controlled for the following covariates in multivariable analyses: sex (women, men), race (White, Black, others), pack-years of smoking (≤ 15 , 16-25, 26-40, >40 pack-years), physical activity (MET-hours/week, continuous), BMI (kg/m^2 , continuous), alcohol consumption (grams/day, continuous), AHEI (quartiles), regular use of non-aspirin NSAIDs (tablets/week, continuous), family history of colorectal cancer (yes, no), history of diabetes mellitus (yes, no), screening colonoscopy or sigmoidoscopy in the past two years (yes, no), menopausal status (women only: premenopausal or no history of postmenopausal hormone use, past menopausal hormone use, current postmenopausal hormone use), multivitamin use (yes, no), total calorie intake (kcal/day, continuous), red or processed meat intake (servings/day, quartiles), fiber intake (g/day, quartiles), folate intake ($\mu\text{g}/\text{day}$, quartiles), calcium intake (mg/day , quartiles), and vitamin D intake (IU/day, quartiles). Time-varying covariates were updated in models throughout follow-up.

Supplementary References

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Supplementary Table 1. Age-standardized participant characteristics according to remote period status of aspirin use in the NHS *

| Characteristics | Remote Period Duration of Aspirin Use ^a | | | | Remote Period Dose of Aspirin Use ^c | | | |
|---|--|-------------|-------------|-------------|--|-------------|-------------|-------------|
| | (Years) | | | | (No. of 325-mg Aspirin Tablets per Week) | | | |
| | 0 | 1 to 5 | 6 to 10 | >10 | <0.5 | 0.5 to <1.5 | 1.5 to <5 | ≥5 |
| Remote period duration of aspirin use ^a (years) | 0.0 (0.0) | 2.9 (1.0) | 7.6 (1.5) | 14.3 (2.5) | 0.0 (0.5) | 5.2 (3.2) | 6.0 (4.3) | 6.2 (4.6) |
| Recent period duration of aspirin use ^b (years) | 1.8 (2.8) | 4.0 (3.6) | 5.2 (3.7) | 6.5 (3.3) | 1.8 (2.8) | 2.9 (3.2) | 4.4 (3.7) | 5.8 (3.7) |
| Duration of non-aspirin NSAIDs use (years) | 2.5 (2.7) | 3.2 (3.4) | 4.0 (4.1) | 6.0 (4.9) | 2.5 (2.7) | 3.5 (3.9) | 3.9 (4.2) | 3.6 (3.8) |
| Remote period dose of aspirin use ^c (tablets/week) | 0.0 (0.0) | 5.1 (5.8) | 5.1 (4.8) | 5.1 (3.3) | 0.0 (0.0) | 1.0 (0.3) | 3.0 (0.9) | 10.2 (6.7) |
| Recent period dose of aspirin use ^d (tablets/week) | 1.1 (2.2) | 2.4 (3.2) | 2.6 (2.8) | 2.9 (2.3) | 1.1 (2.2) | 1.1 (1.8) | 1.9 (2.1) | 4.0 (4.0) |
| Dose of non-aspirin NSAIDs use (tablets/week) | 1.0 (3.3) | 1.6 (3.8) | 2.1 (4.6) | 2.5 (4.9) | 1.0 (3.3) | 1.4 (3.7) | 1.7 (4.0) | 2.2 (4.8) |
| Age, years | 65.2 (8.9) | 66.1 (9.0) | 70.1 (8.4) | 74.6 (7.4) | 65.2 (8.9) | 68.3 (9.5) | 68.9 (9.1) | 68.3 (9.0) |
| White, % | 96.0 | 97.9 | 98.4 | 98.7 | 96.0 | 97.4 | 98.2 | 98.4 |
| Body mass index ^e , kg/m ² | 26.2 (5.1) | 26.6 (5.3) | 26.9 (5.6) | 26.7 (5.3) | 26.2 (5.1) | 26.4 (5.2) | 26.6 (5.3) | 27.0 (5.7) |
| Physical activity ^f , METs-hours/week | 18.3 (23.2) | 17.7 (22.6) | 16.9 (21.4) | 17.8 (22.2) | 18.3 (23.2) | 17.9 (22.8) | 17.9 (22.5) | 16.6 (22.1) |
| Past smoking, % | 45.4 | 46.7 | 47.8 | 47.9 | 45.4 | 46.6 | 47.1 | 47.5 |
| Current smoking, % | 9.6 | 9.8 | 8.5 | 7.0 | 9.6 | 9.7 | 8.8 | 9.4 |
| Pack-years of smoking | 13.0 (20.1) | 13.4 (20.0) | 13.1 (19.8) | 12.9 (18.8) | 13.0 (20.1) | 13.1 (19.7) | 12.8 (19.5) | 14.1 (20.6) |
| Type 2 diabetes, % | 6.9 | 8.3 | 9.2 | 10.9 | 6.9 | 8.1 | 8.5 | 9.8 |
| Family history of colorectal cancer, % | 16.0 | 16.9 | 16.3 | 16.6 | 16.0 | 15.9 | 16.8 | 17.0 |
| Menopausal hormone use, % | 59.1 | 66.4 | 71.3 | 77.1 | 59.2 | 65.0 | 69.7 | 69.8 |
| Multivitamin use, % | 47.7 | 54.5 | 59.4 | 65.0 | 47.6 | 50.5 | 58.5 | 58.2 |
| Total folate intake, ug/day | 590 (292) | 610 (302) | 666 (313) | 748 (308) | 590 (292) | 622 (303) | 649 (314) | 638 (313) |
| Total vitamin D, IU/day | 483 (367) | 515 (393) | 563 (427) | 692 (480) | 483 (367) | 548 (439) | 565 (440) | 541 (409) |
| Total calcium intake, mg/day | 1,235 (587) | 1,277 (606) | 1,356 (622) | 1,490 (604) | 1,235 (587) | 1,290 (608) | 1,336 (620) | 1,324 (629) |
| AHEI | 51.3 (10.5) | 50.8 (10.6) | 51.2 (10.9) | 53.1 (10.9) | 51.3 (10.5) | 52.4 (10.6) | 51.5 (11.0) | 50.3 (10.7) |
| Alcohol, g/day | 4.7 (9.1) | 5.0 (9.3) | 5.2 (9.7) | 6.1 (10.2) | 4.7 (9.0) | 4.8 (9.0) | 5.5 (9.8) | 4.9 (9.6) |
| Red or processed meat, servings/week | 4.3 (3.1) | 4.5 (3.3) | 4.6 (3.3) | 4.8 (3.3) | 4.3 (3.1) | 4.5 (3.1) | 4.6 (3.3) | 4.6 (3.4) |
| Total fiber, g/day | 19.6 (5.7) | 19.5 (5.6) | 19.5 (5.6) | 19.7 (5.3) | 19.6 (5.7) | 19.5 (5.5) | 19.5 (5.6) | 19.4 (5.7) |
| Total calorie intake, kcal/day | 1,675 (496) | 1,706 (520) | 1,718 (535) | 1,722 (529) | 1,675 (496) | 1,685 (512) | 1,717 (534) | 1,711 (531) |

Abbreviations: NHS, Nurses' Health Study; NSAIDs, nonsteroidal anti-inflammatory drugs; kg, kilogram; m, meter; METs, metabolic equivalent tasks; ug, microgram; IU, international unit; mg, milligram; AHEI, Alternate Healthy Eating Index score; g, gram; kcal, kilocalorie.

* Updated information throughout follow-up was used to calculate the mean (SD) for continuous variables and percentage for categorical variables. All variables are age-standardized except age.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Remote period dose of aspirin use: cumulative average aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^d Recent period dose of aspirin use: cumulative average aspirin use during every specific subsequent 10-year period after the remote periods.

^e Body mass index was calculated as weight in kilograms divided by the square of height in meters.

^f Hours of metabolic equivalent tasks.

Supplementary Table 2. Age-standardized participant characteristics according to remote period status of aspirin use in the HPFS *

| Characteristics | Remote Period Duration of Aspirin Use ^a | | | | Remote Period Dose of Aspirin Use ^c | | | |
|---|--|-------------|-------------|-------------|--|-------------|-------------|-------------|
| | (Years) | | | | (No. of 325-mg Aspirin Tablets per Week) | | | |
| | 0 | 1 to 5 | 6 to 10 | >10 | <0.5 | 0.5 to <1.5 | 1.5 to <5 | ≥5 |
| Remote period duration of aspirin use ^a (years) | 0.0 (0.0) | 2.8 (1.0) | 7.5 (1.6) | 13.1 (1.3) | 0.2 (0.8) | 4.2 (2.3) | 4.6 (2.4) | 4.0 (2.3) |
| Recent period duration of aspirin use ^b (years) | 2.7 (3.1) | 5.5 (3.6) | 6.6 (3.3) | 7.5 (2.9) | 2.9 (3.3) | 5.5 (3.7) | 6.4 (3.5) | 7.1 (3.2) |
| Duration of non-aspirin NSAIDs use (years) | 1.8 (3.6) | 3.1 (4.4) | 4.4 (5.1) | 5.9 (5.7) | 3.1 (4.9) | 3.8 (5.2) | 4.5 (5.4) | 5.1 (5.6) |
| Remote period dose of aspirin use ^c (tablets/week) | 0.1 (0.3) | 1.9 (2.4) | 4.2 (3.7) | 4.2 (2.7) | 0.0 (0.1) | 1.0 (0.3) | 3.0 (0.9) | 7.9 (4.1) |
| Recent period dose of aspirin use ^d (tablets/week) | 0.8 (1.4) | 1.6 (1.9) | 2.6 (2.5) | 2.8 (2.5) | 0.8 (1.4) | 1.1 (1.2) | 2.0 (1.8) | 4.2 (3.3) |
| Dose of non-aspirin NSAIDs use (tablets/week) | 4.3 (2.2) | 4.5 (2.8) | 4.9 (3.4) | 5.0 (3.5) | 4.6 (3.0) | 4.5 (3.0) | 4.7 (3.3) | 5.2 (4.0) |
| Age, years | 67.1 (9.2) | 69.3 (9.1) | 72.9 (8.6) | 76.3 (8.0) | 70.5 (8.6) | 73.4 (8.4) | 73.3 (8.5) | 73.0 (8.6) |
| White, % | 94.8 | 96.5 | 97.0 | 97.4 | 95.1 | 96.1 | 97.1 | 97.6 |
| Body mass index ^e , kg/m ² | 25.9 (3.8) | 26.2 (3.8) | 26.2 (3.8) | 26.0 (3.4) | 25.8 (3.8) | 25.8 (3.7) | 26.0 (3.8) | 26.2 (3.8) |
| Physical activity ^f , METs-hours/week | 31.8 (32.1) | 31.3 (31.6) | 33.7 (32.2) | 34.7 (32.0) | 36.1 (34.4) | 36.1 (34.7) | 36.1 (34.4) | 34.9 (34.6) |
| Past smoking, % | 39.4 | 44.6 | 43.9 | 41.8 | 38.4 | 37.5 | 41.5 | 46.7 |
| Current smoking, % | 4.5 | 4.3 | 3.4 | 2.5 | 3.3 | 2.8 | 2.7 | 3.5 |
| Pack-years of smoking | 10.0 (16.7) | 11.5 (17.6) | 11.0 (16.6) | 11.0 (15.5) | 9.3 (15.9) | 8.6 (14.9) | 10.1 (16.1) | 12.3 (18.0) |
| Type 2 diabetes, % | 2.3 | 3.1 | 4.8 | 6.8 | 1.4 | 2.2 | 2.1 | 1.8 |
| Family history of colorectal cancer, % | 13.7 | 13.5 | 13.3 | 13.4 | 13.5 | 14.0 | 13.9 | 13.6 |
| Multivitamin use, % | 50.0 | 58.2 | 61.9 | 64.4 | 53.0 | 58.4 | 61.5 | 64.3 |
| Total folate intake, ug/day | 739 (337) | 781 (344) | 850 (362) | 871 (338) | 786 (364) | 824 (360) | 842 (363) | 850 (370) |
| Total vitamin D, IU/day | 493 (347) | 537 (374) | 590 (411) | 736 (527) | 543 (424) | 632 (490) | 623 (482) | 604 (431) |
| Total calcium intake, mg/day | 1,067 (481) | 1,109 (501) | 1,181 (525) | 1,263 (517) | 1,136 (524) | 1,196 (537) | 1,196 (533) | 1,199 (545) |
| AHEI | 52.1 (10.5) | 52.3 (10.5) | 53.7 (10.8) | 55.4 (10.1) | 54.0 (11.2) | 55.5 (10.7) | 54.8 (10.8) | 53.2 (10.7) |
| Alcohol, g/day | 10.7 (14.6) | 12.4 (15.4) | 13.6 (15.9) | 13.8 (15.0) | 11.6 (15.3) | 12.4 (15.3) | 13.6 (15.9) | 13.8 (16.9) |
| Red or processed meat, servings/week | 5.8 (4.2) | 6.0 (4.3) | 6.2 (4.5) | 6.3 (4.2) | 5.9 (4.4) | 5.8 (4.3) | 6.2 (4.4) | 6.5 (4.6) |
| Total fiber, g/day | 24.3 (7.1) | 24.1 (6.8) | 24.3 (6.8) | 24.8 (6.3) | 24.6 (7.1) | 24.9 (6.8) | 24.6 (6.7) | 24.0 (6.8) |
| Total calorie intake, kcal/day | 1,974 (641) | 2,005 (641) | 2,040 (638) | 2,050 (605) | 1,991 (650) | 2,021 (652) | 2,044 (651) | 2,049 (656) |

Abbreviations: HPFS, Health Professionals Follow-up Study; NSAIDs, nonsteroidal anti-inflammatory drugs; kg, kilogram; m, meter; METs, metabolic equivalent tasks; ug, microgram; IU, international unit; mg, milligram; AHEI, Alternate Healthy Eating Index score; g, gram; kcal, kilocalorie.

* Updated information throughout follow-up was used to calculate the mean (SD) for continuous variables and percentage for categorical variables. All variables are age-standardized except age.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1986, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Remote period dose of aspirin use: cumulative average aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1992, and then was extended by every 2-year subsequent interval at a time, until 2002).

^d Recent period dose of aspirin use: cumulative average aspirin use during every specific subsequent 10-year period after the remote periods.

^e Body mass index was calculated as weight in kilograms divided by the square of height in meters.

^f Hours of metabolic equivalent tasks.

Supplementary Table 3. Age-standardized participant characteristics according to recent period status of aspirin use in the NHS *

| Characteristics | Recent Period Duration of Aspirin Use ^b | | | Recent Period Dose of Aspirin Use ^d | | | |
|---|--|-------------|-------------|--|-------------|-------------|-------------|
| | (Years) | | | (No. of 325-mg Aspirin Tablets per Week) | | | |
| | 0 | 1 to 5 | 6 to 10 | <0.5 | 0.5 to <1.5 | 1.5 to <5 | ≥5 |
| Remote period duration of aspirin use ^a (years) | 1.7 (3.1) | 3.6 (4.2) | 5.5 (5.0) | 2.0 (3.4) | 4.3 (4.6) | 4.7 (4.8) | 5.0 (5.0) |
| Recent period duration of aspirin use ^b (years) | 0.0 (0.0) | 2.9 (1.0) | 8.1 (1.7) | 0.3 (1.2) | 5.5 (2.7) | 6.2 (2.9) | 6.0 (3.2) |
| Duration of non-aspirin NSAIDs use (years) | 2.9 (3.3) | 3.4 (3.7) | 3.5 (3.9) | 3.0 (3.4) | 3.9 (4.3) | 3.4 (3.7) | 3.0 (3.2) |
| Remote period dose of aspirin use ^c (tablets/week) | 1.4 (3.2) | 2.9 (4.4) | 4.9 (5.8) | 1.5 (3.2) | 2.4 (3.0) | 3.5 (3.8) | 7.1 (8.4) |
| Recent period dose of aspirin use ^d (tablets/week) | 0.0 (0.0) | 3.1 (3.1) | 3.5 (2.8) | 0.0 (0.1) | 1.0 (0.3) | 2.8 (0.9) | 7.5 (3.6) |
| Dose of non-aspirin NSAIDs use (tablets/week) | 1.2 (3.6) | 1.6 (4.0) | 1.8 (4.1) | 1.3 (3.6) | 1.6 (4.0) | 1.7 (3.9) | 1.9 (4.4) |
| Age, years | 65.2 (9.0) | 67.2 (9.0) | 69.6 (9.0) | 65.6 (9.1) | 70.8 (8.6) | 68.2 (9.1) | 66.4 (8.7) |
| White, % | 96.3 | 97.6 | 98.2 | 96.3 | 97.5 | 98.1 | 98.4 |
| Body mass index ^e , kg/m ² | 26.2 (5.2) | 26.7 (5.4) | 26.6 (5.4) | 26.3 (5.2) | 26.4 (5.3) | 26.6 (5.3) | 27.1 (5.6) |
| Physical activity ^f , METs-hours/week | 17.5 (22.5) | 17.7 (22.8) | 18.2 (22.9) | 17.5 (22.6) | 18.5 (23.1) | 18.2 (23.0) | 17.1 (22.2) |
| Past smoking, % | 45.4 | 47.4 | 47.1 | 45.5 | 47.5 | 47.0 | 47.0 |
| Current smoking, % | 9.5 | 8.9 | 9.2 | 9.4 | 7.9 | 8.9 | 10.7 |
| Pack-years of smoking | 12.7 (19.8) | 13.1 (19.8) | 13.6 (20.2) | 12.7 (19.7) | 12.0 (18.7) | 13.3 (20.0) | 15.4 (21.7) |
| Type 2 diabetes, % | 6.4 | 8.3 | 9.7 | 6.5 | 8.8 | 9.1 | 9.8 |
| Family history of colorectal cancer, % | 16.0 | 16.3 | 17.0 | 15.9 | 15.9 | 17.1 | 17.4 |
| Menopausal hormone use, % | 59.7 | 66.3 | 69.6 | 60.3 | 69.5 | 68.6 | 66.8 |
| Multivitamin use, % | 44.7 | 53.2 | 62.5 | 44.6 | 57.9 | 61.1 | 58.9 |
| Total folate intake, ug/day | 581 (287) | 619 (302) | 666 (319) | 585 (290) | 673 (311) | 650 (316) | 616 (307) |
| Total vitamin D, IU/day | 480 (375) | 519 (394) | 579 (440) | 484 (378) | 594 (458) | 555 (421) | 515 (386) |
| Total calcium intake, mg/day | 1,225 (583) | 1,284 (601) | 1,360 (629) | 1,230 (584) | 1,371 (615) | 1,335 (624) | 1,284 (621) |
| AHEI | 50.9 (10.4) | 51.2 (10.6) | 51.7 (11.1) | 51.0 (10.4) | 53.0 (11.1) | 51.4 (10.9) | 50.0 (10.5) |
| Alcohol, g/day | 4.5 (8.9) | 4.9 (9.2) | 5.6 (10.1) | 4.5 (8.9) | 5.2 (9.4) | 5.5 (9.9) | 5.1 (9.8) |
| Red or processed meat, servings/week | 4.4 (3.1) | 4.5 (3.2) | 4.6 (3.4) | 4.4 (3.2) | 4.5 (3.2) | 4.5 (3.3) | 4.6 (3.4) |
| Total fiber, g/day | 19.3 (5.5) | 19.5 (5.6) | 19.7 (5.7) | 19.4 (5.5) | 19.9 (5.7) | 19.7 (5.7) | 19.3 (5.7) |
| Total calorie intake, kcal/day | 1,684 (495) | 1,699 (514) | 1,711 (538) | 1,685 (497) | 1,700 (527) | 1,706 (531) | 1,711 (531) |

Abbreviations: NHS, Nurses' Health Study; NSAIDs, nonsteroidal anti-inflammatory drugs; kg, kilogram; m, meter; METs, metabolic equivalent tasks; ug, microgram; IU, international unit; mg, milligram; AHEI, Alternate Healthy Eating Index score; g, gram; kcal, kilocalorie.

* Updated information throughout follow-up was used to calculate the mean (SD) for continuous variables and percentage for categorical variables. All variables are age-standardized except age.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Remote period dose of aspirin use: cumulative average aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^d Recent period dose of aspirin use: cumulative average aspirin use during every specific subsequent 10-year period after the remote periods.

^e Body mass index was calculated as weight in kilograms divided by the square of height in meters.

^f Hours of metabolic equivalent tasks.

Supplementary Table 4. Age-standardized participant characteristics according to recent period status of aspirin use in the HPFS *

| Characteristics | Recent Period Duration of Aspirin Use ^b | | | Recent Period Dose of Aspirin Use ^d | | | |
|---|--|-------------|-------------|--|-------------|-------------|-------------|
| | (Years) | | | (No. of 325-mg Aspirin Tablets per Week) | | | |
| | 0 | 1 to 5 | 6 to 10 | <0.5 | 0.5 to <1.5 | 1.5 to <5 | ≥5 |
| Remote period duration of aspirin use ^a (years) | 1.3 (2.6) | 2.8 (3.6) | 4.7 (4.1) | 1.4 (2.3) | 3.0 (3.0) | 3.6 (2.7) | 4.1 (2.8) |
| Recent period duration of aspirin use ^b (years) | 0.0 (0.0) | 3.0 (1.0) | 8.3 (1.6) | 1.4 (2.7) | 6.6 (2.9) | 7.2 (2.7) | 6.3 (3.3) |
| Duration of non-aspirin NSAIDs use (years) | 2.4 (4.4) | 2.9 (4.4) | 3.4 (4.7) | 3.5 (5.3) | 4.0 (5.3) | 4.3 (5.2) | 4.5 (5.3) |
| Remote period dose of aspirin use ^c (tablets/week) | 0.9 (2.0) | 2.0 (3.0) | 3.2 (3.3) | 0.9 (2.0) | 1.6 (2.0) | 3.4 (2.8) | 6.0 (5.4) |
| Recent period dose of aspirin use ^d (tablets/week) | 0.0 (0.0) | 2.2 (2.6) | 2.4 (2.1) | 0.1 (0.1) | 1.0 (0.3) | 2.8 (0.9) | 7.0 (2.8) |
| Dose of non-aspirin NSAIDs use (tablets/week) | 4.5 (2.6) | 4.6 (2.8) | 4.6 (2.9) | 4.6 (3.1) | 4.6 (3.2) | 4.8 (3.3) | 5.2 (3.9) |
| Age, years | 68.5 (9.6) | 69.0 (9.6) | 70.6 (9.0) | 72.0 (8.9) | 72.3 (8.4) | 72.2 (8.6) | 72.4 (8.6) |
| White, % | 94.3 | 95.9 | 97.0 | 95.1 | 96.8 | 97.0 | 97.1 |
| Body mass index ^e , kg/m ² | 25.9 (3.9) | 26.1 (3.8) | 26.2 (3.7) | 25.8 (3.8) | 25.8 (3.7) | 26.1 (3.7) | 26.3 (3.9) |
| Physical activity ^f , METs-hours/week | 31.5 (32.4) | 31.3 (32.1) | 33.0 (32.2) | 34.8 (34.2) | 37.2 (34.8) | 36.0 (34.2) | 35.0 (33.8) |
| Past smoking, % | 36.6 | 41.3 | 45.4 | 36.0 | 41.0 | 44.0 | 45.3 |
| Current smoking, % | 4.8 | 4.4 | 3.5 | 3.1 | 2.7 | 3.2 | 3.1 |
| Pack-years of smoking | 9.7 (16.3) | 10.8 (17.0) | 11.2 (17.3) | 8.9 (15.3) | 9.6 (15.9) | 10.9 (16.9) | 12.0 (17.8) |
| Type 2 diabetes, % | 2.4 | 3.2 | 3.9 | 1.5 | 2.1 | 1.7 | 2.0 |
| Family history of colorectal cancer, % | 13.1 | 13.3 | 13.8 | 13.7 | 13.7 | 14.0 | 12.9 |
| Multivitamin use, % | 41.9 | 52.5 | 65.4 | 48.4 | 62.6 | 63.8 | 62.5 |
| Total folate intake, ug/day | 721 (333) | 756 (344) | 831 (357) | 772 (360) | 840 (363) | 848 (364) | 836 (371) |
| Total vitamin D, IU/day | 502 (394) | 516 (368) | 579 (405) | 566 (481) | 619 (470) | 593 (418) | 594 (440) |
| Total calcium intake, mg/day | 1,065 (480) | 1,090 (492) | 1,157 (527) | 1,135 (525) | 1,201 (542) | 1,184 (528) | 1,196 (543) |
| AHEI | 52.1 (10.3) | 52.1 (10.4) | 53.3 (10.9) | 54.1 (11.0) | 55.2 (10.9) | 54.0 (10.8) | 53.2 (10.7) |
| Alcohol, g/day | 10.4 (14.7) | 11.5 (15.0) | 13.1 (15.7) | 11.4 (15.3) | 13.0 (15.2) | 13.5 (16.3) | 13.7 (17.0) |
| Red or processed meat, servings/week | 5.9 (4.2) | 6.0 (4.3) | 6.0 (4.4) | 6.0 (4.4) | 5.9 (4.3) | 6.2 (4.5) | 6.5 (4.7) |
| Total fiber, g/day | 23.9 (6.9) | 24.1 (6.8) | 24.5 (7.0) | 24.5 (7.0) | 24.9 (6.9) | 24.4 (6.7) | 23.9 (6.9) |
| Total calorie intake, kcal/day | 1,973 (648) | 1,998 (645) | 2,019 (641) | 1,992 (654) | 2,022 (640) | 2,047 (659) | 2,045 (657) |

Abbreviations: HPFS, Health Professionals Follow-up Study; NSAIDs, nonsteroidal anti-inflammatory drugs; kg, kilogram; m, meter; METs, metabolic equivalent tasks; ug, microgram; IU, international unit; mg, milligram; AHEI, Alternate Healthy Eating Index score; g, gram; kcal, kilocalorie.

* Updated information throughout follow-up was used to calculate the mean (SD) for continuous variables and percentage for categorical variables. All variables are age-standardized except age.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1986, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Remote period dose of aspirin use: cumulative average aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1992, and then was extended by every 2-year subsequent interval at a time, until 2002).

^d Recent period dose of aspirin use: cumulative average aspirin use during every specific subsequent 10-year period after the remote periods.

^e Body mass index was calculated as weight in kilograms divided by the square of height in meters.

^f Hours of metabolic equivalent tasks.

Supplementary Table 5. Remote period duration of aspirin use ^a, recent period duration of aspirin use ^b and colorectal cancer risk in the NHS

| NHS | Years of Regular Aspirin Use | | | | <i>P</i> -trend ^e | Per 5-year increment HR (95% CI) | <i>P</i> -trend ^f |
|--|------------------------------|---------------------|---------------------|---------------------|------------------------------|--|------------------------------|
| | 0 | 1 to 5 | 6 to 10 | >10 | | | |
| Remote period duration of aspirin use ^a | | | | | | | |
| Median values | 0 | 2 | 8 | 14 | | | |
| No. of CRC cases (1,528 in total) | 758 | 419 | 245 | 106 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.79 (0.70 to 0.89) | 0.65 (0.56 to 0.75) | 0.71 (0.57 to 0.88) | <.001 | 0.84 (0.78 to 0.90) | <.001 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.80 (0.71 to 0.91) | 0.67 (0.58 to 0.78) | 0.73 (0.59 to 0.91) | <.001 | 0.85 (0.80 to 0.91) | <.001 |
| MV ^d + recent period duration of aspirin use ^b adjusted model, HR (95%CI) | 1 [Reference] | 0.85 (0.75 to 0.96) | 0.72 (0.62 to 0.85) | 0.81 (0.65 to 1.02) | .002 | 0.89 (0.83 to 0.96) | .002 |
| Recent period duration of aspirin use ^b | | | | | | | |
| Median values | 0 | 2 | 8 | -- | | | |
| No. of CRC cases (1,528 in total) | 684 | 392 | 452 | -- | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.85 (0.75 to 0.96) | 0.71 (0.63 to 0.80) | -- | <.001 | 0.82 (0.76 to 0.88) | <.001 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.86 (0.76 to 0.98) | 0.73 (0.64 to 0.82) | -- | <.001 | 0.83 (0.77 to 0.90) | <.001 |
| MV ^d + remote period duration of aspirin use ^a adjusted model, HR (95%CI) | 1 [Reference] | 0.92 (0.81 to 1.04) | 0.81 (0.71 to 0.93) | -- | .003 | 0.89 (0.82 to 0.96) | .003 |

Abbreviations: NHS, Nurses' Health Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, menopausal status, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e *P*-value for trend was calculated using the mid-point of each category of aspirin use in years.

^f *P*-value for trend was the *P* value for variables modeled as continuous.

Supplementary Table 6. Remote period duration of aspirin use ^a, recent period duration of aspirin use ^b and colorectal cancer risk in the HPFS

| HPFS | Years of Regular Aspirin Use | | | | <i>P</i> -trend ^e | Per 5-year increment HR (95% CI) | <i>P</i> -trend ^f |
|--|------------------------------|---------------------|---------------------|---------------------|------------------------------|--|------------------------------|
| | 0 | 1 to 5 | 6 to 10 | >10 | | | |
| Remote period duration of aspirin use ^a | | | | | | | |
| Median values | 0 | 2 | 8 | 12 | | | |
| No. of CRC cases (619 in total) | 292 | 193 | 108 | 26 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.76 (0.63 to 0.91) | 0.70 (0.55 to 0.89) | 0.62 (0.40 to 0.97) | .002 | 0.80 (0.70 to 0.91) | <.001 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.77 (0.64 to 0.93) | 0.72 (0.57 to 0.93) | 0.66 (0.42 to 1.04) | .008 | 0.82 (0.72 to 0.94) | .004 |
| MV-adjusted model, HR (95%CI) ^d + recent period duration of aspirin use ^b adjusted model, HR (95%CI) | 1 [Reference] | 0.79 (0.65 to 0.97) | 0.75 (0.58 to 0.98) | 0.69 (0.43 to 1.11) | .048 | 0.85 (0.73 to 0.98) | .02 |
| Recent period duration of aspirin use ^b | | | | | | | |
| Median values | 0 | 2 | 8 | -- | | | |
| No. of CRC cases (619 in total) | 171 | 179 | 269 | -- | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.95 (0.76 to 1.17) | 0.75 (0.62 to 0.92) | -- | .002 | 0.83 (0.75 to 0.93) | <.001 |
| MV ^d | 1 [Reference] | 0.97 (0.78 to 1.20) | 0.81 (0.66 to 0.99) | -- | .02 | 0.87 (0.78 to 0.97) | .01 |
| MV ^d + remote period duration of aspirin use ^a adjusted model, HR (95%CI) | 1 [Reference] | 1.03 (0.83 to 1.28) | 0.93 (0.74 to 1.16) | -- | .36 | 0.94 (0.82 to 1.06) | .31 |

Abbreviations: HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1986, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e *P*-value for trend was calculated using the mid-point of each category of aspirin use in years.

^f *P*-value for trend was the *P* value for variables modeled as continuous.

Supplementary Table 7. Remote period dose of aspirin use ^a, recent period dose of aspirin use ^b and colorectal cancer risk in the pooled NHS and HPFS (sensitivity analyses 1)

| Pooled NHS and HPFS | No. of 325-mg Aspirin Tablets per Week (Cumulative Mean) | | <i>P</i> -trend ^e | Per 2.5-standard tablets/week increment HR (95% CI) [*] | <i>P</i> -trend ^f |
|--|---|---------------------|------------------------------|--|------------------------------|
| | <0.5 | ≥0.5 | | | |
| Remote period dose of aspirin use ^a | | | | | |
| Median values | 0 | 3.49 | | | |
| No. of CRC cases (1,764 in total) | 875 | 889 | | | |
| Age-adjusted model, HR (95% CI) ^c | 1 [Reference] | 0.80 (0.74 to 0.88) | <.001 | 0.94 (0.91 to 0.97) | <.001 |
| MV-adjusted model, HR (95% CI) ^d | 1 [Reference] | 0.79 (0.72 to 0.86) | <.001 | 0.94 (0.91 to 0.97) | <.001 |
| MV ^d + recent period aspirin use ^b adjusted model, HR (95% CI) | 1 [Reference] | 0.83 (0.75 to 0.91) | <.001 | 0.95 (0.93 to 0.98) | .002 |
| Recent period dose of aspirin use ^b | | | | | |
| Median values | 0 | 2.50 | | | |
| No. of CRC cases (1,764 in total) | 820 | 944 | | | |
| Age-adjusted model, HR (95% CI) ^c | 1 [Reference] | 0.84 (0.77 to 0.92) | <.001 | 0.88 (0.84 to 0.93) | <.001 |
| MV-adjusted model, HR (95% CI) ^d | 1 [Reference] | 0.82 (0.75 to 0.89) | <.001 | 0.88 (0.84 to 0.92) | <.001 |
| MV ^d + remote period aspirin use ^a adjusted model, HR (95% CI) | 1 [Reference] | 0.87 (0.79 to 0.96) | .005 | 0.91 (0.86 to 0.95) | <.001 |

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period dose of aspirin use: cumulative average dose of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980 (NHS) and 1992 (HPFS), and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period dose of aspirin use: cumulative average dose of aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, sex, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of CRC, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e *P*-value for trend was calculated using the mid-point of each category of aspirin use in tablets/week.

^f *P*-value for trend was the *P* value for variables modeled as continuous.

Supplementary Table 8. Remote period dose of aspirin use ^a, recent period dose of aspirin use ^b and colorectal cancer risk in the pooled NHS and HPFS (sensitivity analyses 2*)

| Pooled NHS and HPFS | No. of 325-mg Aspirin Tablets per Week (Cumulative Mean) | | | <i>P</i> -trend ^e | Per 2.5-standard tablets/week increment HR (95% CI) [*] | <i>P</i> -trend ^f |
|---|--|---------------------|---------------------|------------------------------|--|------------------------------|
| | 0.5 to <1.5 | 1.5 to <5 | ≥5 | | | |
| Remote period dose of aspirin use ^a | | | | | | |
| Median values | 1.00 | 2.90 | 7.54 | | | |
| No. of CRC cases (889 in total) | 88 | 531 | 270 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 1.00 (0.79 to 1.26) | 0.88 (0.69 to 1.13) | .12 | 0.97 (0.93 to 1.01) | .09 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 1.01 (0.80 to 1.27) | 0.90 (0.70 to 1.16) | .15 | 0.97 (0.94 to 1.01) | .13 |
| MV ^d + recent period aspirin use ^b adjusted model, HR (95%CI) | 1 [Reference] | 1.04 (0.82 to 1.31) | 0.96 (0.74 to 1.24) | .41 | 0.98 (0.94 to 1.02) | .36 |
| Recent period dose of aspirin use ^b | | | | | | |
| Median values | 1.05 | 2.63 | 6.25 | | | |
| No. of CRC cases (944 in total) | 247 | 524 | 173 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.97 (0.83 to 1.13) | 0.84 (0.69 to 1.03) | .08 | 0.93 (0.87 to 1.00) | .04 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.96 (0.82 to 1.12) | 0.81 (0.66 to 0.99) | .03 | 0.92 (0.86 to 0.99) | .02 |
| MV ^d + remote period aspirin use ^a adjusted model, HR (95%CI) | 1 [Reference] | 0.98 (0.84 to 1.15) | 0.85 (0.69 to 1.05) | .11 | 0.94 (0.87 to 1.01) | .07 |

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

* Participants who used aspirin at a dose of <0.5 standard tablets per week were excluded from analyses.

^a Remote period dose of aspirin use: cumulative average dose of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980 (NHS) and 1992 (HPFS), and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period dose of aspirin use: cumulative average dose of aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, sex, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of CRC, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e *P*-value for trend was calculated using the mid-point of each category of aspirin use in tablets/week.

^f *P*-value for trend was the *P* value for variables modeled as continuous.

Supplementary Table 9. Remote period dose of aspirin use ^a, recent period dose of aspirin use ^b and colorectal cancer risk in the NHS

| NHS | No. of 325-mg Aspirin Tablets per Week (Cumulative Mean) | | | | <i>P</i> -trend ^e | Per 2.5-standard tablets/week increment HR (95% CI) * | <i>P</i> -trend ^f |
|---|--|---------------------|---------------------|---------------------|------------------------------|---|------------------------------|
| | <0.5 | 0.5 to <1.5 | 1.5 to <5 | ≥5 | | | |
| Remote period dose of aspirin use ^a | | | | | | | |
| Median values | 0 | 1.00 | 2.91 | 7.72 | | | |
| No. of CRC cases (1,523 in total) | 764 | 67 | 457 | 235 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.80 (0.62 to 1.03) | 0.77 (0.68 to 0.86) | 0.67 (0.58 to 0.77) | <.001 | 0.93 (0.90 to 0.96) | <.001 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.81 (0.63 to 1.04) | 0.78 (0.69 to 0.89) | 0.69 (0.59 to 0.80) | <.001 | 0.93 (0.90 to 0.97) | <.001 |
| MV ^d + recent period aspirin use ^b adjusted model, HR (95%CI) | 1 [Reference] | 0.82 (0.64 to 1.06) | 0.82 (0.72 to 0.93) | 0.76 (0.65 to 0.89) | <.001 | 0.96 (0.92 to 0.99) | .01 |
| Recent period dose of aspirin use ^b | | | | | | | |
| Median values | 0 | 1.05 | 2.63 | 6.25 | | | |
| No. of CRC cases (1,523 in total) | 738 | 183 | 451 | 151 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.81 (0.69 to 0.96) | 0.78 (0.69 to 0.88) | 0.67 (0.56 to 0.80) | <.001 | 0.88 (0.83 to 0.93) | <.001 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.85 (0.72 to 1.00) | 0.80 (0.71 to 0.90) | 0.67 (0.56 to 0.80) | <.001 | 0.88 (0.83 to 0.93) | <.001 |
| MV ^d + remote period aspirin use ^a adjusted model, HR (95%CI) | 1 [Reference] | 0.89 (0.75 to 1.06) | 0.86 (0.76 to 0.98) | 0.74 (0.61 to 0.89) | <.001 | 0.92 (0.86 to 0.97) | .003 |

Abbreviations: NHS, Nurses' Health Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period dose of aspirin use: cumulative average dose of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period dose of aspirin use: cumulative average dose of aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, menopausal status, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e *P*-value for trend was calculated using the mid-point of each category of aspirin use in tablets/week.

^f *P*-value for trend was the *P* value for variables modeled as continuous.

Supplementary Table 10. Remote period dose of aspirin use ^a, recent period dose of aspirin use ^b and colorectal cancer risk in the HPFS

| HPFS | No. of 325-mg Aspirin Tablets per Week (Cumulative Mean) | | | | <i>P</i> -trend ^e | Per 2.5-standard tablets/week increment HR (95% CI) * | <i>P</i> -trend ^f |
|---|--|---------------------|---------------------|---------------------|------------------------------|--|------------------------------|
| | <0.5 | 0.5 to <1.5 | 1.5 to <5 | ≥5 | | | |
| Remote period dose of aspirin use ^a | | | | | | | |
| Median values | 0 | 1.10 | 2.83 | 6.40 | | | |
| No. of CRC cases (241 in total) | 111 | 21 | 74 | 35 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.64 (0.39 to 1.03) | 0.74 (0.55 to 1.01) | 0.72 (0.49 to 1.06) | .08 | 0.89 (0.79 to 1.00) | .051 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.66 (0.41 to 1.08) | 0.76 (0.56 to 1.04) | 0.72 (0.48 to 1.06) | .09 | 0.89 (0.79 to 1.00) | .06 |
| MV ^d + recent period aspirin use ^b adjusted model, HR (95%CI) | 1 [Reference] | 0.65 (0.40 to 1.08) | 0.76 (0.53 to 1.07) | 0.71 (0.45 to 1.12) | .15 | 0.89 (0.77 to 1.02) | .09 |
| Recent period dose of aspirin use ^b | | | | | | | |
| Median values | 0 | 1.01 | 2.52 | 6.00 | | | |
| No. of CRC cases (241 in total) | 82 | 64 | 73 | 22 | | | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.90 (0.64 to 1.25) | 0.83 (0.60 to 1.14) | 0.85 (0.53 to 1.37) | .38 | 0.87 (0.74 to 1.03) | .11 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.96 (0.68 to 1.35) | 0.86 (0.62 to 1.20) | 0.86 (0.53 to 1.39) | .40 | 0.87 (0.74 to 1.03) | .11 |
| MV ^d + remote period aspirin use ^a adjusted model, HR (95%CI) | 1 [Reference] | 1.06 (0.74 to 1.51) | 1.02 (0.70 to 1.49) | 1.03 (0.60 to 1.76) | .95 | 0.92 (0.76 to 1.11) | .38 |

Abbreviations: HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period dose of aspirin use: cumulative average dose of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1992, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period dose of aspirin use: cumulative average dose of aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e *P*-value for trend was calculated using the mid-point of each category of aspirin use in tablets/week.

^f *P*-value for trend was the *P* value for variables modeled as continuous.

Supplementary Table 11. Joint associations of remote period duration ^a/dose ^c of aspirin use, and recent period duration ^b/dose ^d of aspirin use (low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent, accordingly to duration and dose respectively) with colorectal cancer risk in the NHS

| NHS | Joint Associations According to Duration of Aspirin Use and Timing | | | | <i>P</i> -interaction ⁱ |
|---|--|--------------------------|--------------------------|---------------------------|------------------------------------|
| | Low to Low ^g | Low to High ^g | High to Low ^g | High to High ^g | |
| No. of CRC cases (1,528 in total) | 915 | 262 | 161 | 190 | |
| Age-adjusted model, HR (95%CI) ^e | 1 [Reference] | 0.80 (0.70 to 0.92) | 0.77 (0.65 to 0.92) | 0.63 (0.53 to 0.74) | .91 |
| MV-adjusted model, HR (95%CI) ^f | 1 [Reference] | 0.82 (0.71 to 0.94) | 0.80 (0.67 to 0.95) | 0.65 (0.55 to 0.76) | .95 |
| NHS | Joint Associations According to Dose of Aspirin Use and Timing | | | | <i>P</i> -interaction ^j |
| | Low to Low ^h | Low to High ^h | High to Low ^h | High to High ^h | |
| No. of CRC cases (1,523 in total) | 631 | 200 | 290 | 402 | |
| Age-adjusted model, HR (95%CI) ^e | 1 [Reference] | 0.78 (0.66 to 0.91) | 0.73 (0.64 to 0.85) | 0.67 (0.59 to 0.76) | .15 |
| MV-adjusted model, HR (95%CI) ^f | 1 [Reference] | 0.78 (0.67 to 0.92) | 0.76 (0.66 to 0.88) | 0.69 (0.60 to 0.78) | .21 |

Abbreviations: NHS, Nurses' Health Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Remote period dose of aspirin use: cumulative average dose of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980, and then was extended by every 2-year subsequent interval at a time, until 2002).

^d Recent period dose of aspirin use: cumulative average dose of aspirin use during every specific subsequent 10-year period after the remote periods.

^e Adjusted for age and follow-up cycle in the follow-up period.

^f Adjusted for age, follow-up cycle, sex, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, menopausal status, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^g Remote period duration of aspirin use and recent period duration of aspirin use were dichotomized into low category (≤ 5 years) versus high category (> 5 years), resulting in four categories (low to low, low to high, high to low, and high to high, i.e. low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent duration of aspirin use).

^h Remote period dose of aspirin use and recent period dose of aspirin use were dichotomized into low category (< 1.5 tablets/week) versus high category (≥ 1.5 tablets/week), resulting in four categories (low to low, low to high, high to low, and high to high, i.e. low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent dose of aspirin use).

ⁱ *P*-value for interaction was calculated using the multiplication of mid-point of each low/high category of duration of aspirin use in years.

^j *P*-value for interaction was calculated using the multiplication of mid-point of each low/high category of dose of aspirin use in tablets/week.

Supplementary Table 12. Joint associations of remote period duration^a/dose^c of aspirin use, and recent period duration^b/dose^d of aspirin use (low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent, accordingly to duration and dose respectively) with colorectal cancer risk in the HPFS

| HPFS | Joint Associations According to Duration of Aspirin Use and Timing | | | | <i>P</i> -interaction ⁱ |
|---|--|--------------------------|--------------------------|---------------------------|------------------------------------|
| | Low to Low ^g | Low to High ^g | High to Low ^g | High to High ^g | |
| No. of CRC cases (619 in total) | 310 | 175 | 40 | 94 | |
| Age-adjusted model, HR (95%CI) ^e | 1 [Reference] | 0.80 (0.66 to 0.96) | 0.82 (0.58 to 1.16) | 0.69 (0.53 to 0.88) | .81 |
| MV-adjusted model, HR (95%CI) ^f | 1 [Reference] | 0.84 (0.69 to 1.02) | 0.81 (0.57 to 1.15) | 0.74 (0.57 to 0.95) | .70 |
| HPFS | Joint Associations According to Dose of Aspirin Use and Timing | | | | <i>P</i> -interaction ^j |
| | Low to Low ^h | Low to High ^h | High to Low ^h | High to High ^h | |
| No. of CRC cases (241 in total) | 98 | 34 | 48 | 61 | |
| Age-adjusted model, HR (95%CI) ^e | 1 [Reference] | 1.38 (0.93 to 2.06) | 1.09 (0.76 to 1.56) | 0.75 (0.54 to 1.04) | .01 |
| MV-adjusted model, HR (95%CI) ^f | 1 [Reference] | 1.41 (0.94 to 2.11) | 1.12 (0.78 to 1.61) | 0.76 (0.55 to 1.05) | .01 |

Abbreviations: HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1986, and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^c Remote period dose of aspirin use: cumulative average dose of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1992, and then was extended by every 2-year subsequent interval at a time, until 2002).

^d Recent period dose of aspirin use: cumulative average dose of aspirin use during every specific subsequent 10-year period after the remote periods.

^e Adjusted for age and follow-up cycle in the follow-up period.

^f Adjusted for age, follow-up cycle, sex, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^g Remote period duration of aspirin use and recent period duration of aspirin use were dichotomized into low category (≤ 5 years) versus high category (> 5 years), resulting in four categories (low to low, low to high, high to low, and high to high, i.e. low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent duration of aspirin use).

^h Remote period dose of aspirin use and recent period dose of aspirin use were dichotomized into low category (< 1.5 tablets/week) versus high category (≥ 1.5 tablets/week), resulting in four categories (low to low, low to high, high to low, and high to high, i.e. low remote to low recent, low remote to high recent, high remote to low recent, and high remote to high recent dose of aspirin use).

ⁱ *P*-value for interaction was calculated using the multiplication of mid-point of each low/high category of duration of aspirin use in years.

^j *P*-value for interaction was calculated using the multiplication of mid-point of each low/high category of dose of aspirin use in tablets/week.

Supplementary Table 13. Joint associations of remote period duration ^a and dose ^b of aspirin use (low duration and low dose, low duration and high dose, high duration and low dose, and high duration and high dose) with colorectal cancer risk in the NHS and HPFS

| | Joint Associations According to Remote Period Status of Aspirin Use | | | | <i>P</i> -interaction ^h |
|--|---|---------------------------|---------------------------|----------------------------|------------------------------------|
| | Low and Low ^g | Low and High ^g | High and Low ^g | High and High ^g | |
| Pooled NHS and HPFS | | | | | |
| No. of CRC cases (1,773 in total) | 922 | 405 | 47 | 399 | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.80 (0.71 to 0.90) | 0.77 (0.57 to 1.04) | 0.68 (0.60 to 0.77) | .64 |
| MV-adjusted model, HR (95%CI) ^{d,e} | 1 [Reference] | 0.81 (0.72 to 0.91) | 0.78 (0.58 to 1.05) | 0.69 (0.61 to 0.78) | .62 |
| NHS | | | | | |
| No. of CRC cases (1,528 in total) | 800 | 377 | 33 | 318 | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.80 (0.71 to 0.90) | 0.79 (0.56 to 1.13) | 0.66 (0.58 to 0.76) | .80 |
| MV-adjusted model, HR (95%CI) ^{d,f} | 1 [Reference] | 0.81 (0.72 to 0.92) | 0.80 (0.56 to 1.14) | 0.69 (0.60 to 0.79) | .81 |
| HPFS | | | | | |
| No. of CRC cases (245 in total) | 122 | 28 | 14 | 81 | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.84 (0.55 to 1.27) | 0.75 (0.42 to 1.32) | 0.74 (0.55 to 0.98) | .66 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.84 (0.55 to 1.28) | 0.76 (0.43 to 1.35) | 0.74 (0.55 to 0.99) | .69 |

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period duration of aspirin use: duration of regular aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980 (NHS) and 1986 (HPFS), and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Remote period dose of aspirin use: cumulative average dose of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980 (NHS) and 1992 (HPFS), and then was extended by every 2-year subsequent interval at a time, until 2002).

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e Additionally adjusted for sex.

^f Additionally adjusted for menopausal status.

^g Remote period duration of aspirin use were dichotomized into low category (≤ 5 years) versus high category (> 5 years), and remote period dose of aspirin use were dichotomized into low category (< 1.5 tablets/week) versus high category (≥ 1.5 tablets/week), resulting in four categories (low and low, low and high, high and low, and high and high, i.e. low duration and low dose, low duration and high dose, high duration and low dose, and high duration and high dose of aspirin use).

^h *P*-value for interaction was calculated using the multiplication of mid-point of each low/high category of aspirin use in years/tablets per week in remote period.

Supplementary Table 14. Joint associations of recent period duration ^a and dose ^b of aspirin use (low duration and low dose, low duration and high dose, high duration and low dose, and high duration and high dose) with colorectal cancer risk in the NHS and HPFS

| | Joint Associations According to Recent Period Status of Aspirin Use | | | | <i>P</i> -interaction ^h |
|--|---|---------------------------|---------------------------|----------------------------|------------------------------------|
| | Low and Low ^g | Low and High ^g | High and Low ^g | High and High ^g | |
| Pooled NHS and HPFS | | | | | |
| No. of CRC cases (2,001 in total) | 1,037 | 310 | 176 | 478 | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.83 (0.73 to 0.95) | 0.84 (0.72 to 1.00) | 0.75 (0.67 to 0.83) | .83 |
| MV-adjusted model, HR (95%CI) ^{d,e} | 1 [Reference] | 0.83 (0.73 to 0.95) | 0.88 (0.74 to 1.04) | 0.75 (0.67 to 0.84) | .95 |
| NHS | | | | | |
| No. of CRC cases (1,742 in total) | 923 | 285 | 129 | 405 | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.85 (0.74 to 0.97) | 0.91 (0.75 to 1.09) | 0.74 (0.66 to 0.83) | .75 |
| MV-adjusted model, HR (95%CI) ^{d,f} | 1 [Reference] | 0.86 (0.75 to 0.98) | 0.94 (0.78 to 1.14) | 0.75 (0.66 to 0.84) | .53 |
| HPFS | | | | | |
| No. of CRC cases (259 in total) | 114 | 25 | 47 | 73 | |
| Age-adjusted model, HR (95%CI) ^c | 1 [Reference] | 0.68 (0.44 to 1.06) | 0.68 (0.48 to 0.96) | 0.76 (0.56 to 1.02) | .09 |
| MV-adjusted model, HR (95%CI) ^d | 1 [Reference] | 0.68 (0.44 to 1.07) | 0.72 (0.50 to 1.03) | 0.78 (0.57 to 1.06) | .12 |

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Recent period duration of aspirin use: duration of regular aspirin use during every specific subsequent 10-year period after the remote periods.

^b Recent period dose of aspirin use: cumulative average dose of aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e Additionally adjusted for sex.

^f Additionally adjusted for menopausal status.

^g Recent period duration of aspirin use were dichotomized into low category (≤ 5 years) versus high category (> 5 years), and recent period dose of aspirin use were dichotomized into low category (< 1.5 tablets/week) versus high category (≥ 1.5 tablets/week), resulting in four categories (low and low, low and high, high and low, and high and high, i.e. low duration and low dose, low duration and high dose, high duration and low dose, and high duration and high dose of aspirin use).

^h *P*-value for interaction was calculated using the multiplication of mid-point of each low/high category of aspirin use in years/tablets per week in recent period.

Supplementary Table 15. Joint associations of overall status (combined duration and dose) and timing ^{a,b} of aspirin use with colorectal cancer risk in the NHS and HPFS

| | Joint Associations According to Status of Aspirin Use and Timing | | | | <i>P</i> -interaction ^h |
|---|--|--------------------------|--------------------------|---------------------------|------------------------------------|
| | Low to Low ^g | Low to High ^g | High to Low ^g | High to High ^g | |
| Pooled NHS and HPFS | | | | | |
| No. of CRC cases (1,764 in total) | 681 | 188 | 399 | 496 | |
| Age-adjusted model, HR (95% CI) ^c | 1 [Reference] | 0.87 (0.74 to 1.02) | 0.76 (0.67 to 0.86) | 0.67 (0.60 to 0.75) | .79 |
| MV-adjusted model, HR (95% CI) ^{d,e} | 1 [Reference] | 0.87 (0.73 to 1.02) | 0.77 (0.68 to 0.87) | 0.68 (0.60 to 0.76) | .81 |
| NHS | | | | | |
| No. of CRC cases (1,523 in total) | 596 | 162 | 358 | 407 | |
| Age-adjusted model, HR (95% CI) ^c | 1 [Reference] | 0.82 (0.69 to 0.98) | 0.77 (0.68 to 0.89) | 0.65 (0.58 to 0.74) | .83 |
| MV-adjusted model, HR (95% CI) ^{d,f} | 1 [Reference] | 0.83 (0.70 to 0.99) | 0.80 (0.70 to 0.91) | 0.67 (0.59 to 0.76) | .95 |
| HPFS | | | | | |
| No. of CRC cases (241 in total) | 85 | 26 | 41 | 89 | |
| Age-adjusted model, HR (95% CI) ^c | 1 [Reference] | 1.26 (0.80 to 1.97) | 0.65 (0.44 to 0.96) | 0.76 (0.56 to 1.03) | .80 |
| MV-adjusted model, HR (95% CI) ^d | 1 [Reference] | 1.25 (0.79 to 1.97) | 0.65 (0.44 to 0.97) | 0.78 (0.57 to 1.06) | .87 |

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MV, multivariate; HR, hazard ratio; CI, confidence interval.

^a Remote period status of aspirin use: status of aspirin use during every specific remote period (>10 years before every follow-up period, i.e. begin from 1980 (NHS) and 1992 (HPFS), and then was extended by every 2-year subsequent interval at a time, until 2002).

^b Recent period status of aspirin use: status of aspirin use during every specific subsequent 10-year period after the remote periods.

^c Adjusted for age and follow-up cycle in the follow-up period.

^d Adjusted for age, follow-up cycle, race, pack-years of smoking, physical activity, BMI, alcohol consumption, AHEI, regular use of non-aspirin NSAIDs, family history of colorectal cancer, history of diabetes mellitus, screening colonoscopy or sigmoidoscopy in the past two years, multivitamin use, total calorie intake, red or processed meat intake, fiber intake, folate intake, calcium intake, and vitamin D intake in the follow-up period.

^e Additionally adjusted for sex.

^f Additionally adjusted for menopausal status.

^g Based on results from Table 3 and 4, remote period status of aspirin use were dichotomized into high category (any use irrespective of dose or duration) versus low category (all other scenarios in the same period), and recent period status of aspirin use were dichotomized into high category (>5 years and ≥1.5 tablets/week) versus low category (all other scenarios in the same period), resulting in four categories (low to low, low to high, high to low, and high to high, i.e. low remote status of aspirin use to low recent status of aspirin use, low remote status of aspirin use to high recent status of aspirin use, high remote status of aspirin use to low recent status of aspirin use, and high remote status of aspirin use to high recent status of aspirin use).

^h *P*-value for interaction was calculated using the multiplication of mid-point of each low/high category of status of aspirin use.