Supplementary Online Content

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

eMethods. Ascertainment of Covariates; Statistical Analyses

Ascertainment of Covariates

In both NHS and HPFS, we obtained information on several CRC risk factors at baseline and updated biennially, including age, first-degree family history of CRC, body mass index (BMI), alcohol consumption, physical activity, smoking pack-years, lower endoscopy, diabetes, hyperlipidemia, hypertension, cardiovascular diseases (stroke, angina, myocardial infarction and coronary bypass surgery), total energy intake, calcium intake, folate intake, and Alternative Healthy Eating Index (AHEI) 2010 score, regular use of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), multivitamin, cholesterol-lowering drugs (e.g. statins), and menopausal hormone (for women only). Consistent with our prior studies,[1,2] regular use of other NSAIDs was defined as regularly use of any amount of any non-aspirin NSAIDs. For physical activity, the metabolic equivalent of task (MET) score was assigned to each type of physical activity. The amount of total physical activity was estimated by multiplying the MET score by the reported hours spent per week.[3] AHEI 2010 score was used to represent diet quality, for which a higher score has been associated with reduced risk of cancer.[4] We carried forward missing data on covariates using available information from prior questionnaires. Cumulative average values were calculated for alcohol consumption, physical activity, MET score, AHEI 2010 score and intakes of total calories, calcium, folate to minimize variance and better reflect long-term patterns.

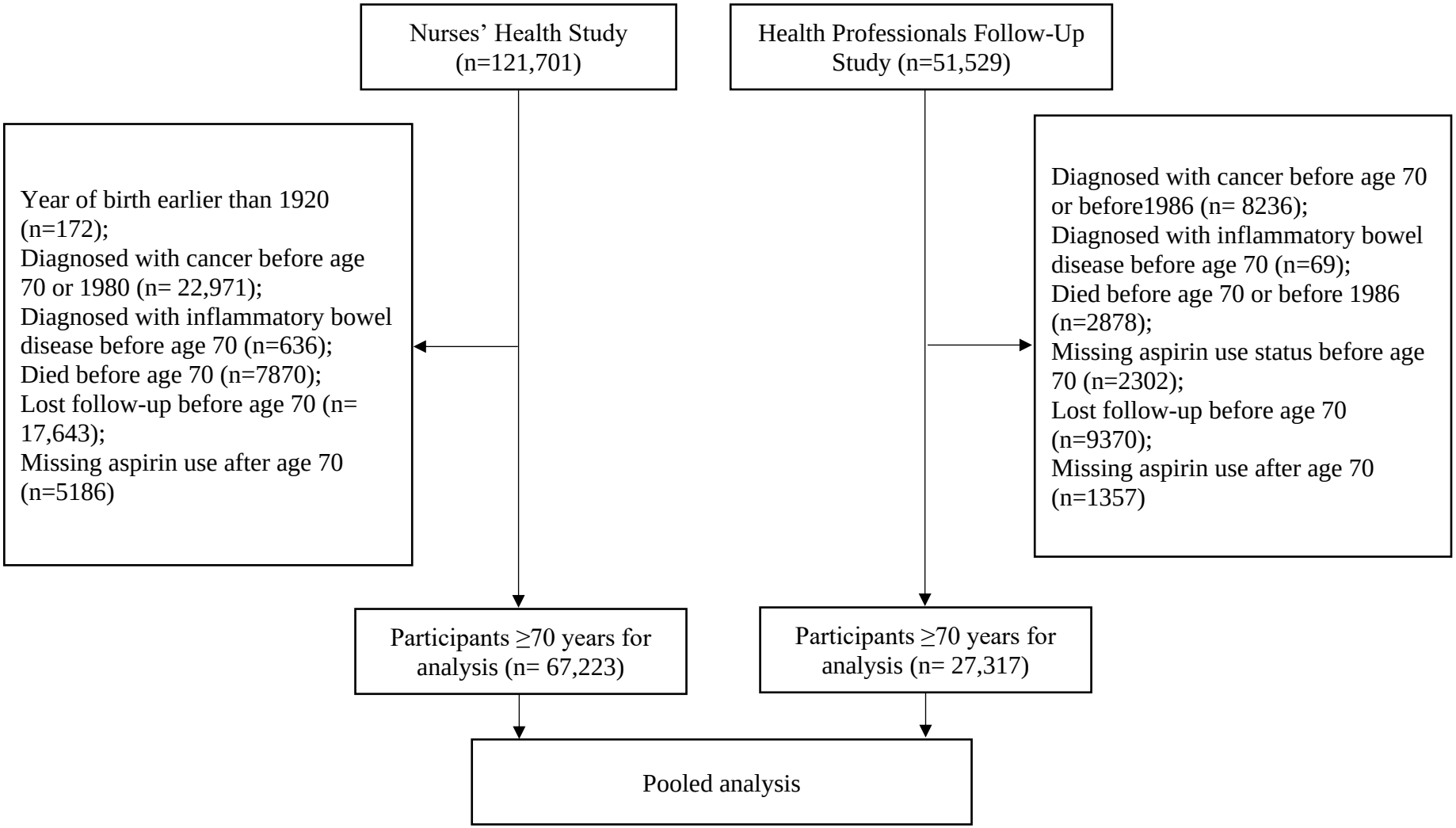
Statistical Analyses

Cox proportional hazards regression model stratified on age (continuous years) and calendar time (2-year intervals) was used to estimate HRs and 95% CIs. All covariates were updated biennially and included as time-varying covariates, as appropriate. In the multivariable model (model 2), covariates including family history of CRC (yes/no), personal history of diabetes (yes/no), BMI (<23, 23–24.9, 25–29.9, 30–34.5, and ≥35 kg/m^2), alcohol (non-drinker, <5, 5–14.9, 15–29.9, and ≥30 g/d), physical activity (quintile), smoking pack-years (non-smoker, <10, 10–39.9 and ≥40 pack-years), non-aspirin NSAIDs (yes/no), multivitamin (yes/no), lower endoscopy (yes/no),

AHEI 2010 score (quintile), and intakes of total calories (quintile), calcium (quintile), folate (quintile), menopausal hormone (for women only: never/unknown use, current hormone use, past hormone use) were adjusted. To address the potential influence of cardiovascular diseases (CVD) risk on the association, a model (model 3) further adjusted for regular use of cholesterol-lowering drugs (yes/no), hyperlipidemia (yes/no), hypertension (yes/no), as well as CVD (yes/no) was performed. Multi-categorical variables were included as indicators/dummy variables in the model. Analyses were performed separately in the cohort of NHS and HPFS and then used meta-analysis using random-effect models for pooled estimates.

As a secondary analysis, we further evaluated the association of aspirin initiated at different age categories and risk of subsequent incident CRC through separate cohort analyses among participants who had not used aspirin before reaching the corresponding age category in NHS. In NHS, all women aged between 33–60 (median = 47) years when we began collecting data on aspirin use in 1980 at which time we also inquired about their duration of use. Therefore, we were able to determine the age of initiation for all included participants. In each cohort, we followed participants from the lower limit of the age category until CRC, death or the end of the follow-up. In this secondary analysis, for each cohort defined according to categories of age of initiation, we evaluated the risk of any incident CRC after the baseline age category. Regular aspirin users were those who initiated regular aspirin use within the corresponding age category, and non-regular users were those who did not use aspirin regularly. For those who initiated regular aspirin use after the corresponding age category, they were considered non-regular users and then censored once they started using aspirin. We limited this analysis to NHS because we were unable to determine the age of initiation for a large proportion of participants in HPFS, in which we did not inquire about duration of aspirin use before enrollment and 33.5% of men in HPFS were at or over aged 60 years at enrollment.

eFigure. Flowchart of the Study



eTable 1. Age-Standardized Characteristics of Participants Aged 70 or Above in Nurses' Health Study (1980-2014) and Health Professionals Follow-up Study (1986-2014)

Characteristics[a]	**NHS (n=67,223)**		**HPFS (n=27,317)**	
	Non-regular user of aspirin	**Regular user of aspirin**	**Non-regular user of aspirin**	**Regular user of aspirin**
Age, years (SD)[b]	75.1 (4.5)	77.3 (5.0)	75.7 (5.0)	78.4 (5.7)
Body mass index, kg/m^2, mean (SD)	25.6 (5)	26 (5.1)	25.3 (3.8)	25.6 (3.6)
Alcohol, g/d, mean (SD)	5.4 (8.6)	5.7 (8.6)	10.8 (13.9)	11.5 (13.4)
Physical activity, MET-h/week, mean (SD)	16.4 (22.7)	16.5 (21.9)	28.3 (30.7)	29.2 (30.8)
Ever smokers, %	51.7	53.9	51.5	55.5
Pack-years among ever smokers, mean (SD)	26.7 (22.9)	27.2 (23.1)	27.7 (20.9)	27.7 (20.6)
Family history of CRC, %	19.8	19.6	17.2	17.0
Prior lower endoscopy, %	30.2	31.8	31.2	36.8
Hypertension, %	60.5	72.0	45.6	59.3
Dyslipidemia, %	67.3	77.0	44.9	61.4
Diabetes, %	11.9	15.9	11.1	14.3
Cardiovascular diseases, %	11.6	23.3	17.4	38.4
Prior history of regular use of aspirin before age 70, %	56.3	82.7	40.2	80.3
Regular use of multivitamins, %	65.1	72.4	57.5	68.8
Regular use of non-aspirin NSAIDs, %	27.7	30.5	12.3	17.2

Regular use of cholesterol-lowering drugs, %	23.4	40.9	14.4	35.1
Menopausal hormone use				
Never/unknown, %	32.8	29.3	-	-
Current use, %	23.0	20.4	-	-
Past use, %	44.3	50.4	-	-
Total calories intake, kcal/d, mean (SD)	1665 (423)	1675 (418)	1955 (534)	1969 (520)
Folate intake, µg/d, mean (SD)	509 (200)	536 (191)	586 (253)	630 (241)
Calcium, mg/d, mean (SD)	1097 (396)	1148 (392)	981 (382)	1014 (365)
AHEI 2010 score, mean (SD)	47.7 (8.9)	47.7 (8.4)	50.5 (10.0)	50.8 (9.3)

Abbreviations: AHEI, Alternative Healthy Eating Index; CRC, colorectal cancer; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of tasks; NHS, Nurses' Health Study; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard difference.

[a] All data are present as percentage (%) or mean (SD), unless noted otherwise. As the exposure is time varying, the values were not calculated at baseline by individual but rather according to the average over follow-up.

[b] Value is not age adjusted.

eTable 2. Regular Aspirin Use at or After Age 70 and Risk of Colorectal Cancer Developed at or After Age 70 According to Cancer Stage

	No. of cases[a]	Overall	Non-regular use of aspirin before age 70[b]	Prior history of regular use of aspirin before age 70[b]
Stage I/II/III	941	0.85 (0.74–0.97)	1.03 (0.81–1.30)	0.83 (0.69–1.00)
Stage IV	221	0.59 (0.45–0.78)	0.84 (0.35–2.01)	0.45 (0.15–1.38)

[a] Numbers in pooled overall analyses.

[b] Multivariable-adjusted HR (95% CI) in pooled analyses; Conditioned on age (continuous years) and calendar time (2-year intervals), and adjusted for family history of colorectal cancer (yes/no), diabetes (yes/no), body mass index (<23, 23–24.9, 25–29.9, 30–34.5, ⩾ 35 kg/m2), alcohol consumption (non-drinker, <5, 5–14.9, 15–29.9, ⩾30 g/d), physical activity (quintile), smoking pack-years (non-smoker, <10, 10–39.9 and ⩾40 pack-years), lower endoscopy (yes/no), total energy intake (quintile), calcium intake (quintile), folate intake (quintile), Alternative Healthy Eating Index 2010 score (quintile), and regular use of non-aspirin NSAIDs (yes/no), multivitamin (yes/no), and menopausal hormone (for women: never/unknown use, current hormone use, past hormone use).

eReferences

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3. Liu PH, Wu K, Ng K, et al. Association of obesity with risk of early-onset colorectal cancer among women. *JAMA Oncol.* 2019;5(1):37–44.
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