**Supplementary Methods.** Study population, ascertainment of covariates, ascertainment of outcomes and participant deaths, construction of multivariable models, ascertainment of timeline in secondary analyses according the remote and recent periods, and references

**Study population**

The NHS and HPFS are ongoing US large cohort studies, the details of which have been previously described.(1-3) The NHS, began in 1976,(2, 3) included 121,700 female registered nurses who were aged 30 to 55 years at enrollment. The HPFS was initiated in 1986,(1) when 51,529 male health professionals aged 40 and 75 years were enrolled. Demographics were collected at cohort enrollment. Via self-administered questionnaires, data on anthropometrics, lifestyles, dietary factors, menstrual and reproductive history (women only), family history, and medical history were assessed biennially or quadrennially thereafter throughout follow-up, with follow-up rates have consistently exceeded 90%. The NHS and HPFS were approved by the Institutional Review Boards of the Brigham and Women’s Hospital and the Harvard T.H. Chan School of Public Health (Boston, MA), and those of participating registries as required.The completion and return of the questionnaires were considered to imply informed consent. Written informed consent was required to retrieve medical records. Participants who were alive and free of cancer at the time when information on exposures were first assessed were eligible for inclusion.

**Ascertainment of covariates**

All covariates were selected a priori as potential confounders, including age, sex, race, pack-years of smoking, physical activity, cumulative average body mass index (BMI), alcohol consumption, regular use of aspirin, family history of CRC, history of diabetes mellitus, history hypercholesterolemia, history of hypertriglyceridemia (information available in the HPFS only), screening colonoscopy or sigmoidoscopy, menopausal status, multivitamin use, and diet. In sensitivity analyses, we additionally considered other cardiometabolic risk factors (history of hypertension, waist circumference, and family history of cardiovascular disease). Throughout follow-up, cohort 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), waist circumference, menopausal status (including postmenopausal hormone use; women only), history of aspirin and multivitamin use, and history of diabetes mellitus, hypercholesterolemia, hypertriglyceridemia (in the HPFS only), hypertension, and screening colonoscopy or sigmoidoscopy. Dietary data (e.g., intake of total calories, alcohol, red or processed meat, fiber, folate, calcium, and vitamin D, via food frequency questionnaires), family history of CRC, and family history of cardiovascular disease were updated quadrennially. Alternate Healthy Eating Index (AHEI) was calculated to measure overall dietary quality. Except for the above-mentioned time-varying covariates, height, sex, and race were assessed. The validity and reproducibility of information on anthropometrics, lifestyle and dietary data, and disease outcomes have previously been reported.(4-18)

**Ascertainment of outcomes and participant deaths**

Participants biennially reported physician-diagnosed incident CRC events via questionnaires. For those who reported CRC diagnosis, cohort investigators retrieved medical records and pathology reports after obtaining their written informed consent to ascertain CRC diagnoses. Cohort investigators referred to state cancer registries if medical records were unavailable. Death events were ascertained through the National Death Index and next-of-kin or postal authorities, with an identifying rate exceeding 96%.(19, 20) Cohort investigators reviewed death certificates and medical records after obtaining permission from next of kin of dead participants.

**Construction of multivariable models**

Multivariable analyses were stratified by age (in months) and follow-up cycle (each 2-year interval), and additionally adjusted for 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/m2, continuous), alcohol consumption (grams/day, continuous), AHEI (quartiles), regular use of aspirin (tablets/week, continuous), family history of colorectal cancer (yes, no), history of diabetes mellitus (yes, no), history of hypercholesterolemia (yes, no), history of hypertriglyceridemia (yes, no; in the HPFS only), screening colonoscopy or sigmoidoscopy within the past 10 years and later, menopausal status (premenopausal or no history of postmenopausal hormone use, past menopausal hormone use, current postmenopausal hormone use; women only), 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 (ug/day, quartiles), calcium intake (mg/day, quartiles), and vitamin D intake (IU/day, quartiles). In sensitivity analyses, we additionally adjusted for other cardiometabolic risk factors, including history of hypertension (yes, no), waist circumference (continuous, cm), and family history of cardiovascular disease (yes, no). Specifically in secondary analyses according to the remote and recent periods, considering remote and recent period statin use could confound each other, as use is correlated over time, we mutually controlled for statin use in above-mentioned time-periods in separate multivariate-adjusted models.

**Ascertainment of timeline in secondary analyses according to the remote and recent periods**

To further assess effects of statin use according to timing, in secondary analyses, we considered duration of use in the remote and recent periods as exposures to disentangle their mixed effect in the subsequent independent follow-up period. 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 statin use were first assessed (i.e. 1994 in the NHS and 1990 in HPFS), and it was then extended by every subsequent 2-year interval at a time in each model, until 2004 in the NHS and 2002 in HPFS. 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 2014 in the NHS and 2012 in HPFS. The follow-up in each model began from the end of the first “subsequent 10-year period” to 2016 in the NHS and 2014 in HPFS. Timelines of these analyses were illustrated in Supplementary Figure 1.

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