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**Supplementary Methods**

*Assessment of UPF consumption*

Based on FFQs with about 130 food items, we applied the NOVA (a name, not an acronym) classification to categorize foods into four groups: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and ultra-processed foods, which has been described in detail elsewhere (1). Briefly, three researchers worked independently to assign each food item to a NOVA group. There was a consensus on over 70% of all food times at the first attempt of categorization, based on published definitions that account for differences in processing between groups and their accompanying example products. The approach to classifying the remaining food items involved discussions with an expert group and use of additional resources (research dieticians, cohort-specific documents, and online grocery store scans). For nine food items that lacked sufficient details to support their classification (i.e., "Popcorn"; "Soy milk"; "Pancakes or waffles", "Pie, home-baked or ready-made"; "Beef, Pork, Lamb Sandwich"; "Tomato Sauce"), we adopted a conservative approach by assigning these items to a non-UPF group as their primary categorization and to the UPF group for a sensitivity analysis. Because alcohol consumption is an established risk factor for CRC, we removed this item from the UPF group. We estimated UPF consumption as servings per day, which was energy adjusted using the residual methods (1).

*Assessment of covariates*

Covariates were collected through self-administered questionnaires at baseline and biennially thereafter, including smoking, alcohol consumption, body mass index (BMI, weight in kilograms divided by the square of height in meters), physical activity, regular use of aspirin, family history of CRC, endoscopic variables, and for women menopausal status and postmenopausal hormone use, as previously described (2-4). Western dietary pattern was derived from principal component analyses using dietary data from FFQs (5).

*Ascertainment of colorectal polyps*

Ascertainment of colorectal polyps in the three cohorts has been described elsewhere (6). Briefly, on each biennial questionnaire, participants were asked whether they had undergone a colonoscopy or sigmoidoscopy and whether any colorectal polyp had been diagnosed in the past two years. For participants who reported polypectomy, their endoscopic and pathologic records were reviewed to confirm the diagnosis and obtain data on histology, size, number and anatomic location of polyps. Conventional adenomas included tubular, tubulovillous and villous adenomas, and adenomas with high-grade dysplasia, while serrated lesions comprised hyperplastic polyps, traditional serrated adenomas, sessile serrated adenomas/polyps, and mixed serrated polyps. High-risk polyps included advanced conventional adenomas (at least one adenoma of ≥10 mm in diameter or any size with tubulovillous, villous, or high-grade dysplasia) and large serrated lesions (≥10 mm) (7). When a participant had more than one adenoma or serrated lesion in a sublocation (proximal colon, distal colon, or rectum) in an endoscopy, the histology of the most advanced lesion and the size of the largest polyp were used for that sublocation.

**Supplementary References**

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7.    Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* 2012;143(3):844-857.

**Supplementary Table 1.** Classification of ultra-processed food subgroups for food items collected in the food frequency questionnaire

| Ultra-processed food subgroups | Food items |
| --- | --- |
| Meat/poultry/seafood-based ready-to-eat products | Bacons; beef, pork hotdogs; chicken or turkey hotdogs; salami, bologna, processed meat sandwiches; processed meats, sausages; breaded fish cakes, pieces, sticks |
| Ultra-processed breads and breakfast food | Breakfast bar; cold breakfast cereal; English muffins, bagels, rolls; rye, pumpernickel bread; white bread; whole grain bread |
| Packaged sweet snacks and desserts | Brownies; cake, ready-made; cookies, ready-made; doughnuts; pie, ready-made; muffins or biscuits; ready-made sweet roll, coffee cake; candy bars; chocolate bars; energy bar; high protein, low carb candy bar; applesauce; jams, jellies, preserves, honey |
| Fat, condiment, and sauces | Ketchup, red chili sauce, salad dressings, mayonnaise (regular and low fat), salsa, margarines, spread butter, soy sauce, non-dairy coffee whitener, cream cheese |
| Beverages | Caffeine free coke pepsi; coke pepsi cola; dairy coffee drink; Hawaiian punch low calorie soda, caffeine free; low calorie soda, pepsi, 7-up; other carbon beverage; other low calorie carb; other low calorie cola with caffeine |
| Yogurt and dairy based desserts | Frozen yogurt, sherbet, ice cream, yogurt artificially sweetened; flavored yogurt without nutrasweet |
| Ready-to-eat/heat mixed dishes | Pizza; chowder or cream soup; soup made with bouillon; ready-made soup from cans; French fries |
| Packaged savory snacks | Regular crackers; fat free, light crackers; fat free popcorn |
| Other ultra-processed foods | Nutrasweet or equal; other artificial sweeteners; Splena |

**Supplementary Table 2.** Basic characteristics of study participants in the three cohort studies (NHS, NHS2, HPFS) by ultra-processed food consumption [a]

| Characteristics | Energy adjusted servings per day of UPF intake | | | | |
|---|---|---|---|---|---|
| | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 |
| Number of participants | 27,322 | 29,452 | 29,095 | 28,810 | 27,373 |
| Median UPF intake | 4.0 | 5.2 | 6.2 | 7.3 | 9.3 |
| Age in years, mean (SD) | 60.5 (10.4) | 60.4 (10.6) | 60.4 (10.7) | 60.3 (10.8) | 60.1 (10.7) |
| Male, % | 21 | 22 | 22 | 23 | 23 |
| White, % | 93 | 95 | 96 | 97 | 97 |
| Family history of colorectal cancer, % | 21 | 21 | 21 | 21 | 21 |
| BMI in kg/m², mean (SD) | 24.7 (4.1) | 25.4 (4.3) | 25.8 (4.6) | 26.4 (4.8) | 27.0 (5.3) |
| Current smoker, % | 6 | 5 | 5 | 6 | 7 |
| Pack-years of smoking, mean (SD) | 8.3 (14.6) | 8.1 (14.4) | 8.4 (14.8) | 9.4 (15.8) | 11.7 (17.9) |
| Alcohol in g/day, mean (SD) | 8.5 (11.5) | 7.0 (9.7) | 6.2 (8.8) | 5.4 (8.2) | 4.6 (7.5) |
| Physical activity in MET-h/wk, mean (SD) | 25.9 (23.3) | 23.1 (20.9) | 21.6 (19.7) | 20.2 (18.9) | 18.8 (18.4) |
| Postmenopausal, % [b] | 81 | 80 | 80 | 80 | 81 |
| Postmenopausal hormone use, % [b] | 56 | 57 | 58 | 58 | 58 |
| Regular aspirin use (2 or more tablets/wk), % | 38 | 41 | 42 | 44 | 45 |
| Dietary intake, mean (SD) | | | | | |
| Western dietary pattern score [c] | -0.58 (0.77) | -0.20 (0.83) | 0.01 (0.88) | 0.18 (0.94) | 0.29 (1.00) |
| Total fiber in g/d | 21.9 (6.2) | 20.6 (5.3) | 19.9 (5.0) | 19.4 (4.9) | 18.9 (5.0) |
| Total folate intake in ug/d | 594 (235) | 560 (212) | 544 (205) | 530 (203) | 521 (215) |
| Total calcium in mg/d | 1222 (467) | 1165 (424) | 1138 (412) | 1110 (404) | 1095 (421) |
| Total vitamin D in IU/d | 483 (249) | 444 (223) | 428 (216) | 415 (213) | 407 (224) |

Abbreviations: NHS, Nurses' Health Study; NHS II, the Nurses' Health Study II; HPFS, Health Professionals Fellow-up Study; SD, standard deviation; BMI, body mass index; MET, metabolic equivalent tasks; UPF, ultra-processed food.
[a] All variables were adjusted for age except for age itself.
[b] Calculated among women.
[c] Western dietary pattern score was derived from principal component analysis.

**Supplementary Table 3.** Association between ultra-processed food consumption and risk of conventional adenomas and serrated lesions in the three cohort studies (NHS, NHS II, HPFS): Sensitivity analysis for alternative classification

| | Energy adjusted servings per day of UPF intake, OR (95% CI) [a] | | | | | P for nonlinearity [b] | P for overall significance [b] |
|---|---|---|---|---|---|---|---|
| | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | | |
| Median intake | 4 | 5.2 | 6.2 | 7.3 | 9.3 | | |
| Conventional adenomas | | | | | | | |
|   Cases | 2041 | 2321 | 2392 | 2534 | 2356 | | |
|   Model 1 | 1 (referent) | 1.06 (1.00 to 1.12) | 1.09 (1.03 to 1.16) | 1.19 (1.12 to 1.26) | 1.18 (1.11 to 1.26) | <.0001 | <.0001 |
|   Model 2 | 1 (referent) | 1.06 (1.00 to 1.13) | 1.10 (1.03 to 1.16) | 1.19 (1.12 to 1.27) | 1.18 (1.11 to 1.26) | <.0001 | <.0001 |
|   Model 2+BMI | 1 (referent) | 1.05 (0.99 to 1.12) | 1.08 (1.02 to 1.15) | 1.17 (1.11 to 1.25) | 1.16 (1.09 to 1.23) | <.0001 | <.0001 |
|   Model 2+Western dietary pattern score | 1 (referent) | 1.04 (0.97 to 1.10) | 1.05 (0.99 to 1.12) | 1.14 (1.07 to 1.21) | 1.12 (1.05 to 1.20) | .003 | <.0001 |
|   Model 2+dietary fiber, folate, calcium, and vitamin D | 1 (referent) | 1.05 (0.98 to 1.11) | 1.07 (1.01 to 1.14) | 1.17 (1.10 to 1.24) | 1.16 (1.09 to 1.24) | .0004 | <.0001 |
| Serrated lesions | | | | | | | |
|   Cases | 1788 | 2063 | 2153 | 2310 | 2164 | | |
|   Model 1 | 1 (referent) | 1.07 (1.00 to 1.14) | 1.11 (1.04 to 1.18) | 1.22 (1.15 to 1.30) | 1.23 (1.15 to 1.31) | <.0001 | <.0001 |
|   Model 2 | 1 (referent) | 1.08 (1.01 to 1.15) | 1.13 (1.05 to 1.20) | 1.24 (1.16 to 1.32) | 1.21 (1.14 to 1.30) | <.0001 | <.0001 |
|   Model 2+BMI | 1 (referent) | 1.07 (1.00 to 1.14) | 1.10 (1.03 to 1.18) | 1.20 (1.13 to 1.28) | 1.16 (1.09 to 1.24) | <.0001 | <.0001 |
|   Model 2+Western dietary pattern score | 1 (referent) | 1.05 (0.99 to 1.13) | 1.08 (1.01 to 1.16) | 1.18 (1.10 to 1.26) | 1.15 (1.07 to 1.23) | <.0001 | <.0001 |
|   Model 2+dietary fiber, folate, calcium, and vitamin D | 1 (referent) | 1.06 (1.00 to 1.13) | 1.10 (1.03 to 1.18) | 1.21 (1.13 to 1.29) | 1.19 (1.11 to 1.27) | <.0001 | <.0001 |

Abbreviations: NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; HPFS, Health Professionals Fellow-up Study; UPF, ultra-processed food; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index.

[a] Model 1 was adjusted for age (years), race (Caucasian or non-Caucasian), cohort (NHS, NHS II, or HPFS), time period of endoscopy (in 2-year intervals), number of prior endoscopies (continuous), and time in years since the most recent endoscopy (continuous).

Model 2 was further adjusted for family history of colorectal cancer (yes or no), total alcohol intake (in g/day, <5, 5-10, 10-15, 15-30, or ≥30), physical activity (in metabolic equivalent-hours/week; <3, 3-9, 9-18, 18-27, or ≥27), smoking status and pack-years of smoking (never, past smoker with pack-years

<5, past smoker with pack-years ≥5, current smoker with pack-years <20, current smoker with pack-years ≥20), regular aspirin use (yes or no), and additionally for menopausal status (yes or no) and postmenopausal hormone use (never or ever) in women.

The other models were further adjusted for BMI (continuous), Western dietary pattern score (continuous), and individual dietary factors (quintiles), respectively.

[b] Derived from the restricted cubic spline analysis.

**Supplementary Figure 1.** Flowchart of study participant selection. Abbreviation: IBD, inflammatory bowel disease.