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Brief Communication

# Coffee Intake and Colorectal Cancer Incidence According to T-Cell Response

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## Abstract

We hypothesized that the associations between coffee intake and colorectal cancer (CRC) incidence might differ by immune cell densities in CRC tissue. Using the Nurses' Health Study and the Health Professionals Follow-up Study, we examined the association of coffee intake with incidence of CRC classified by intraepithelial or stromal T-cell subset densities by multiplex immunofluorescence assay for CD3, CD4, CD8, CD45RO (PTPRC), and FOXP3. We applied an inverse probability-weighted Cox proportional hazardsregression model to control for selection bias and potential confounders. During follow-up of 133 924 participants (3 585 019 person-years), we documented 3161 incident CRC cases, including 908 CRC cases with available data on T-cell densities in tumor tissue. The association between coffee intake and CRC was not statistically significantly different by intraepithelial or stroma T-cell subset ($P_{heterogeneity} > .38$). Hence, there is no sufficient evidence for differential effect of coffee intake on incidence of CRC subtypes classified by T-cell infiltrates.

Observational studies have found conflicting evidence on the association between coffee consumption and the incidence of colorectal cancer (CRC) (1). Coffee contains complex mixtures of biochemically active compounds, some of which, including polyphenols and caffeine, are suggested to influence adaptive immune responses (2-5). However, the human data linking coffee to immune cells in CRC are lacking. We hypothesized that the associations between coffee intake and CRC incidence might differ by T-cell response to CRC.

We used data from 2 large prospective cohort studies in the United States: the Nurses' Health Study (NHS, n = 121 701 women aged 30-55 years at enrollment followed since 1976) and the Health Professionals Follow-up Study (HPFS, n = 51 529 men aged 40-75 years at enrollment followed since 1986) (6,7). Study participants have been sent follow-up questionnaires biennially to update information on demographics, diet, lifestyle factors, and medical history. The follow-up rate has been over 90% for each questionnaire cycle in both cohorts. To assess dietary

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**Table 1.** Age-standardized characteristics according to coffee intake in the NHS (women, 1980-2012) and the HPFS (men, 1986-2012)[a]

| Characteristic | Coffee intake | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Women | | | | Men | | | |
| | 0 cups/d (n = 19 497) | <1 cups/d (n = 7388) | 1-3 cups/d (n = 38 147) | ≥3 cups/d (n = 21 666) | 0 cups/d (n = 7594) | < 1 cups/d (n = 9416) | 1-3 cups/d (n = 21 041) | ≥3 cups/d (n = 9175) |
| Coffee intake, cup/d (median, IQR) | 0 | 0.5 (0.2, 0.8) | 2.2 (1.5, 2.5) | 4.3 (3.5, 5.0) | 0 | 0.5 (0.2, 0.8) | 2.0 (1.4, 2.5) | 4.3 (3.5, 4.9) |
| Age, y | 56.2 (11.4) | 62.2 (11.4) | 61.9 (11.3) | 59.7 (10.6) | 61.2 (11.1) | 65.3 (11.4) | 65.1 (11.2) | 62.7 (10.4) |
| Body mass index, kg/m$^2$ | 25.9 (5.2) | 25.6 (5.0) | 25.3 (4.5) | 25.0 (4.3) | 25.5 (3.5) | 25.5 (3.5) | 25.9 (3.4) | 26.2 (3.4) |
| Physical activity, METS-h/wk[b] | 15.7 (18.0) | 16.5 (16.8) | 16.9 (17.5) | 16.2 (17.3) | 26.6 (24.4) | 26.6 (23.8) | 25.6 (22.8) | 24.8 (21.6) |
| Pack-years of smoking | 8.4 (16.6) | 7.7 (14.9) | 11.8 (17.6) | 20.7 (22.7) | 5.2 (12.7) | 8.4 (14.9) | 13.5 (18.3) | 20.3 (22.2) |
| Family history of CRC, % | 11.9 | 13.3 | 13.6 | 13.2 | 11.5 | 12.5 | 12.5 | 12.5 |
| History of diabetes, % | 9.3 | 9.5 | 7.2 | 5.5 | 7.0 | 7.7 | 7.8 | 7.5 |
| History of previous endoscopy, % | 35.6 | 43.6 | 39.9 | 36.6 | 50.7 | 55.6 | 53.9 | 52.7 |
| Current multivitamin use, % | 50.1 | 55.1 | 52.4 | 49.4 | 41.8 | 44.8 | 43.6 | 44.6 |
| Regular aspirin use, % | 29.4 | 30.9 | 32.6 | 33.9 | 40.8 | 45.4 | 48.7 | 50.3 |
| Regular NSAID use, % | 13.6 | 18.0 | 18.0 | 18.8 | 12.1 | 13.9 | 16.4 | 17.7 |
| Postmenopausal, % | 73.9 | 78.0 | 78.3 | 78.7 | | | | |
| Current hormone use, %[c] | 22.8 | 28.4 | 27.2 | 26.3 | | | | |
| Dietary intake | | | | | | | | |
| Total calorie, kcal/d | 1650 (467) | 1668 (437) | 1672 (433) | 1709 (442) | 1954 (551) | 1904 (543) | 1974 (548) | 2082 (573) |
| Alcohol, g/d (median, IQR) | 0.3 (0.0,2.4) | 1.1 (0.0,4.6) | 2.7 (0.5,9.2) | 2.8 (0.6,9.6) | 0.7 (0.0,5.5) | 4.6 (0.9,11.9) | 8.2 (2.2,17.3) | 9.2 (2.4,20.1) |
| Total red meat, servings/wk | 6.7 (4.1) | 6.1 (3.5) | 6.5 (3.5) | 7.0 (3.7) | 5.8 (4.4) | 5.6 (4.0) | 6.4 (4.3) | 7.5 (4.8) |
| Calcium, mg/d | 879 (387) | 958 (371) | 925 (345) | 932 (337) | 999 (412) | 962 (395) | 908.9 (357) | 915.2 (345) |
| Folate, μg/d | 423 (253) | 452 (229) | 426 (203) | 400 (194) | 552 (267) | 576 (270) | 537 (246) | 509 (233) |
| AHEI score | 45.1 (10.5) | 47.1 (9.9) | 46.4 (9.5) | 45.9 (9.4) | 48.3 (10.9) | 49.6 (10.0) | 48.1 (9.8) | 46.7 (9.8) |

[a]Cumulative average values are presented. Mean (±SD) or median (IQR) for continuous variable or percentages for categorical variables are presented. All variables are age-standardized except age. AHEI = Alternative Healthy Eating Index; CRC = colorectal cancer; HPFS = Health Professionals Follow-up Study; IQR = interquartile range; METS = metabolic equivalent task score; NHS = Nurses' Health Study; NSAID = nonsteroidal antiinflammatory drug.

[b]Physical activity is represented by the product sum of the metabolic equivalent score (METS) of each specific recreational activity and hours spent on that activity per week.

[c]Proportion of current menopausal hormone use is calculated among postmenopausal women only.

intake in each cohort, food frequency questionnaires (FFQs) were initially collected in 1980 for the NHS and in 1986 for the HPFS. For the NHS, a 61-item semi-quantitative FFQ was used at baseline (8), which was expanded to approximately 130 foods and beverage items in 1984, 1986, and every 4 years thereafter. For the HPFS cohorts, baseline dietary intake was assessed using a 131-item FFQ that was also used for updates generally every 4 years subsequently (9). For each item, FFQs prompted participants to report their average intake over the preceding year for a specified serving size of each food and beverage from 9 possible responses, ranging from never or almost never to 6 or more times per day. Intakes of various nutrients were calculated by multiplying the frequency of each food or beverage consumed by the nutrient content of the specified portion size and then summing the contributions from all foods and beverages in the FFQ. To capture long-term exposure, we calculated the cumulative average of each factor from baseline up to the most updated cycle. We excluded participants who had a history of cancer (except for nonmelanoma skin cancer), inflammatory bowel disease, implausibly high or low caloric intake, and incomplete data on coffee intake. The follow-up durations for this analysis were 1980 to 2012 for the NHS and 1986 to 2012 for the HPFS. In addition to self-reported incident CRC cases, lethal unreported CRC cases were ascertained through use of the National Death Index, and all CRC cases were confirmed by medical record review.

We simultaneously measured the expression of CD3, CD4, CD8, CD45RO (PTPRC), and FOXP3 in T cells within tumor epithelial and stromal regions in CRC tissue microarrays by a multiplex immunofluorescence assay. For 908 CRC patients, there were 1694 available tissue microarray cores (mean 1.9 cores per patient), while 192 of 1886 (10%) tumor cores from these patients were missing or unrepresentative, based on pathologist review. Informed consent was obtained from all study participants at enrollment. This study was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, MA) and those of the participating registries as required.

All statistical analyses were conducted using SAS software (version 9.4, SAS Institute, Cary, NC). All *P* values were 2-sided, and a *P* less than .005 was considered statistically significant given multiple hypothesis testing. Our primary hypothesis testing was an assessment of heterogeneity in the associations of coffee intake with incidence of CRC classified by each T-cell subset. All other assessments were secondary analyses. Leveraging covariate data of 3161 CRC cases, the inverse probability weighting method was integrated into the Cox proportional hazards model (10) to control for selection bias due to tissue availability and potential confounders. The Cox model was used with stratification by age, sex (ie, cohort), and calendar year of the current questionnaire cycle. We also included the covariates described in the footnote to Table 2. The assumption of proportionality of hazards was verified by including an interaction term between coffee intake and follow-up time. To test whether strength of the coffee-CRC association might differ across the ordinal subtypes, we used the meta-regression method with a subtype-specific random effect term (11).

Table 1 shows age-standardized characteristics of participants according to coffee intake in the NHS and the HPFS. During follow-up of 133 924 participants (3 585 019

**Table 2.** Incidence of CRC, overall and by intraepithelial and stroma T-cell subset density, according to coffee intake in the combined cohorts of the NHS (1980-2012) and HPFS (1986-2012)

| Characteristics | Coffee intake, cups/d | | | | $P_{trend}$[a] | $P_{heterogeneity}$[b] |
|---|---|---|---|---|---|---|
| | 0 | <1 | 1-3 | ≥3 | | |
| Overall | | | | | | |
| Person-years | 402 273 | 604 468 | 1 712 111 | 866 168 | | |
| Cases (n = 3161), No. | 269 | 579 | 1621 | 692 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.08 (0.94 to 1.26) | 1.08 (0.94 to 1.23) | 0.99 (0.89 to 1.15) | .22 | |
| Intraepithelial | | | | | | |
| $CD3^+CD4^+FOXP3^+$ cells | | | | | | |
| Low density (n = 625), No. | 48 | 110 | 328 | 139 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.23 (0.87 to 1.73) | 1.26 (0.93 to 1.72) | 1.11 (0.79 to 1.55) | .68 | .39 |
| Intermediate density (n = 142), No. | 11 | 18 | 79 | 34 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.79 (0.38 to 1.63) | 1.29 (0.70 to 2.36) | 1.05 (0.54 to 2.04) | .50 | |
| High density (n = 141), No. | 17 | 26 | 71 | 27 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.68 (0.37 to 1.26) | 0.62 (0.36 to 1.07) | 0.53 (0.29 to 0.98) | .099 | |
| $CD3^+CD4^+CD45RO^+$ cells | | | | | | |
| Low density (n = 302), No. | 28 | 48 | 161 | 65 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.04 (0.65 to 1.67) | 1.11 (0.74 to 1.67) | 0.92 (0.58 to 1.44) | .94 | .71 |
| Intermediate density (n = 305), No. | 27 | 51 | 159 | 68 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.92 (0.58 to 1.45) | 1.06 (0.71 to 1.60) | 0.91 (0.58 to 1.43) | .76 | |
| High density (n = 301), No. | 21 | 55 | 158 | 67 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.16 (0.70 to 1.92) | 1.17 (0.74 to 1.86) | 1.07 (0.65 to 1.76) | .81 | |
| $CD3^+CD4^+CD45RO^-$ cells | | | | | | |
| Low density (n = 514), No. | 41 | 94 | 264 | 115 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.22 (0.85 to 1.77) | 1.17 (0.84 to 1.63) | 1.05 (0.73 to 1.52) | .47 | .72 |
| Intermediate density (n = 197), No. | 16 | 21 | 115 | 45 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.69 (0.36 to 1.30) | 1.38 (0.83 to 2.31) | 1.06 (0.60 to 1.87) | .31 | |
| High density (n = 197), No. | 19 | 39 | 99 | 40 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.92 (0.53 to 1.60) | 0.80 (0.49 to 1.32) | 0.71 (0.41 to 1.23) | .17 | |
| $CD3^+CD8^+CD45RO^+$ cells | | | | | | |
| Low density (n = 423), No. | 37 | 87 | 206 | 93 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.26 (0.86 to 1.86) | 1.06 (0.74 to 1.51) | 0.96 (0.65 to 1.42) | .15 | .39 |
| Intermediate density (n = 242), No. | 20 | 25 | 144 | 53 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.62 (0.35 to 1.12) | 1.26 (0.80 to 2.00) | 0.96 (0.57 to 1.59) | .39 | |
| High density (n = 243), No. | 19 | 42 | 128 | 54 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.03 (0.59 to 1.77) | 1.06 (0.65 to 1.73) | 0.97 (0.57 to 1.66) | .77 | |
| $CD3^+CD8^+CD45RO^-$ cells | | | | | | |
| Low density (n = 571), No. | 43 | 107 | 295 | 126 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.29 (0.90 to 1.84) | 1.29 (0.93 to 1.79) | 1.11 (0.78 to 1.58) | .55 | .51 |
| Intermediate density (n = 168), No. | 20 | 28 | 88 | 32 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.71 (0.40 to 1.26) | 0.72 (0.44 to 1.16) | 0.59 (0.34 to 1.03) | .16 | |
| High density (n = 169), No. | 13 | 19 | 95 | 42 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.72 (0.35 to 1.48) | 1.15 (0.63 to 2.09) | 1.04 (0.55 to 1.99) | .42 | |
| Stroma | | | | | | |
| $CD3^+CD4^+FOXP3^+$ cells | | | | | | |
| Low density (n = 485), No. | 43 | 81 | 253 | 108 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.00 (0.69 to 1.45) | 1.07 (0.77 to 1.49) | 0.91 (0.63 to 1.30) | .38 | .80 |
| Intermediate density (n = 211), No. | 14 | 34 | 111 | 52 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.18 (0.63 to 2.19) | 1.40 (0.80 to 2.45) | 1.39 (0.77 to 2.53) | .29 | |
| High density (n = 211), No. | 19 | 39 | 113 | 40 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.99 (0.57 to 1.72) | 0.98 (0.60 to 1.60) | 0.77 (0.44 to 1.33) | .19 | |
| $CD3^+CD4^+CD45RO^+$ cells | | | | | | |
| Low density (n = 302), No. | 26 | 52 | 148 | 76 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.10 (0.68 to 1.77) | 1.03 (0.68 to 1.57) | 1.08 (0.69 to 1.71) | .93 | .51 |
| Intermediate density (n = 304), No. | 28 | 47 | 167 | 62 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.86 (0.54 to 1.37) | 1.10 (0.73 to 1.64) | 0.85 (0.54 to 1.34) | .62 | |
| High density (n=301), No. | 22 | 55 | 162 | 62 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.17 (0.71 to 1.92) | 1.22 (0.77 to 1.91) | 0.97 (0.59 to 1.59) | .38 | |

(continued)

**Table 2.** (continued)

| Characteristics | Coffee intake, cups/d | | | | $P_{trend}$[a] | $P_{heterogeneity}$[b] |
|---|---|---|---|---|---|---|
| | 0 | <1 | 1-3 | ≥3 | | |
| $CD3^+CD4^+CD45RO^-$ cells | | | | | | |
| Low density (n = 365), No. | 31 | 64 | 190 | 80 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.04 (0.68 to 1.59) | 1.06 (0.73 to 1.55) | 0.92 (0.60 to 1.39) | .41 | .74 |
| Intermediate density (n = 270), No. | 22 | 37 | 146 | 65 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.86 (0.50 to 1.46) | 1.21 (0.77 to 1.91) | 1.11 (0.68 to 1.83) | .33 | |
| High density (n = 272), No. | 23 | 53 | 141 | 55 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.19 (0.73 to 1.95) | 1.09 (0.69 to 1.70) | 0.88 (0.54 to 1.45) | .18 | |
| $CD3^+CD8^+CD45RO^+$ cells | | | | | | |
| Low density (n = 383), No. | 32 | 74 | 185 | 92 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.30 (0.85 to 1.97) | 1.11 (0.76 to 1.63) | 1.06 (0.70 to 1.60) | .42 | .75 |
| Intermediate density (n = 262), No. | 18 | 40 | 147 | 57 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.04 (0.59 to 1.82) | 1.45 (0.88 to 2.37) | 1.28 (0.75 to 2.18) | .28 | |
| High density (n = 262), No. | 26 | 40 | 145 | 51 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.75 (0.46 to 1.21) | 0.90 (0.59 to 1.37) | 0.67 (0.42 to 1.08) | .19 | |
| $CD3^+CD8^+CD45RO^-$ cells | | | | | | |
| Low density (n = 503), No. | 37 | 94 | 254 | 118 | | |
| HR (95% CI)[c] | 1 (Referent) | 1.35 (0.92 to 1.99) | 1.29 (0.91 to 1.83) | 1.20 (0.82 to 1.76) | .83 | .94 |
| Intermediate density (n = 202), No. | 19 | 32 | 121 | 30 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.80 (0.46 to 1.39) | 1.05 (0.65 to 1.70) | 0.58 (0.33 to 1.03) | .070 | |
| High density (n = 202), No. | 20 | 28 | 102 | 52 | | |
| HR (95% CI)[c] | 1 (Referent) | 0.70 (0.40 to 1.24) | 0.86 (0.53 to 1.41) | 0.89 (0.53 to 1.51) | .69 | |

[a]Trend test was performed using the median intake of each category. CI = confidence interval; CRC = colorectal cancer; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; METS = metabolic equivalent task score; NHS = Nurses' Health Study.

[b]The meta-regression method with a subtype-specific random effect term was used to evaluate the heterogeneity.

[c]Cox proportional hazards model was used with stratification by age, sex (ie, cohort), and calendar year of current questionnaire cycle. We additionally adjusted for family history of CRC, history of diabetes, history of endoscopy, pack-years of smoking (0, 0 to <5, 5 to <20, 20 to <40, and ≥40), body mass index (quartiles), physical activity (METS, quartiles), multivitamin use, regular use of aspirin, regular use of nonsteroidal antiinflammatory drugs, alcohol consumption (0 to <5, 5 to <15, 15 to <30, ≥30 g/d), total calorie intake (quartiles), total red meat intake (quartiles), folate intake (quartiles), calcium intake (quartiles), and Alternative Healthy Eating Index (quartiles). For women, we further adjusted for menopause status and menopausal hormone therapy (premenopause vs postmenopause with never, past, or current use of menopausal hormone therapy).

person-years), we documented 3161 CRC cases, including 908 CRC cases with available data on T-cell densities in tumor tissue.

Table 2 shows hazard ratios for incidence of CRC overall and by intraepithelial and stromal T-cell subset in relation to coffee intake. We did not observe a statistically significant association between coffee intake and overall CRC incidence. Furthermore, the association of coffee intake with CRC incidence did not statistically significantly differ by intraepithelial or stroma T-cell subset ($P_{interaction} > .38$). Supplementary Table 1 (available online) shows CRC by intraepithelial and stromal T-cell subset, according to coffee intake.

Evidence indicates that certain modifiable factors may influence the immune system and reduce CRC incidence, thereby suggesting their antitumor effects through immunomodulation (12,13). In fact, epidemiological studies showed that the inverse association of marine omega-3 polyunsaturated fatty acids intake with CRC incidence was stronger for tumors containing a higher density of $FOXP3^+$ cells (14) and that the association of cigarette smoking with CRC risk was stronger for tumors containing a higher density of $CD3^+$ cells (7). However, the current study does not support the hypothesis that coffee may modify CRC incidence through its effect on T cells. One of the limitations of this study is modest statistical power. With the sample size of 908 cases and 80% power, the maximum detectable ratio of hazard ratio (ie, a test for heterogeneity) is 0.66. Therefore, it is possible that we were not able to detect smaller effects than this number. Considering the importance of cancer immunology and the paucity of immuno-epidemiological studies (12,13,15), additional efforts are needed to study the relationships of modifiable factors with incidence CRC classified by various types of immune cells.

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**Author contributions:** T.U., K.H., J.A.N., and S.O.: developed the main concept and designed the study. C.S.F., M.G., J.A.N., and S.O.: wrote grant applications. T.U., K.H., J.P.V., R.Z., J.B., K.F., M.C.L., M.Z., N.A., T.C., J.K., K.A., S.S., S.G., C.S.F., J.A.N., and S.O.: were responsible for collection of tumor tissue, and acquisition of epidemiologic, clinical and tumor tissue data, including histopathological, immunohistochemical, and immunofluorescent characteristics. T.U., K.H., and S.O.: performed data analysis and interpretation. T.U., K.H., and S.O.: drafted the manuscript. All authors contributed to editing and critical revision for important intellectual contents.

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**Use of Standardized Official Symbols**: We use HUGO (Human Genome Organisation)-approved official symbols (or root symbols) for genes and gene products, including CD3, CD4, CD8, FOXP3, PTPRC; all of which are described at www.genenames.org. Gene symbols are italicized, whereas symbols for gene products are not italicized.

## Data Availability

The data underlying this article cannot be shared publicly. Further information including the procedures to obtain and access data from the Nurses' Health Studies and Health Professionals Follow-up Study is described at https://www.nurseshealthstudy.org/researchers (contact email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

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