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Coffee Intake of Colorectal Cancer Patients and Prognosis According to Histopathologic Lymphocytic Reaction and T-Cell Infiltrates

Tomotaka Ugai^{1,2}, Koichiro Haruki¹, Juha P. Väyrynen^{1,3,4}, Jennifer Borowsky⁵, Kenji Fujiyoshi¹, Mai Chan Lau¹, Naohiko Akimoto¹, Rong Zhong^{1,2}, Junko Kishikawa¹, Kota Arima¹, Shan-shan Shi¹, Melissa Zhao¹, Charles S. Fuchs^{6,7,8}, Xuehong Zhang^{9,10}, Marios Giannakis^{3,11,12}, Mingyang Song^{9,13,14}, Hongmei Nan^{15,16}, Jeffrey A. Meyerhardt³, Molin Wang^{2,10,17}, Jonathan A. Nowak¹, Shuji Ogino^{1,2,11,18}

¹Program in MPE Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA

²Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

³Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA

⁴Cancer and Translational Medicine Research Unit, Medical Research Center Oulu, Oulu University Hospital, and University of Oulu, Oulu, Finland

⁵Conjoint Gastroenterology Department, QIMR Berghofer Medical Research Institute, Queensland, Australia

⁶Yale Cancer Center, New Haven, CT, USA

⁷Department of Medicine, Yale School of Medicine, New Haven, CT, USA

⁸Smilow Cancer Hospital, New Haven, CT, USA

⁹Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

¹⁰Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Co-corresponding authors Tomotaka Ugai, MD, PhD, Program in MPE Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Ave. EBRC Room 404, Boston, MA, 02115, USA, Tel: 617-525-4304, tugai@bwh.harvard.edu; Shuji Ogino, MD, PhD, MS, Program in MPE Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Ave. EBRC Room 404A, Boston, MA, 02115, USA, Tel: 617-525-8953, sogino@bwh.harvard.edu. T.U., K.H., J.P.V., and J.B. contributed equally as co-first authors. J.A.M., M.W., J.A.N., and S.O. contributed equally as co-last authors.

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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.

¹¹Broad Institute of MIT and Harvard, Cambridge, MA, USA

¹²Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

¹³Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

¹⁴Division of Gastroenterology, Massachusetts General Hospital, Boston, MA, USA

¹⁵Department of Global Health, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA

¹⁶Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA

¹⁷Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA

¹⁸Cancer Immunology and Cancer Epidemiology Programs, Dana-Farber Harvard Cancer Center; Boston, MA, USA.

Abstract

Given previous biological evidence of immunomodulatory effects of coffee, we hypothesized that the association between coffee intake of colorectal cancer patients and survival differs by immune responses. Using a molecular pathological epidemiology database of 4,465 incident colorectal cancer cases, including 1,262 cases with molecular data, in the Nurses' Health Study and the Health Professionals Follow-up Study, we examined the association between coffee intake of colorectal cancer patients and survival in strata of levels of histopathologic lymphocytic reaction and T-cell infiltrates in tumor tissue. We did not observe a significant association of coffee intake with colorectal cancer-specific mortality [multivariable-adjusted hazard ratio (HR) for one cup increase of coffee intake per day, 0.93; 95% confidence interval (CI), 0.84-1.03]. Although statistical significance was not reached at the stringent level ($\alpha=0.005$), the association of coffee intake with colorectal cancer-specific mortality differed by Crohn's-like lymphoid reaction ($P_{\text{interaction}}=.007$). Coffee intake was associated with lower colorectal cancer-specific mortality in patients with high Crohn's-like reaction (multivariable HR for one cup increase of coffee intake per day, 0.55; 95% CI, 0.37–0.81; $P_{\text{trend}}=.002$), but not in patients with intermediate Crohn's-like reaction (the corresponding HR, 1.02; 95% CI, 0.72–1.44) or negative/low Crohn's-like reaction (the corresponding HR, 0.95; 95% CI, 0.83–1.07). The associations of coffee intake with colorectal cancer-specific mortality did not significantly differ by levels of other lymphocytic reaction or any T-cell subset ($P_{\text{interaction}}>.18$). There is suggestive evidence for differential prognostic effects of coffee intake by Crohn's-like lymphoid reaction in colorectal cancer.

Keywords

colorectal neoplasms; beverage; immunofluorescence; tumor microenvironment

INTRODUCTION

The biological importance of the immune system in colorectal cancer is well supported by previous studies.¹ For example, a high-level immune response featuring cytotoxic and memory T-cells in colorectal cancer has been associated with better patient survival.² Evidence also suggests that certain dietary factors influence both the immune system and colorectal cancer mortality.^{3, 4} Therefore, elucidating the interplay between the immune system and modifying diet in colorectal cancer progression is of considerable importance, potentially contributing to the development of novel cancer treatment strategies.

Among dietary factors, coffee has been hypothesized to provide a positive prognostic effect against colorectal cancer mortality. Several studies recently reported a statistically significant association of higher coffee intake after colorectal cancer diagnosis with lower tumor recurrence and improved survival.^{5, 6} However, the mechanisms behind these associations remain to be elucidated. Coffee contains a complex mixture of bioactive compounds,⁷ some of which, including polyphenols and caffeine, have been suggested to influence adaptive immune responses.⁷⁻⁹ Colorectal cancers are heterogeneous tumors with complex interactions between neoplastic and immune cells in the tumor microenvironment,¹⁰ potentially influenced by the immunomodulatory effects of coffee. However, no study has yet examined the effect of coffee on colorectal cancer survival according to immune responses in cancer tissue.

We therefore tested our hypothesis that the association between coffee intake of colorectal cancer patients and survival differs by histopathologic lymphocytic reaction and T-cell infiltrates in colorectal cancer tissue. To test our hypothesis, we used a database of 4,465 incident colorectal cancer cases, including 1,262 cases with available data on coffee intake and tumor molecular markers from two large prospective cohort studies in the US.

PATIENTS AND METHODS

Study Population

We utilized data from two large US prospective cohort studies, the Nurses' Health Study (NHS, 121,701 women aged 30-55 years followed since 1976) and the Health Professionals Follow-up Study (HPFS, 51,529 men aged 40 to 75 years followed since 1986). Study participants were sent follow-up questionnaires every two years to update information on their demographic and lifestyle factors, medical history, and newly diagnosed diseases including colorectal cancer. The follow-up rate has been over 90% for each questionnaire cycle in these two cohorts. The National Death Index was used to confirm deaths of study participants and identify patients with unreported lethal colorectal cancer.

We documented 4,465 colorectal cancer cases in the two cohort studies through 2012, including 1,262 colorectal cancer cases with available data on coffee intake and immune responses. Patients were followed until death or end of follow-up (June 1, 2016 for the NHS; January 1, 2016 for the HPFS), whichever came first. Participating physicians, blinded to exposure data, reviewed medical records of colorectal cancer patients to collect data on tumor characteristics and to identify causes of death for deceased patients.

Informed consent was obtained from all study participants at study enrolment. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, MA, USA), and those of participating registries as required.

Assessment of Coffee Intake and Other Covariates

To assess dietary intake, food frequency questionnaires (FFQs) were initially collected in 1980 for NHS and in 1986 for HPFS. For the NHS, a 61-item semi-quantitative FFQ was used at baseline,¹¹ which was expanded to approximately 130 food and beverage items in 1984, 1986, and every four years thereafter. For the HPFS cohort, baseline dietary intake was assessed with a 131-item FFQ that was also used for updates generally every four years thereafter.¹² 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 nine possible responses, ranging from (almost) never to 6 times per day. In addition, questionnaires were sent every two years to collect data on lifestyle factors, including smoking status, body weight, and physical activity. Data on coffee intake and other covariates in colorectal cancer patients were obtained from the first questionnaire returned between 6 and 48 months after colorectal cancer diagnosis. Data on prediagnostic coffee intake were obtained from the last questionnaire prior to colorectal cancer diagnosis.

Tumor Tissue Analyses

The details of tumor tissue analyses have been described.¹³⁻¹⁵ Briefly, we obtained formalin-fixed paraffin-embedded tumor tissue samples from hospitals throughout the U.S. where colorectal cancer patients underwent surgical resection. The study pathologist (S. Ogino), who was blinded to other data, reviewed hematoxylin and eosin-stained tissue sections, and recorded histopathological findings, including tumor differentiation and lymphocytic reactions. Each of lymphocytic reaction patterns (Crohn's-like lymphoid reaction, peritumoural lymphocytic reaction, intratumoural periglandular reaction, and tumor-infiltrating lymphocytes) was graded as negative/low, intermediate, and high (Figure).^{13, 15} The second pathologist (J.N. Glickman), who was unaware of other data, independently re-reviewed 398 selected cases, and a good inter-observer correlation was observed, as previously described.¹⁵

We also constructed tissue microarrays, including up to four tumor cores from each case.¹⁶ We simultaneously measured the expression of CD3, CD4, CD8, CD45RO (one isoform of PTPRC gene products), and FOXP3 in T cells within tumor epithelial and stromal regions in CRC tissue microarrays by a multiplex immunofluorescence assay,¹⁷ following recommendations of standardized protein nomenclature.¹⁸ For the Wald test, we used log-transformed T-cell density variables to improve normality.

Statistical Analysis

All statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC). All *P* values were two-sided, and a *P* < .005 was considered statistically significant given multiple hypothesis testing. Our primary hypothesis testing was statistical interaction (using the Wald test on the cross-product) between coffee intake of colorectal

cancer patients (cup/day, continuous) and each lymphocytic reaction (ordinal) in the Cox proportional hazards regression model for colorectal cancer-specific mortality analyses. We also assessed a statistical interaction between coffee intake of colorectal cancer patients and each T-cell density (log-transformed, continuous). All other analyses were secondary. We estimated hazard ratios (HRs) for one cup increase of coffee per day in strata of levels of lymphocytic reactions or T-cell subsets using a re-parameterization of the interaction term in a single regression model.¹⁹ Survival time was defined as the period from return of the first questionnaire after colorectal cancer diagnosis to death or the end of follow-up whichever came first.

We applied an inverse probability weighting (IPW) method to reduce selection bias due to the availability of questionnaire data after colorectal cancer diagnosis.²⁰ Multivariable Cox proportional hazards models initially included covariates described in the footnote to Table 2. A backward stepwise elimination procedure was performed with a threshold of $P = 0.05$ to select variables for the final models (Supplementary Table 1). To limit degrees of freedom of the models, the cases with missing data on categorical variables were included in the majority category. For cases with missing data on continuous variables, we substituted the mean value and included a separate indicator variable in the model. It was confirmed that no substantial alteration occurred in results when we excluded cases with missing information in any of the covariates. The proportionality of hazards assumption was generally satisfied using the assessment of the cross-product of coffee intake of colorectal cancer patients and survival time in strata of each lymphocytic reaction component and T cell subset ($P > .24$).

RESULTS

We included 1,262 colorectal cancer cases with available data on coffee intake and immune responses. Table 1 summarizes the clinical, pathological, and molecular characteristics of colorectal cancer cases according to coffee intake of colorectal cancer patients. During the median follow-up time of 10 years (interquartile range, 5.6 to 16 years), there were 237 colorectal cancer-specific deaths.

Table 2 shows colorectal cancer survival according to coffee intake in strata of each lymphocytic reaction pattern and T-cell subset. In this molecular pathological epidemiology database, we did not observe a significant association of coffee intake with colorectal cancer-specific mortality [multivariable-adjusted HR for one cup increase of coffee intake per day, 0.93; 95% confidence interval (CI), 0.84-1.03].

In our primary hypothesis testing, although statistical significance was not reached at the stringent level ($\alpha = 0.005$), the association of coffee intake with colorectal cancer-specific mortality differed by Crohn's-like lymphoid reaction ($P_{\text{interaction}} = .007$). Coffee intake was associated with lower colorectal cancer-specific mortality in patients with high Crohn's-like reaction (multivariable HR for one cup increase of coffee intake per day, 0.55; 95% CI, 0.37-0.81; $P_{\text{trend}} = .002$), but not in patients with intermediate Crohn's-like reaction (the corresponding HR, 1.02; 95% CI, 0.72-1.44) or negative/low Crohn's-like reaction (the corresponding HR, 0.95; 95% CI, 0.83-1.07). The associations of coffee intake with colorectal cancer-specific mortality did not significantly differ by levels of other

lymphocytic reaction (peritumoral lymphocytic reaction, intratumoral periglandular reaction, or tumor-infiltrating lymphocytes) or any T-cell subset ($P_{\text{interaction}} > .18$).

We also confirmed that results of Cox regression analyses without IPW (Supplementary Table 2) were similar to those with IPW. Lastly, considering possible effects of cancer treatment on coffee intake of colorectal cancer patients, we conducted a sensitivity analysis using questionnaire data between 12 and 48 months after colorectal cancer diagnosis. We confirmed that the results did not change substantially (Supplementary Table 3).

DISCUSSION

We conducted this study to test the hypothesis that the association of coffee intake of colorectal cancer patients and survival differs by histopathologic lymphocytic reaction and T-cell infiltrates in tumor tissue. Our study has provided suggestive evidence for an interaction of coffee intake and Crohn's-like lymphoid reaction in the survival analysis. Coffee intake was associated with lower CRC-specific mortality only in CRC with high-level Crohn's-like reaction.

Current evidence indicates that certain modifiable lifestyle factors may influence the immune system and reduce colorectal cancer mortality.^{21, 22} Previous epidemiological studies showed that the inverse association of physical activity after colorectal cancer diagnosis with colorectal cancer mortality was stronger for tumors containing a higher density of CD3⁺ cells,²³ and that the association of vitamin D score after colorectal cancer diagnosis with colorectal cancer mortality was stronger for tumors with lower peritumoral lymphocytic reaction.⁴ Coffee intake has also been suggested to be one of immunomodulatory lifestyle factors.^{7, 8}

Crohn's-like lymphoid reaction is a specific lymphocytic reaction pattern of transmural lymphoid aggregates exhibited by a subset of colorectal tumors.^{13, 15} These lymphoid follicles represent important sites for antigen presentation and lymphocyte proliferation and differentiation.²⁴ They have been associated with improved survival in multiple tumor types, including colorectal cancer,^{13, 24} and have attracted interest as a potential marker for immunotherapy response.²⁵ Our results suggest that coffee intake of colorectal cancer patients may affect the tumor-immune interaction differentially by the degree of Crohn's-like lymphoid reaction, although our results must be replicated by independent studies. Further efforts are needed to clarify the complex relationships of coffee intake with colorectal cancer mortality classified by various types of immune cells.

The current study has several limitations. First, detailed cancer treatment information was not available. However, treatment strategies would not have been influenced by lymphocytic reactions. Second, cancer recurrence data were unavailable, but colorectal cancer-specific mortality was considered a reasonable endpoint, considering the long follow-up duration of censored cases. Third, we used questionnaire data reported 6-48 months after cancer diagnosis to minimize the effect of active cancer treatment, but we acknowledge that 6-48 months after cancer diagnosis is a broad range of time periods. More specific time periods should be considered in future clinical trials or observational studies. In addition, to address

selection bias due to availability of questionnaire data after colorectal cancer diagnosis, we used the inverse probability weighting (IPW) method.²⁰ Fourth, with a sample size of 237 events and 80% power, the minimum detectable HR is 1.44. Therefore, it is possible that we were unable to detect smaller effects.

CONCLUSION

There is suggestive evidence for differential effects of coffee intake on the mortality of colorectal cancer patients subclassified by Crohn's-like lymphoid reaction. It is possible that coffee intake might be beneficial for colorectal cancer patients with high-level Crohn's-like reaction. Additional efforts are needed to replicate our findings and elucidate mechanisms of coffee in influencing colorectal cancer outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CI	confidence interval
FFQ	food frequency questionnaires
HPFS	Health Professionals Follow-up Study
HR	hazard ratio

IPW	inverse probability weighting
NHS	Nurses' Health Study

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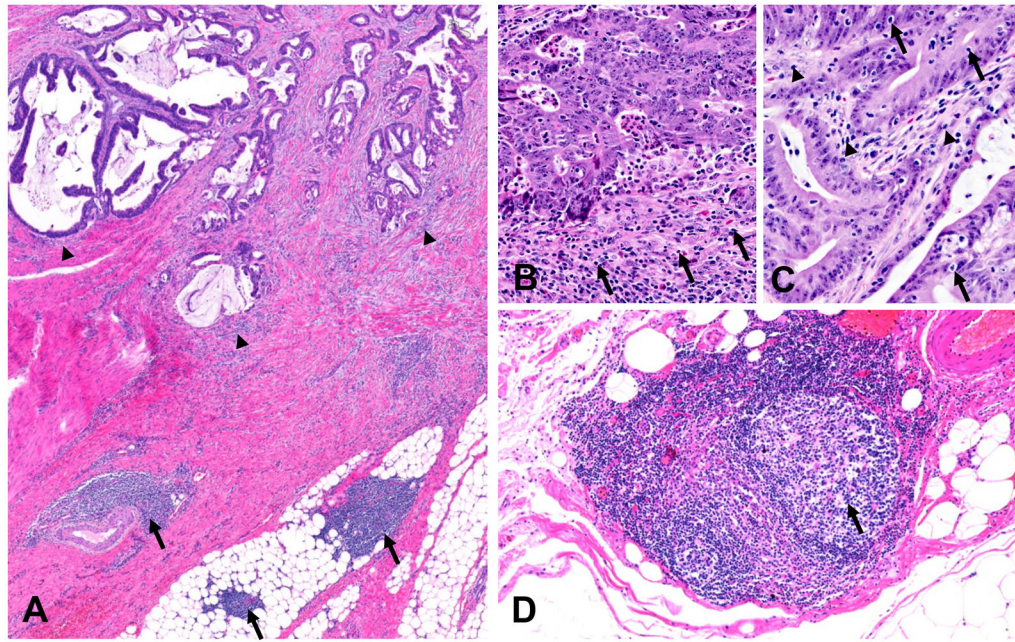


Figure.

The four lymphocytic reaction patterns in colorectal cancer. (A) Low-power view showing peritumoral lymphocytic reaction (arrowheads) and Crohn's-like lymphoid reaction (arrows). (B-C) Higher-power views from the invasive front (B) and tumor center (C) showing peritumoral lymphocytic reaction (B: arrows), intratumoral periglandular lymphocytic reaction (C: arrowheads), and tumor-infiltrating lymphocytes (C: arrows). (D) Higher-power view showing a lymphoid follicle with germinal center (arrow) involved in the Crohn's-like lymphoid reaction.

Table 1. Clinical, pathological, and molecular characteristics of colorectal cancer cases according to coffee intake

Characteristic ^b	All cases (N=1,262)	0 cups/day (N=225)	≤1 cups/day (N=444)	1-3 cups/day (N=452)	≥3 cups/day (N=141)
Coffee intake of colorectal cancer patients (cup/d) (median, range)	1.0 (0-10.5)	0	1.0 (0.1-1.0)	2.5 (1.1-2.9)	4.5 (3.3-11)
Prediagnostic coffee intake (cup/d) (median, range)	1.2 (0-10.5)	0 (0-6.0)	1.0 (0-7.0)	2.5 (0-6.0)	4.5 (0-11)
Sex					
Female (NHS)	720 (57%)	122 (54%)	247 (56%)	268 (59%)	83 (59%)
Male (HPFS)	542 (43%)	103 (46%)	197 (44%)	184 (41%)	58 (41%)
Age (years)	69 ± 9.0	69 ± 9.6	70 ± 8.9	69 ± 8.9	68 ± 8.1
Year of diagnosis	434 (34%)	56 (25%)	132 (30%)	170 (37%)	76 (54%)
1995 or before					
1996-2000	359 (28%)	61 (27%)	134 (30%)	134 (29%)	30 (21%)
2001 or after	449 (37%)	108 (48%)	178 (40%)	148 (33%)	35 (24%)
Body mass index (kg/m ²) (mean, SD)	26 ± 4.5	27 ± 4.7	26 ± 4.5	26 ± 4.4	26 ± 4.1
Physical activity (METS-h/week) (median, IQR)	10 (3.0-28)	8.6 (2.6-24)	9.3 (3.3-26)	12 (3.0-34)	11 (3.7-21)
Pack-year of smoking (median, IQR)	6.0 (0-29.0)	0 (0-15.0)	2.0 (0-21.0)	12 (0-33.0)	20.0 (0-43.0)
Alcohol intake (g/d) (median, IQR)	2.0 (0-12.0)	0 (0-3.6)	2.0 (0-9.9)	3.0 (0-14.3)	4.1 (0-15.9)
Regular aspirin use (%)	463 (36%)	82 (36%)	166 (38%)	165 (37%)	50 (35%)
Total fat intake (g/d) (median, IQR)	59 (49-69)	59 (51-70)	58 (48-67)	59 (48-70)	60 (50-68)
Folate intake (mcg/d) (median, IQR)	625 (389-866)	659 (422-853)	621 (394-930)	633 (378-826)	566 (377-817)
Calcium intake (mg/d) (median, IQR)	994 (714-1,459)	994 (679-1,563)	994 (710-1,447)	998 (716-1,447)	974 (741-1,379)
Vitamin D intake (IU/d) (median, IQR)	455 (211-678)	486 (198-687)	438 (219-679)	469 (222-673)	402 (184-663)
Family history of colorectal cancer in first-degree relative(s)	1010 (80%)	187 (83%)	351 (79%)	357 (79%)	115 (82%)
Absent					
Present	250 (20%)	38 (17%)	93 (21%)	93 (21%)	26 (18%)
Tumor location	214 (17%)	53 (24%)	79 (18%)	69 (15%)	13 (9%)
Cecum					
Ascending to transverse	374 (30%)	63 (28%)	125 (28%)	139 (31%)	47 (33%)
Descending to sigmoid	389 (31%)	61 (27%)	139 (31%)	141 (31%)	48 (34%)
Rectum	282 (22%)	48 (21%)	99 (22%)	102 (23%)	33 (23%)
Tumor differentiation	1150 (92%)	204 (91%)	416 (94%)	409 (91%)	121 (88%)
Well to moderate					
Poor	102 (8.2%)	20 (9.0%)	27 (6.1%)	38 (8.5%)	17 (12%)
AJCC disease stage	345 (30%)	61 (30%)	128 (31%)	119 (28%)	37 (28%)
I					

Characteristic ^b	All cases (N=1,262)	0 cups/day (N=225)	≤1 cups/day (N=444)	1-3 cups/day (N=452)	≥3 cups/day (N=141)
II	415 (36%)	72 (35%)	141 (35%)	152 (37%)	50 (38%)
III	327 (28%)	55 (27%)	115 (28%)	120 (29%)	37 (28%)
IV	71 (6.1%)	15 (7.4%)	25 (6.1%)	25 (6.0%)	6 (4.6%)
MSI status	918 (82%)	158 (78%)	321 (84%)	336 (83%)	103 (84%)
MSI-high	195 (18%)	44 (22%)	63 (16%)	69 (17%)	19 (16%)
CIMP status	875 (82%)	151 (79%)	304 (83%)	323 (83%)	97 (81%)
Low/negative	195 (18%)	41 (22%)	64 (17%)	67 (17%)	23 (19%)
High	64 ± 10	65 ± 10	64 ± 10	64 ± 10	63 ± 10
LINE-1 methylation level (mean, SD)					
KRAS mutation	621 (59%)	113 (60%)	221 (61%)	215 (56%)	72 (59%)
Wild-type	443 (42%)	78 (41%)	144 (40%)	170 (44%)	51 (42%)
Mutant	967 (86%)	171 (82%)	340 (88%)	351 (86%)	105 (84%)
BRAF mutation	157 (14%)	35 (18%)	47 (12%)	55 (14%)	20 (16%)
Mutant	874 (84%)	157 (82%)	303 (83%)	312 (84%)	102 (86%)
Wild-type	173 (16%)	35 (18%)	62 (17%)	60 (16%)	16 (14%)
PIK3CA mutation	757 (73%)	136 (75%)	270 (73%)	265 (71%)	86 (73%)
Negative/low	196 (19%)	29 (16%)	75 (20%)	71 (19%)	21 (18%)
Intermediate	87 (8.4%)	16 (8.8%)	24 (6.5%)	35 (9.4%)	12 (10%)
High	143 (11%)	31 (14%)	49 (11%)	54 (12%)	9 (6.4%)
Peritumoral lymphocytic reaction	890 (71%)	152 (68%)	311 (71%)	325 (72%)	102 (72%)
Intermediate	222 (18%)	40 (18%)	80 (18%)	72 (16%)	30 (21%)
High	143 (11%)	32 (14%)	47 (10%)	55 (12%)	9 (6.4%)
Intratumoral periglandular reaction	933 (74%)	161 (71%)	330 (74%)	338 (75%)	104 (74%)
Intermediate	184 (15%)	32 (14%)	66 (15%)	58 (13%)	28 (20%)
High	924 (73%)	165 (73%)	332 (75%)	332 (74%)	95 (67%)
Tumor-infiltrating lymphocytes	197 (16%)	34 (15%)	65 (15%)	69 (15%)	29 (21%)
Intermediate	138 (11%)	26 (12%)	46 (10%)	49 (11%)	17 (12%)
High					

^a Abbreviations: AJCC, American Joint Committee on Cancer; CIMP, CpG island methylator phenotype; HPFS, Health Professionals Follow-up Study; LINE-1, long-interspersed nucleotide element-1; METS, metabolic equivalent task score; MSI, microsatellite instability; NHS, Nurses' Health Study; SD, standard deviation; IQR, interquartile range.

^b Continuous variables are shown as mean (SD) or median (IQR or range). Percentage (%) indicates the proportion of cases with a specific clinical or pathological characteristic in all cases or in strata of coffee intake of colorectal cancer patients.

Colorectal cancer-specific mortality according to coffee intake in strata of lymphocytic reaction patterns and T-cell subsets

Table 2.

		Colorectal cancer-specific mortality		
		HR for one cup increase of coffee per day ^a		
No. of Cases	No. of Events	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI) ^b	
All colorectal cancer cases	1262	237	1.01 (0.92-1.11)	0.93 (0.84-1.03)
Lymphocytic reaction				
Crohn's-like lymphoid reaction				
Negative/low	757	168	1.00 (0.89-1.12)	0.95 (0.83-1.07)
Intermediate	196	25	1.12 (0.81-1.57)	1.02 (0.72-1.44)
High	87	7	0.69 (0.45-1.06)	0.55 (0.37-0.81)
<i>P</i> _{interaction} ^c			.088	.007
Peritumoral lymphocytic reaction				
Negative/low	143	45	0.91 (0.72-1.15)	0.92 (0.71-1.18)
Intermediate	880	173	1.06 (0.95-1.19)	0.98 (0.87-1.10)
High	222	17	0.94 (0.67-1.31)	0.81 (0.54-1.20)
<i>P</i> _{interaction} ^c			.63	.42
Intratumoral periglandular reaction				
Negative/low	143	41	0.94 (0.74-1.20)	0.87 (0.66-1.13)
Intermediate	933	180	1.04 (0.93-1.16)	0.96 (0.86-1.08)
High	184	15	1.06 (0.79-1.42)	0.95 (0.68-1.33)
<i>P</i> _{interaction} ^c			.77	.94
Tumor-infiltrating lymphocytes				
Negative/low	924	196	1.00 (0.90-1.11)	0.94 (0.84-1.04)
Intermediate	197	33	1.07 (0.80-1.42)	0.93 (0.70-1.23)
High	138	7	1.13 (0.80-1.58)	1.03 (0.71-1.52)
<i>P</i> _{interaction} ^c			.53	.66
T-cell subset				
CD3 ⁺ CD4 ⁺ FOXP3 ⁺ cell density				

Colorectal cancer-specific mortality					
HR for one cup increase of coffee per day ^a					
	No. of Cases	No. of Events	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI) ^b	
C1 (low)	376	86	1.00 (0.86-1.18)	0.94 (0.80-1.11)	
C2 (Intermediate)	202	33	1.11 (0.84-1.48)	1.03 (0.78-1.35)	
C3 (high)	202	30	0.90 (0.71-1.13)	0.87 (0.67-1.13)	
<i>P</i> _{interaction} ^c			.59		.72
CD3 ⁺ CD4 ⁺ CD45RO ⁺ cell density					
C1 (low)	260	57	1.03 (0.84-1.27)	0.92 (0.75-1.13)	
C2 (Intermediate)	260	54	1.00 (0.80-1.25)	0.95 (0.77-1.17)	
C3 (high)	260	38	1.00 (0.84-1.19)	1.05 (0.88-1.25)	
<i>P</i> _{interaction} ^c			.63		.74
CD3 ⁺ CD4 ⁺ CD45RO ⁻ cell density					
C1 (low)	264	51	1.04 (0.84-1.28)	1.00 (0.80-1.24)	
C2 (Intermediate)	258	57	1.04 (0.86-1.27)	0.92 (0.77-1.10)	
C3 (high)	258	41	0.91 (0.72-1.15)	0.91 (0.72-1.16)	
<i>P</i> _{interaction} ^c			.67		.87
CD3 ⁺ CD8 ⁺ CD45RO ⁺ cell density					
C1 (low)	260	55	1.05 (0.89-1.23)	1.01 (0.87-1.17)	
C2 (Intermediate)	260	61	1.02 (0.79-1.32)	0.96 (0.74-1.23)	
C3 (high)	260	33	0.88 (0.65-1.19)	0.90 (0.69-1.16)	
<i>P</i> _{interaction} ^c			.35		.73
CD3 ⁺ CD8 ⁺ CD45RO ⁻ cell density					
C1 (low)	356	67	1.06 (0.88-1.29)	1.02 (0.85-1.22)	
C2 (Intermediate)	212	51	1.21 (0.98-1.50)	1.10 (0.94-1.30)	
C3 (high)	212	31	0.73 (0.52-1.01)	0.74 (0.54-1.00)	
<i>P</i> _{interaction} ^c			.19		.27

^aCoffee intake of colorectal cancer patients was obtained from the first questionnaire returned between 6 and 48 months after diagnosis. The inverse probability weighting method was applied to reduce selection bias due to the availability of questionnaire data after cancer diagnosis.

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^bThe multivariable Cox regression model initially included sex, age, year of diagnosis, prediagnostic coffee intake, lifestyle factors after colorectal cancer diagnosis (physical activity, pack-year of smoking, alcohol intake, total fat intake, folate intake, calcium intake, vitamin D intake, and regular use of aspirin), family history of colorectal cancer, tumor location, tumor differentiation, disease stage, microsatellite instability, CpG island methylator phenotype, *KRAS*, *BRAF*, and *PIK3CA* mutations, and long-interspersed nucleotide element-1 methylation level. A backward elimination with a threshold of $P = 0.05$ was used to select variables for the final models. The variables that remained in the final models are described in Supplementary Table 1.

^c*P-interaction* was calculated using Wald test for the cross-product of coffee intake of colorectal cancer patients (continuous) and each lymphocytic reaction variables (ordinal) or each T-cell density (log-transformed, continuous) in the multivariable Cox regression model.