IMPORTANCE Several compounds found in coffee possess antioxidant, anti-inflammatory, and insulin-sensitizing effects, which may contribute to anticancer activity. Epidemiological studies have identified associations between increased coffee consumption and decreased recurrence and mortality of colorectal cancer. The association between coffee consumption and survival in patients with advanced or metastatic colorectal cancer is unknown.

OBJECTIVE To evaluate the association of coffee consumption with disease progression and death in patients with advanced or metastatic colorectal cancer.

DESIGN, SETTING, AND PARTICIPANTS This prospective observational cohort study included 1171 patients with previously untreated locally advanced or metastatic colorectal cancer who were enrolled in Cancer and Leukemia Group B (Alliance)/SWOG 80405, a completed phase 3 clinical trial comparing the addition of cetuximab and/or bevacizumab to standard chemotherapy. Patients reported dietary intake using a semiquantitative food frequency questionnaire at the time of enrollment. Data were collected from October 27, 2005, to January 18, 2018, and analyzed from May 1 to August 31, 2018.

EXPOSURES Consumption of total, decaffeinated, and caffeinated coffee measured in cups per day.

MAIN OUTCOMES AND MEASURES Overall survival (OS) and progression-free survival (PFS).

RESULTS Among the 1171 patients included in the analysis (694 men [59%]; median age, 59 [interquartile range, 51-67] years). The median follow-up time among living patients was 5.4 years (10th percentile, 1.3 years; IQR, 3.2-6.3 years). A total of 1092 patients (93%) had died or had disease progression. Increased consumption of coffee was associated with decreased risk of cancer progression (hazard ratio [HR] for 1-cup/d increment, 0.95; 95% CI, 0.91-1.00; P = .04 for trend) and death (HR for 1-cup/d increment, 0.93; 95% CI, 0.89-0.98; P = .004 for trend). Participants who consumed 2 to 3 cups of coffee per day had a multivariable HR for OS of 0.82 (95% CI, 0.67-1.00) and for PFS of 0.82 (95% CI, 0.68-0.99), compared with those who did not drink coffee. Participants who consumed at least 4 cups of coffee per day had a multivariable HR for OS of 0.64 (95% CI, 0.46-0.87) and for PFS of 0.78 (95% CI, 0.59-1.05). Significant associations were noted for both caffeinated and decaffeinated coffee.

CONCLUSIONS AND RELEVANCE Coffee consumption may be associated with reduced risk of disease progression and death in patients with advanced or metastatic colorectal cancer. Further research is warranted to elucidate underlying biological mechanisms.
Despite advances in treatment, colorectal cancer (CRC) remains a deadly disease in the United States.\(^1,2\) Abundant experimental and epidemiological data support a link between dietary and other lifestyle factors and the incidence and mortality of this disease.\(^3,4\) One such factor that has garnered increasing interest is the consumption of coffee, which possesses antineoplastic properties in the laboratory and may play a role in CRC development and progression. The potential for coffee to slow the growth of cancer may be related to coffee’s ability to decrease blood insulin levels by sensitizing tissues to the effects of insulin, because insulin-resistant states have been associated with worse CRC outcomes.\(^5,7\) Alternatively, coffee’s anticancer effects may be related to biologically active constituents of coffee that have been shown to have antioxidant, anti-inflammatory, and antiangiogenic effects.\(^8-11\)

Recent epidemiological studies found that higher coffee intake was associated with improved survival in patients with stage III CRC.\(^12,13\) However, the association between coffee consumption and survival of patients with metastatic CRC is unknown. A significant number of patients with CRC may ultimately develop metastatic disease, and treatment for this group is palliative, with a 5-year survival of 14%.\(^1,2\) Therefore, identifying novel treatment strategies to improve the outcomes of patients with metastatic CRC is of particular research and clinical importance. We conducted a prospective study evaluating the association of coffee consumption with overall survival (OS) and progression-free survival (PFS) in patients with advanced or metastatic CRC who were enrolled in a National Cancer Institute–sponsored, multi-institutional phase 3 randomized clinical trial of combined cytotoxic and biologic therapy. We hypothesized that increased coffee consumption is associated with longer survival in patients who were starting first-line chemotherapy for CRC.

**Methods**

**Study Participants**

The patients in this analysis were drawn from a cohort of participants enrolled in the completed phase 3 randomized clinical trial, Cancer and Leukemia Group B (CALGB; now a part of the Alliance for Clinical Trials in Oncology)/SWOG 80405. Eligible patients had pathologically confirmed, unresectable, locally advanced or metastatic CRC. The primary objective of the original clinical trial was to determine the optimal biologic therapy (cetuximab and/or bevacizumab) with a concurrent standard chemotherapy backbone, either leucovorin calcium, fluorouracil, and irinotecan hydrochloride (FOLFIRI) or leucovorin, fluorouracil, and oxaliplatin (mFOLFOX6) (investigator’s choice). Patients were required to have had no previous treatment for advanced or metastatic disease, no known concurrent cancers, adequate blood counts and organ function, good performance status, and no contraindications to bevacizumab or cetuximab treatment. When the trial was initiated, molecularly unselected participants were randomized in nonblinded fashion to cetuximab, bevacizumab, or both antibodies. Based on emerging clinical data on the detrimental effect of double antibodies in other trials\(^14,15\) and the effect of KRAS mutation status on anti–epidermal growth factor receptor antibody efficacy,\(^16\) the study was subsequently amended such that only patients with KRAS wild-type tumors were included, and, in a subsequent amendment, enrollment to the dual antibody arm was halted. Informed consent was obtained from all participants, and the trial was approved by the institutional review board of all participating sites. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

At the time of enrollment in the clinical trial, patients were given the option of inclusion in the diet and lifestyle companion study. Patients who consented to participate completed a diet and lifestyle survey within the first month of enrollment. Ultimately, 1561 (67%) patients consented to the companion study, of whom 1354 (87%) completed the questionnaire. Compared with others in the trial, patients who completed the questionnaire were more likely to be white, had better performance status, and were less likely to have indeterminate or missing KRAS status, but did not differ in other baseline characteristics.\(^17\)

Figure 1 shows the cohort’s derivation. Because the results of the CALGB (Alliance)/SWOG 80405 trial did not show a significant difference in OS or PFS between patients treated with cetuximab vs bevacizumab,\(^18\) all patients who completed the diet questionnaire were pooled into a prospective cohort for analysis of coffee intake. Participants were excluded if they reported aberrant caloric intake (<600 or >4200 kcal/d for men; <500 or >3500 kcal/d for women) or left blank any of the questions related to coffee intake. Participants were also excluded if they had cancer progression or death within 90 days of enrollment to avoid dietary assessment bias related to a decline in general health. Data were collected from October 27, 2005, to January 18, 2018.

**Assessment of Coffee Consumption**

Patients who consented completed a diet and lifestyle survey within the first month of enrollment, including a semiquantitative food frequency questionnaire that asked participants how often during the previous 3 months they consumed a specific food portion for 131 food items and vitamin/mineral supplements.\(^19,20\) The consumption of caffeinated coffee and

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**Key Points**

**Question** Is increased coffee consumption associated with improved survival in patients with advanced or metastatic colorectal cancer?

**Findings** In this cohort study of 1171 patients with advanced or metastatic colorectal cancer, increased coffee consumption at the time of study enrollment was associated with lower risk of disease progression and death. Significant associations were noted for both caffeinated and decaffeinated coffee.

**Meaning** Among patients with advanced or metastatic colorectal cancer, this study found increased coffee intake to be associated with lower risk of disease progression and death.
decaffeinated coffee was asked separately, with 10 possible responses ranging from never to at least 6 cups/d. The frequency of consumption was then converted into a continuous variable in cups per day using the following values for reported frequencies: 0 indicates never; 0.03, less than 1 cup/month; 0.07, 1 to 3 cups/month; 0.43, 2 to 4 cups/month; 0.79, 5 to 6 cups/month; 1.00, 1 cup/day; 2.50, 2 to 3 cups/day; 4.50, 4 to 5 cups/day; and 6.00, at least 6 cups/day. Total coffee consumption was calculated as the sum of caffeinated and decaffeinated coffee. Prespecified cutoffs were applied for total coffee intake (never or <1, 1, 2-3, or ≥4 cups/d), caffeinated coffee intake (never or <1, 1, 2-3, or ≥4 cups/d), and decaffeinated coffee intake (never or <1, 1, or ≥2 cups/d).

**Study End Points**
The primary end point was OS, defined as time from randomization to death due to any cause. Patients who were still alive were censored for OS at their last known follow-up. The secondary end point was PFS, defined as time from randomization until first documented disease progression or death per Response Evaluation Criteria in Solid Tumors, version 1.0. Patients alive without documented progression were censored for PFS at the most recent disease assessment.

**Assessment of Covariates**
Body mass index (BMI) was calculated from weight in kilograms divided by and height in meters squared, measured at study entry. A physical activity score was calculated by summing the weekly expenditure of metabolic equivalent for a list of leisure-time activities in the diet and lifestyle questionnaire. Current use of medication, including aspirin intake, was assessed in the questionnaire. Diabetes status was ascertained from the medical record at enrollment and supplemented by the self-report on the questionnaire. Caffeine intake was computed by multiplying the frequency of consumption of each food by its caffeine content and summing contributions from all foods. Caffeine and alcohol intake were adjusted for total energy intake. The RAS wild-type tumors were defined as those lacking mutations in both KRAS and NRAS, and the RAS mutant tumors were those with either a KRAS or an NRAS mutation (eMethods in the Supplement).

**Statistical Analysis**
Data were analyzed from May 1 to August 31, 2018. The primary exposure was total consumption of coffee, whereas the specific type of coffee (caffeinated vs decaffeinated) was considered in secondary analyses. Baseline characteristics by frequency of total coffee consumption were compared using the Kruskal-Wallis test, χ² test, or Fisher exact test. Survival curves were generated using the Kaplan-Meier method with statistical significance measured by the log-rank test. Cox proportional hazards regression was used to examine the association of coffee consumption with OS and PFS while controlling for other factors. The assumption of proportional hazards was tested and satisfied by evaluating a time-dependent variable, which was the product of total coffee intake and time. In both the log-rank test and Cox proportional hazards regression, we tested for a linear trend using frequency of consumption as a continuous variable.

We created a baseline model that was adjusted for age at enrollment and total energy intake, as well as a multivariable model to control for additional factors known or suspected to affect survival in patients with CRC, including sex, Eastern Cooperative Oncology Group performance status, prior adjuvant chemotherapy, chemotherapy backbone, assigned treatment arm, BMI, and physical activity. Missing covariates...
After the exclusions, a total of 1171 patients with advanced or metastatic CRC were included in the analysis (Figure 1). The median patient age was 59 (interquartile range [IQR], 51-67) years, with 694 men (59%) and 477 women (41%). Most of the patients were White (1007 [86%]). Baseline characteristics by frequency of total coffee consumption are displayed in the eTable in the Supplement. Frequent coffee drinkers were more likely to be White (≥4 cups/d, 61 of 63 [97%]; never, 223 of 280 [80%]; P < .001) and male (≥4 cups/d, 52 of 63 [83%]; never, 142 of 280 [51%]; P < .001). They were also more likely to be current or former smokers (≥4 cups/d, 50 of 62 [81%]; never, 107 of 277 [39%]; P < .001), to have a higher median daily energy intake (≥4 cups/d, 2237 [range, 791-4122] kcal/d; never, 1729 [range, 601-4038] kcal/d; P < .001), and to have a higher median consumption of alcohol (≥4 cups/d, 1 [range, 0-29] g/d; never, 0 [range, 0-9]; P < .001).

Association of Coffee Intake With Cancer Progression and Death

The median follow-up time among living patients was 5.4 years (10th percentile, 1.3 years; IQR, 3.2-6.3 years). A total of 1092 patients (93%) had died or had disease progression. Survival curves by frequency of total coffee consumption are shown in Figure 2 for OS (log-rank P = .01 for trend) and PFS (P = .04 for trend). In multivariable analyses (Table), higher total coffee intake was associated with a significant improvement in OS (hazard ratio [HR] for 1-cup/d increment, 0.95; 95% CI, 0.91-1.00; P = .004 for trend). Compared with never-drinkers, participants who consumed 2 to 3 cups/d had a multivariable HR for OS of 0.82 (95% CI, 0.67-1.00); those who consumed at least 4 cups of coffee per day, 0.64 (95% CI, 0.46-0.87). When total coffee intake and total caffeine intake were included in the model simultaneously, total coffee intake remained significantly associated with OS (HR for 1-cup/d increment, 0.90; 95% CI, 0.83-0.97; P = .01 for trend), whereas no association was noted for total caffeine intake (HR for 100-mg/d increment, 1.04; 95% CI, 0.97-1.11; P = .29 for trend). Higher total coffee intake was also associated with improved PFS (HR for 1-cup/d increment, 0.95; 95% CI, 0.91-1.00; P = .04 for trend). The multivariable HRs for PFS were 0.82 (95% CI, 0.68-0.99) for 2 to 3 cups/d and 0.78 (95% CI, 0.59-1.05) for at least 4 cups/d, compared with abstainers. Additional adjustment for race/ethnicity, smoking status, alcohol intake, aspirin use, diabetes status, RAS status, and intakes of milk, nondairy creamer, and sweeteners did not materially alter the association with OS or PFS.
Table. Associations of Total, Caffeinated, and Decaffeinated Coffee Consumption With Overall and Progression-Free Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency of consumption</th>
<th>1-Cup/d increment</th>
<th>P value for trenda</th>
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<tr>
<td><strong>Total coffee consumption</strong></td>
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<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>266/280</td>
<td>274/301</td>
<td>281/398</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)b</td>
<td>1 [Reference]</td>
<td>0.85 (0.72-1.01)</td>
<td>0.95 (0.80-1.13)</td>
</tr>
<tr>
<td>Multivariable HR (95% CI)c</td>
<td>1 [Reference]</td>
<td>0.86 (0.72-1.01)</td>
<td>0.96 (0.81-1.14)</td>
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<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
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<td>266/280</td>
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</tr>
<tr>
<td><strong>Caffeinated coffee consumption</strong></td>
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<tr>
<td>Overall survival</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
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<td>303/361</td>
<td>151/179</td>
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<tr>
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<tr>
<td>Multivariable HR (95% CI)c</td>
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<td><strong>Progression-free survival</strong></td>
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<td>335/361</td>
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<td>Adjusted HR (95% CI)b</td>
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<td>0.95 (0.82-1.11)</td>
<td>1.07 (0.89-1.28)</td>
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<tr>
<td>Multivariable HR (95% CI)c</td>
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<td><strong>Decaffeinated coffee consumption</strong>d</td>
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<td>Overall survival</td>
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<td>0.68 (0.48-0.96)</td>
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<td><strong>Progression-free survival</strong></td>
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<td>38/44</td>
</tr>
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<td>0.85 (0.61-1.19)</td>
</tr>
<tr>
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<td>1 [Reference]</td>
<td>1.02 (0.88-1.18)</td>
<td>0.85 (0.61-1.19)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; NA, not applicable.

a Calculated by entering frequency of consumption as a continuous variable.

b Adjusted for age (continuous) and total energy intake (continuous).

c Adjusted for age (continuous), total energy intake (continuous), sex (female or male), Eastern Cooperative Oncology Group performance status (0 or 1-2), prior adjuvant chemotherapy (yes or no), chemotherapy backbone (bevacizumab, fluorouracil, and oxaliplatin [mFOLFOX6] or leucovorin, fluorouracil, and irinotecan [FOLFIRI]), assigned treatment arm (bevacizumab, cetuximab, bevacizumab plus cetuximab), body mass index (continuous), and physical activity (continuous).

d Cutoffs for intake included never, less than 1, 1, or at least 2 cups/d.

Improved outcomes were also found when caffeinated or decaffeinated coffee was individually analyzed (Table). Compared with those who never consumed coffee, those who consumed at least 2 cups/d of decaffeinated coffee had a multivariable HR for OS of 0.64 (95% CI, 0.43-0.95; P = .003 for trend) and for PFS of 0.75 (95% CI, 0.52-1.09; P = .05 for trend). Consumption of at least 4 cups/d of caffeinated coffee was associated with improved OS with a multivariable HR of 0.66 (95% CI, 0.47-0.94; P = .04 for trend), whereas no significant association was noted between caffeinated coffee consumption and PFS (HR, 0.85; 95% CI, 0.62-1.17; P = .15 for trend).

To eliminate potential differences between participants who drank coffee and those who did not, we analyzed survival among those who drank any amount of coffee. Higher total coffee intake continued to be associated with improved OS (HR for 1-cup/d increment, 0.94; 95% CI, 0.89-0.99) and PFS (HR for 1-cup/d increment, 0.96; 95% CI, 0.92-1.01) in this subset of patients. To further address the possible influence of occult cancer or impending death on dietary habits, we performed a sensitivity analysis by extending the exclusion period to 180 days. Higher total coffee intake remained significantly associated with improvement in OS (HR for 1-cup/d increment, 0.94; 95% CI, 0.89-0.99); the association with PFS was generally unchanged, although slightly attenuated (HR for 1-cup/d increment, 0.96; 95% CI, 0.92-1.01).

Subgroup Analysis

In subgroup analyses (Figure 3), the association of increasing coffee consumption with improved OS was stronger in patients with BMI of less than 25.0 than those with BMI of at least 25.0.
In 1171 patients with advanced or metastatic CRC, we found that increased total coffee intake was associated with a statistically significant improvement in both OS and PFS. When caffeine- and decaffeinated coffee were considered separately, both were associated with improved OS, whereas the association with PFS was attenuated for caffeinated coffee. The significant association between higher coffee intake and improved patient outcomes remained even after multivariate adjustment for potential confounding and prognostic variables.

Previous studies have suggested an association between coffee consumption and CRC risk and outcome, with mixed findings. A recent meta-analysis examining coffee consumption and CRC risk[^25] detected a significant protective effect of coffee in 7 US studies but not among the total 26 studies. A subsequent study among participants in the UK Biobank[^27] found...
Coffee Intake and Survival in Advanced or Metastatic Colorectal Cancer

Coffee intake and their effect on cancer in humans. Both insulin sensitivity of tissues and therefore has anti-hyperinsulinemic effects. Studies have associated indicators of insulin resistance, such as increased levels of circulating C-peptide (a marker of insulin secretion) and higher dietary intake was associated with reduced cancer recurrence and death in 953 patients with stage III colon cancer from the CALGB 89803 (Alliance) Diet and Lifestyle Companion study. In another study of 1599 patients with stages I to III CRC from 2 prospective cohorts, higher coffee intake was associated with a lower risk of overall and CRC-specific mortality, particularly among those with stage III disease.

One possible hypothesis to explain the underlying biological mechanism of the anticancer effects of coffee consumption involves coffee’s effects on the insulin pathway. Caffeine increases insulin sensitivity of tissues and therefore has anti-hyperinsulinemic effects. Studies have associated indicators of insulin resistance, such as increased levels of circulating C-peptide (a marker of insulin secretion) and higher dietary intake was associated with reduced cancer recurrence and death in 953 patients with stage III colon cancer from the CALGB 89803 (Alliance) Diet and Lifestyle Companion study. In another study of 1599 patients with stages I to III CRC from 2 prospective cohorts, higher coffee intake was associated with a lower risk of overall and CRC-specific mortality, particularly among those with stage III disease.

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Alternative hypotheses focus on coffee’s other biological effects. Coffee is the largest source of dietary antioxidants in the United States. Studies have implicated high oxidative stress in CRC development and metastases. As such, a greater consumption of antioxidants could potentially slow the development of such cancers. In addition, kahweol is another component in coffee with anti-inflammatory and proapoptotic effects that may decrease mutagenesis and cancer progression. Further research is ongoing to identify other bioactive molecules in coffee and their effect on cancer in humans. Both insulin sensitization and other anticancer effects may work in combination to slow tumor growth and development.

The data analyzed for this study were derived from a large, multicenter, randomized clinical trial. This source of data is advantageous owing to the trial’s detailed patient eligibility criteria, standardized treatment procedures, and careful follow-up for end points such as OS and PFS. Dietary information was prospectively collected using a validated food frequency questionnaire. Our results remained statistically significant after controlling for demographic, lifestyle, disease, and treatment-related variables thought to affect outcomes of patients with CRC, which were collected at the time of patient enrollment in the clinical trial.

Limitations
Despite these considerations, our results may have been confounded by factors that were not captured in the clinical trial or associated questionnaire, such as sleep habits, employment, physical activity not related to dedicated exercise, or changes in coffee consumption after cancer diagnosis. Furthermore, most patients who consume coffee while being treated for cancer likely consumed coffee before the cancer diagnosis, so these results do not allow us to discern whether the consumption of coffee acts directly on active tumors or whether coffee drinkers tend to develop less aggressive tumors. In a population of patients with advanced cancer, we considered the possibility that coffee drinkers may be more robust or have a lesser burden of cancer; however, we did not find any significant differences in performance status or disease characteristics across categories of coffee consumption. The population of patients with cancer enrolled in CALGB/SWOG 80405 may not be representative of the general population of patients with CRC. However, this clinical trial recruited patients from academic and community hospitals across North America, and similar randomized clinical trials are routinely used to determine the standards of care for treatment of CRC and other forms of cancer. In addition, these results do not represent a causal relationship between coffee and survival, which requires randomized intervention studies.

Conclusions
This large cohort study detected an association between increased consumption of coffee and improved CRC outcomes. These findings are consistent with those of previous epidemiological studies, although this is the first such study, to our knowledge, to show a protective effect of coffee consumption in patients with advanced or metastatic CRC. Further research is needed to elucidate the specific mechanism driving these associations.
Coffee Intake and Survival in Advanced or Metastatic Colorectal Cancer

Carolina (Chang), Department of Medicine, Indiana University School of Medicine, Indianapolis (O’Neill); Division of Medical Oncology, Henry Ford Hospital, Detroit; Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles (Lenz); SWOG Group Chair’s Office/Knight Cancer Institute, Oregon Health and Science University, Portland (Blanke); Department of Medicine, University of California, San Francisco, School of Medicine (Venook); Yale Cancer Center and Smilow Cancer Hospital, New Haven, Connecticut (Fuchs); Eshelman School of Pharmacy and Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill (Innocenti); Duke Cancer Institute, Duke University Medical Center, Durham, North Carolina (Nixon); West Virginia University Cancer Institute, Morgantown (Goldberg); Weill Cornell Medical College, Cornell University and Memorial Sloan Kettering Cancer Center, New York, New York (O’Reilly).

Author Contributions: Mr Mackintosh and Dr Yuan contributed equally to this work. Drs Yuan and Ng had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Mackintosh, Mayer, Fuchs, Ng. Acquisition, analysis, or interpretation of data: Mackintosh, Yuan, Ou, Zhang, Niedzwiecki, Chang, O’Neill, Mackintosh, Lenz, Blankie, Venook, Fuchs, Innocenti, Nixon, Goldberg, O’Reilly, Meyerhardt, Ng.

Drafting of the manuscript: Mackintosh, Yuan, Niedzwiecki, Chang, Ng. Critical revision of the manuscript for important intellectual content: Mackintosh, Yuan, Ou, Zhang, Niedzwiecki, O’Neill, Mullen, Lenz, Blankie, Venook, Mayer, Fuchs, Innocenti, Nixon, Goldberg, O’Reilly, Meyerhardt, Ng.

Statistical analysis: Yuan, Ou, Zhang, Niedzwiecki, Mullen, Ng.

Obtained funding: Meyerhardt, Ng.

Administrative, technical, or material support: Mackintosh, Lenz, Venook, Fuchs, Goldberg, O’Reilly, Ng.

Supervision: O’Neill, Venook, Mayer, Goldberg, Ng.

Conflict of Interest Disclosures: Dr Ou reported receiving grants from the National Cancer Institute (NCI) during the conduct of the study and outside the submitted work. Dr O’Neill reported other from Eli Lilly and Company outside the submitted work. Dr Blanke reported receiving grants from the NCI during the conduct of the study. Dr Venook reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study and grants from Genentech/Roche outside the submitted work. Dr Fuchs reported receiving personal fees from Agios Pharmaceuticals, Inc, Amylin Pharmaceuticals, Bain Capital, CytoDyn Therapeutics, Inc, Daiichi-Sankyo Company, Limited, Eli Lilly and Company, Ensintric Health, EvolveWell Therapeutics, Inc, Genentech, Inc, Merck & Co, Taiho Pharmaceutical Co, Ltd, and Unum Therapeutics, Inc, outside the submitted work; serving as a director for CytoDyn Therapeutics, Inc; owning unexercised stock options for CytoDyn Therapeutics, Inc, and Ensintric Health; co-founding and having equity in EvolveWell Therapeutics, Inc, and providing expert testimony for Amylin Pharmaceuticals and Eli Lilly and Company. Dr Nixon reported receiving personal fees from Pfizer, Inc, Chengu Kanghong Pharmaceutical Group Co, Ltd, Eli Lilly and Company, and Prometheus Corporation and grants from Acceleron Pharma, Inc, Amgen, Inc, AstraZeneca MedImmune, Axiomexa Therapeutics, Genentech, Inc, Leadiant Biosciences, Inc, MedPacto, Inc, Seattle Genetics, Inc, and Tracor Pharmaceuticals, Inc, outside the submitted work; and having patents to Methods of Developing a Prognosis For Pancreatic Cancer and Predicting Responsiveness to Cancer Therapeutics issued and patents to Methods of Predicting Responsiveness of a Cancer to a VEGF Targeting Agent and Methods of Prognosing and Treating Cancer pending.

Dr Goldberg reported receiving personal fees from Genentech, Inc, Taiho Pharmaceutical Co, Ltd, Novartis International AG, and Merck & Co outside the submitted work. Dr O’Reilly reported receiving grants from Acta Biologica, MabVax Therapeutics, Inc, Celsegene Corporation, AstraZeneca, and Silenseed and personal fees from Ipsen Group, Rafael Therapeutics, CytoX Therapeutics, Inc, Merck & Co, Polaris Pharmaceuticals, and Swedish Orphan BioVittmun AB outside the submitted work. Dr Meyerhardt reported receiving personal fees from Taiho Pharmaceutical Co, Ltd, COTA Healthcare, and Ignitya, Inc, outside the submitted work. Dr Ng reported receiving grants from the NCI, the Department of Defense, and Cancer Research UK during the conduct of the study and grants and nonfinancial support from Pharmavite, LLC, grants from Revolution Medicines, Inc, Evergrande Group, Genentech, Inc, Gilead Sciences, Inc, Celsegene Corporation, Trovagene, Inc, and Tarrex Biopharma, Ltd, and personal fees from Bayer, Seattle Genetics, Inc, and Array BioPharma, Inc, outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by U10CA180821 (Alliance for Clinical Trials in Oncology), U10CA180882 (Alliance for Clinical Trials in Oncology), U10CA180795, U10CA180838, U10CA180867, U24CA196571, UG1CA89858, and P50CA127003 (Dr Fuchs, Meyerhardt, and Ng), R01CA118553 (Dr Fuchs, Meyerhardt, and Ng), R01CA205406 (Dr Ng), U10CA180826 (Dr Fuchs), U10CA180830 (Dr Lenz), and U10CA180888 (Dr Blankie) from the NCI, and in part by funds from Project P Fund, Genentech, Inc, Sanofi, and Pfizer, Inc (Alliance for Clinical Trials in Oncology and Alliance Foundation Trials).

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Coffee Intake and Survival in Advanced or Metastatic Colorectal Cancer

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Coffee occupies a unique space in nutrition and health research. First, it is widely consumed globally; in the United States, for example, 3 of 4 adults report drinking coffee, making it potentially important for public health. Second, coffee drinking is often a daily and, likely a long-term, habit, making it potentially important for individual health. Because coffee is consumed regularly, it is likely captured with relatively little measurement error by self-report; consequently, studies of coffee with mortality and incident disease are less prone to measurement error–induced bias than those of other nutritional exposures. Finally, unlike intake of other foods with perceived health benefits, coffee drinking is usually positively correlated with chronic disease risk factors, including age, cigarette smoking, and alcohol drinking, contributing to long-standing concerns that coffee drinking might increase the risk of cancer and other chronic diseases.

In 2016, an International Agency for Research on Cancer working group concluded that there was “inadequate evidence in humans for the carcinogenicity of coffee drinking” and, on the contrary, found strong evidence for inverse associations with liver and endometrial cancer. This conclusion is consistent with an umbrella review that found coffee drinking is associated with lower risk of endometrial and liver cancer as well as mortality, cardiovascular disease, chronic liver disease, and type 2 diabetes. Owing to potential benefits and a lack of consistent evidence showing harm except during pregnancy, the 2015 US Dietary Guidelines Advisory Committee stated that coffee drinking (≤5 cups/d) is compatible with a healthy diet. However, other expert panels, including the World Cancer Research Fund, have not issued recommendations, citing uncertainty around coffee’s health effects.

One area of coffee research that remains largely unexplored is a possible link with cancer survival. Studies of coffee and cancer survival are vulnerable to bias from reverse causality, because individuals may drink less coffee after the onset of disease symptoms. Nevertheless, such studies may yield novel insight into disease progression; moreover, they are needed to inform dietary guidance for the growing number of cancer survivors worldwide.

In this issue of JAMA Oncology, Mackintosh et al12 report on their prospective investigation of coffee drinking and survival among 1171 patients with previously untreated locally advanced (17 [1.5%]) or metastatic (1146 [97.9%]) colorectal cancer (CRC) who were enrolled in a phase 3 clinical trial to determine the optimal biologic therapy (cetuximab and/or...