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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prospective Study of Coffee Consumption and Cancer Incidence in Non-White Populations

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Abstract

Background: Coffee intake has been associated with risk of various cancers, but the findings, mostly from studies in white populations, are inconsistent. We examined the association of coffee consumption with overall cancer incidence and specific cancer sites in a large prospective study of African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites.

Methods: 167,720 participants of the Multiethnic Cohort Study in Hawaii and Los Angeles were included. Baseline coffee intake was assessed by a validated food-frequency questionnaire. HRs and 95% confidence intervals (CIs) for sixteen cancers associated with coffee intake were calculated using Cox regressions.

Results: During a mean follow-up of 15.3 years, 34,031 incident cancer cases were identified among study participants. Coffee intake was associated inversely with liver ($\geq$4 cups/day vs. none: HR = 0.57; 95% CI, 0.38–0.87; $P_{trend} < 0.001$), ovarian (HR = 0.33; 95% CI, 0.17–0.65; $P_{trend} = 0.007$), and thyroid (HR = 0.44; 95% CI, 0.23–0.87; $P_{trend} = 0.007$) cancers and melanoma (HR = 0.72; 95% CI, 0.52–0.99; $P_{trend} = 0.002$). Coffee intake was also inversely associated with endometrial cancer among women with a body mass index >30 kg/m^2 (HR=0.31; 95% CI, 0.14–0.72; $P_{trend} = 0.04$). The associations were similar across five ethnic groups ($P_{heterogeneity} > 0.06$) and were mainly observed among those who drank caffeinated coffee.

Conclusions: On the basis of our prospective data in diverse populations, we found a decreased risk of liver, ovarian, thyroid, and endometrial cancers and melanoma associated with higher coffee intake.

Impact: These results suggest that coffee drinking may protect against liver, ovarian, thyroid, and endometrial cancers, and melanoma. *Cancer Epidemiol Biomarkers Prev; 27(8); 928–35.* ©2018 AACR.

Introduction

Coffee intake has been studied in relation to risk of various cancer sites due to its popularity and constituents with potential to alter cancer risk, but the findings are not consistent (1–3). In 1991, the International Agency for Research on Cancer (IARC) Working Group evaluated coffee as a possible carcinogen to humans, particularly for bladder (4). However, after reviewing more than 1,000 studies in humans and animals including much larger and stronger evidence for bladder cancer, the Working Group concluded that there was inadequate evidence for the carcinogenicity of coffee drinking overall (5). Similar conclusions were reached in recent reports by the World Cancer Research Foundation (WCRF)/American Institute of Cancer Research (AICR), which reviewed the literature and indicated that coffee intake probably lowers the risk of endometrial and liver cancers (6–16). However, as most previous studies of coffee consumption and cancer risks have been set in populations with non-Hispanic white ancestry, data from non-white populations are scarce. As populations around the world vary by genetics and lifestyles, it is important to evaluate associations between coffee drinking and risk of cancer in diverse populations.

In the Multiethnic Cohort Study (MEC), we previously reported an inverse association between coffee intake and liver cancer incidence (17) and overall and specific mortality (18). In this study, we expanded the investigation to include other cancer sites as well as all cancer combined, and provide data for five different racial/ethnic populations.

Materials and Methods

Study population

The MEC was established in Hawaii and California (mainly in Los Angeles County) to investigate the association of dietary, lifestyle, and genetic factors with the incidence of cancer and other chronic disease. Details of the study have been described previously (19). Briefly, African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites were the primary targets for recruitment, identified through drivers' license records in both states and additionally voter registration records in Hawaii and Health Care Financing Administration files in California. Between 1993 and 1996, more than 215,000 men and women ages 45–75 years entered the cohort by completing a 26-page, self-administered, mailed questionnaire. The study was approved by

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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the review boards of the University of Hawaii and the University of Southern California. For this analysis, we excluded participants who were not in one of the targeted 5 racial/ethnic groups ($n = 13,986$), who had a prevalent cancer at cohort entry based on self-report ($n = 17,645$) or tumor registries (invasive tumors only, $n = 2,070$), and who reported invalid dietary intakes based on total energy intake or its components ($n = 7,401$), as described previously (20). We also excluded those with missing information on smoking ($n = 6,828$). The final analytic dataset included 167,720 participants.

Assessment of coffee, tea, and potential confounders

Dietary intake at baseline was assessed using a comprehensive quantitative food frequency questionnaire (QFFQ) designed for use in this multiethnic population. The QFFQ included 3 coffee items ("cappuccino including café au lait, café latte, café con leche"; "regular coffee, brewed or instant"; and "decaffeinated coffee, brewed or instant") and 2 tea items ("black tea such as Lipton's, oolong, and ice tea" and "green, herbal, or other tea") with 9 frequency categories from never or hardly ever to 4 or more cups a day. A calibration study showed that the median correlation coefficient for coffee intake was 0.72 between the QFFQ and three 24-hour recalls (17, 21). Daily nutrient intakes were computed using a food composition table that has been developed and maintained at the University of Hawaii Cancer Center. Total coffee intake was calculated as the sum of the 3 coffee items and total tea intake as sum of the 2 tea items (green and black tea). The baseline questionnaire also provided data on potential confounders such as body mass index (BMI; based on self-reported weight and height), education, smoking status, diabetes status, and alcohol intake.

Ascertainment of outcomes

Incident cancer cases were identified by linking the cohort to the NCI's Surveillance, Epidemiology, and End Results (SEER) cancer registries covering Hawaii and California. We also linked the cohort to the state death certificate files in Hawaii and California and to the National Death Index. Case and death ascertainment was complete through December 31, 2012. In the current analysis, we only considered invasive tumors. During a mean follow-up of 15.3 years, 34,031 invasive cases of any cancer were identified including 7,508 prostate, 5,240 breast, 4,096 colorectal, 3,954 lung, 2,580 non-Hodgkin lymphoma, 1,156 stomach, 1,136 pancreatic, 921 melanoma, 844 endometrial, 838 kidney, 670 liver, 651 bladder, 427 ovarian, 320 thyroid, 304 gallbladder, and 272 esophageal cancers.

Statistical analysis

Coffee consumption was categorized into none, 1–3 cups/month, 1–6 cups/week, 1 cup/day, 2–3 cups/day and ≥4 cups/day. For tea and decaffeinated coffee consumption, the top 2 categories were combined as ≥2 cups/day. We compared baseline characteristics according to coffee consumption categories. Cox proportional hazard models with age as the time metric were used to estimate HRs and 95% confidence intervals (CIs) of cancer incidence related to coffee and tea intake. Because smoking is associated with both coffee consumption and cancer incidence, we comprehensively adjusted for smoking using a model developed for smoking and lung cancer analysis in the MEC (22). The model explicitly included 4 indicator variables for race/ethnicity; average number of cigarettes; average number of cigarettes squared; indicator variables for former and current smokers; number of years smoked (time-dependent); number of years

Table 1. Baseline characteristics of the participants by coffee consumption in the Multiethnic Cohort Study[a]

	Coffee consumption						
	None	**1–3 cups/month**	**1–6 cups/week**	**1 cup/day**	**2–3 cups/day**	**≥4 cups/day**	**Total**
Number of participants	26,985	12,011	22,244	51,536	43,033	11,911	167,720
Age at cohort entry (years)	58.7 (9.2)	59.4 (8.9)	59.4 (8.8)	61.1 (8.7)	58.8 (8.6)	57.5 (8.2)	59.5 (8.8)
Female	15,894 (58.9)	7,036 (58.6)	11,640 (52.3)	28,659 (55.6)	22,455 (52.2)	5,398 (45.3)	91,082 (54.3)
Race/ethnicity							
African American	6,919 (25.6)	2,826 (23.5)	4,622 (20.8)	8,240 (16.0)	4,421 (10.3)	912 (7.7)	27,940 (16.7)
Native Hawaiian	2,716 (10.1)	1,053 (8.8)	1,796 (8.1)	3,502 (6.8)	2,489 (5.8)	727 (6.1)	12,283 (7.3)
Japanese American	6,863 (25.4)	3,433 (28.6)	6,206 (27.9)	16,862 (32.7)	12,629 (29.3)	3,021 (25.4)	49,014 (29.2)
Latino	3,965 (14.7)	2,312 (19.2)	5,516 (24.8)	11,620 (22.5)	11,172 (26.0)	3,214 (27.0)	37,799 (22.5)
White	6,522 (24.2)	2,387 (19.9)	4,104 (18.4)	11,312 (21.9)	12,322 (28.6)	4,037 (33.9)	40,684 (24.3)
BMI (kg/m^2)	26.8 (5.7)	26.8 (5.5)	27.1 (5.3)	26.3 (4.9)	26.4 (4.8)	26.5 (4.8)	26.6 (5.1)
Smoking status							
Never	15,814 (58.6)	6,566 (54.7)	10,919 (49.1)	23,123 (44.9)	16,481 (38.3)	3,086 (25.9)	75,989 (45.3)
Former	8,534 (31.6)	4,178 (34.8)	8,417 (37.8)	20,735 (40.2)	17,865 (41.5)	4,607 (38.7)	64,336 (38.4)
Current	2,637 (9.8)	1,267 (10.5)	2,908 (13.1)	7,678 (14.9)	8,687 (20.2)	4,218 (35.4)	27,395 (16.3)
Pack-years among ever smokers	15.8 (14.9)	15.3 (14.5)	15.5 (14.3)	17.7 (15.5)	19.3 (16.1)	24.6 (17.4)	18.2 (15.8)
History of diabetes	3,141 (11.6)	1,480 (12.3)	2,881 (13.0)	6,080 (11.8)	4,412 (10.3)	1,220 (10.2)	19,214 (11.5)
Alcohol intake (g/day)	6.5 (24.6)	6.8 (23.4)	7.5 (21.5)	10.1 (25.7)	10.2 (25.4)	11.0 (29.7)	9.0 (25.1)
Education							
≤12th grade	10,762 (40.1)	5,029 (42.1)	10,205 (46.1)	24,052 (46.9)	17,839 (41.6)	4,945 (41.7)	72,832 (43.6)
Vocational/some college	8,018 (29.9)	3,517 (29.4)	6,315 (28.5)	15,115 (29.4)	12,879 (30.0)	3,449 (29.1)	49,293 (29.5)
≥College graduate	8,067 (30.0)	3,403 (28.5)	5,615 (25.4)	12,160 (23.7)	12,145 (28.3)	3,473 (29.3)	44,863 (26.9)
Physical activity (hours/day)[b]	0.39 (0.85)	0.35 (0.77)	0.39 (0.82)	0.38 (0.83)	0.40 (0.83)	0.45 (0.90)	0.39 (0.83)
Menopausal status and MHT use among women							
Premenopausal	2,759 (19.1)	1,067 (16.4)	1,778 (16.6)	3,294 (12.3)	3,511 (16.9)	918 (18.5)	13,327 (15.7)
Postmenopausal-never	5,428 (37.6)	2,373 (36.5)	4,161 (38.9)	10,487 (39.2)	7,556 (36.4)	1,899 (38.4)	31,767 (37.3)
Postmenopausal-former	2,355 (16.3)	1,102 (17.0)	1,778 (16.6)	4,783 (17.9)	3,443 (16.6)	837 (16.9)	14,349 (16.9)
Postmenopausal-current	3,877 (26.9)	1,955 (30.1)	2,975 (27.8)	8,170 (30.6)	6,271 (30.2)	1,297 (26.2)	25,658 (30.2)

Abbreviation: MHT, menopausal hormone therapy.

[a]Mean (SD) for continuous variables and n (column %) for categorical variables.

[b]Hours spent in vigorous activity per day.

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since quitting (time-dependent); and interactions of race/ethnicity with the following variables: average number of cigarettes, average number of cigarettes squared, smoking status, and number of years smoked. We also performed analyses that were stratified by smoking status.

The models were further adjusted for the following strata variables: age at cohort entry (<50, 50–54, 55–59, 60–64, 65–59, 70–74, ≥75 years), sex, BMI (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2, and missing), education (≤12th grade, vocational school/some college, ≥college graduate, and missing), physical activity (hours spent in vigorous activity per day; <0.1, 0.1–<0.25, 0.25–<0.80, ≥0.80, and missing for men; <0.1, 0.1–<0.25, 0.25–<0.5, ≥0.5, and missing for women), alcohol consumption (ethanol; 0, 1–<5.2, 5.2-<23, ≥23 g/day for men; 0, 1–<2.5, 2.5–<10, ≥10 g/day for women), history of diabetes (yes, no), and family history of corresponding cancer (yes, no). For women, the models were additionally adjusted for menopausal status and menopausal hormone therapy (MHT) use (premenopause; postmenopause: never, past, current, missing use of MHT; and missing status). For endometrial cancer, women who reported hysterectomy, and for ovarian cancer, women who reported oophorectomy at baseline were excluded. For gallbladder cancer, participants who reported cholecystectomy at baseline were excluded. To examine heterogeneity of effect by BMI, the associations between coffee intake and each cancer site were further stratified by BMI category (<30, ≥30 kg/m^2). To test for linear trend, a sex- and racial/ethnic–specific median value was assigned to each category of coffee intake and then modeled as a continuous variable. Tests for heterogeneity across subgroups were based on the Wald statistics for cross-product terms of trend variables and subgroup membership. The proportional hazard assumption over all ages was tested by modeling the interaction of age with coffee or tea consumption and no violations were found. All statistical tests were two-sided. Analyses were conducted with SAS 9.4 software.

Results

Approximately 33% of participants drank 2 or more cups per day, whereas 16% were not coffee drinkers at cohort entry. Participants with high coffee consumption were more likely to be younger, male, Latino and white, smokers, and physically active, and to drink more alcohol, while they were less likely to report a history of diabetes (Table 1).

The associations between coffee intake and cancer risk are presented in men and women combined (Table 2) because the results were similar in both sexes ($P_{heterogeneity} \geq 0.16$, Table 3). None of the coffee intake categories were associated inversely with cancer overall, although a trend test was borderline significant for an inverse association ($P = 0.05$; Table 2). Previously, we reported an inverse association for liver cancer (17), which was also found in this updated analysis with two additional years of follow-up (HR = 0.57; 95% CI, 0.38–0.87 for ≥4 cups/day vs. none; P_{trend} <0.001). In addition to liver cancer, an inverse association was found for ovarian cancer (HR = 0.33; 95% CI, 0.17–0.65; P_{trend} = 0.007), melanoma (HR = 0.72; 95% CI, 0.52–0.99; P_{trend} = 0.002), and thyroid cancer (HR = 0.44; 95% CI, 0.23–0.87; P_{trend} = 0.007). For thyroid cancer, the inverse association was mainly observed in women (HR = 0.37; 95% CI, 0.15–0.91; P_{trend} = 0.009), from whom 74% of the cases were obtained (Table 3). On the contrary, we observed a positive trend with lung cancer (HR = 1.08; 95% CI, 0.92–1.26; P_{trend} = 0.04).

Table 2. Coffee consumption and cancer risk in the Multiethnic Cohort Study, 1993–2012[a]

	No. of cases	Coffee consumption							
		None	1–3 cups/month	1–6 cups/week	1 cup/day	2–3 cups/day	≥4 cups/day	P_{trend}	Per cup
All cancers	34,031	1.00 (ref.)	1.00 (0.95–1.06)	1.00 (0.96–1.05)	0.99 (0.95–1.03)	0.98 (0.94–1.02)	0.96 (0.91–1.01)	0.05	0.99 (0.98–1.00)
Prostate	7,508	1.00 (ref.)	0.94 (0.84–1.05)	0.99 (0.91–1.08)	0.95 (0.88–1.03)	0.98 (0.91–1.07)	0.89 (0.79–1.00)	0.29	0.99 (0.97–1.01)
Aggressive[b]	3,378	1.00 (ref.)	0.90 (0.75–1.06)	1.02 (0.89–1.17)	1.00 (0.89–1.12)	1.01 (0.89–1.13)	0.92 (0.77–1.08)	0.62	0.99 (0.96–1.02)
Female breast	5,240	1.00 (ref.)	1.04 (0.91–1.18)	1.05 (0.94–1.18)	1.06 (0.97–1.17)	1.07 (0.97–1.18)	1.08 (0.93–1.25)	0.21	1.02 (0.99–1.04)
Colorectum	4,096	1.00 (ref.)	1.04 (0.89–1.21)	0.99 (0.87–1.13)	0.97 (0.87–1.09)	1.06 (0.94–1.18)	1.11 (0.95–1.30)	0.08	1.02 (0.99–1.05)
Lung	3,954	1.00 (ref.)	0.85 (0.70–1.04)	0.91 (0.78–1.06)	1.04 (0.91–1.18)	1.06 (0.93–1.21)	1.08 (0.92–1.26)	0.04	1.03 (1.00–1.06)
NHL	2,580	1.00 (ref.)	1.16 (0.95–1.40)	1.07 (0.91–1.26)	1.16 (1.01–1.32)	1.11 (0.96–1.28)	1.19 (0.98–1.45)	0.36	1.02 (0.98–1.05)
Stomach	1,156	1.00 (ref.)	1.08 (0.80–1.46)	0.99 (0.77–1.27)	0.91 (0.73–1.12)	0.99 (0.79–1.23)	1.13 (0.83–1.53)	0.45	1.01 (0.96–1.07)
Pancreas	1,136	1.00 (ref.)	1.29 (0.97–1.72)	1.20 (0.94–1.52)	1.06 (0.86–1.30)	1.10 (0.88–1.37)	1.10 (0.81–1.50)	0.92	1.01 (0.96–1.06)
Melanoma	921	1.00 (ref.)	0.76 (0.54–1.07)	0.85 (0.65–1.12)	0.97 (0.79–1.21)	0.68 (0.54–0.86)	0.72 (0.52–0.99)	0.002	0.92 (0.87–0.97)
Kidney	838	1.00 (ref.)	0.77 (0.54–1.11)	1.20 (0.93–1.56)	0.98 (0.78–1.24)	0.86 (0.67–1.10)	0.89 (0.64–1.23)	0.13	0.95 (0.90–1.01)
Endometrium[c]	838	1.00 (ref.)	0.79 (0.57–1.11)	0.98 (0.75–1.29)	0.92 (0.73–1.15)	0.90 (0.71–1.15)	0.68 (0.45–1.03)	0.22	0.96 (0.90–1.02)
Liver	670	1.00 (ref.)	1.10 (0.76–1.58)	0.97 (0.71–1.32)	0.88 (0.68–1.15)	0.64 (0.48–0.85)	0.57 (0.38–0.87)	<0.001	0.85 (0.79–0.91)
Bladder	651	1.00 (ref.)	0.98 (0.64–1.52)	1.09 (0.77–1.53)	1.08 (0.81–1.45)	1.16 (0.86–1.56)	0.88 (0.58–1.32)	0.94	1.01 (0.94–1.07)
Ovary[d]	404	1.00 (ref.)	0.89 (0.55–1.44)	0.67 (0.44–1.03)	0.82 (0.59–1.13)	0.72 (0.51–1.03)	0.33 (0.17–0.65)	0.007	0.85 (0.77–0.94)
Thyroid	320	1.00 (ref.)	0.74 (0.43–1.29)	1.03 (0.68–1.55)	1.01 (0.71–1.44)	0.73 (0.50–1.07)	0.44 (0.23–0.87)	0.007	0.87 (0.79–0.97)
Gallbladder[e]	292	1.00 (ref.)	1.53 (0.85–2.77)	1.10 (0.65–1.87)	1.33 (0.86–2.07)	1.26 (0.79–2.01)	1.78 (0.98–3.22)	0.22	1.05 (0.95–1.16)
Esophagus	272	1.00 (ref.)	1.83 (1.00–3.35)	1.04 (0.60–1.80)	1.20 (0.76–1.89)	0.96 (0.60–1.54)	1.03 (0.57–1.86)	0.34	0.95 (0.86–1.06)

Abbreviation: NHL, non-Hodgkin lymphoma.

[a]HR (95% CI). The following variables were included to rigorously control for the effects of smoking: ethnicity, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time-dependent), number of years since quitting (time-dependent), and interactions between ethnicity and smoking status, average number of cigarettes, squared average number of cigarettes, and number of years smoked. The models were further adjusted for sex, age at cohort entry, BMI, education, alcohol intake, physical activity, history of diabetes, family history of corresponding cancer, and menopausal status and menopausal hormone therapy for women only.

[b]Advanced stage or high grade.

[c]Excluding female participants who reported hysterectomy at baseline.

[d]Excluding female participants who reported oophorectomy at baseline.

[e]Excluding participants who reported cholecystectomy at baseline.

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Table 3. Coffee consumption and cancer risk in men and women in the Multiethnic Cohort Study, 1993–2012[a]

	No. of cases	Coffee consumption							
		None	1–3 cups/month	1–6 cups/week	1 cup/day	2–3 cups/day	≥4 cups/day	P_{trend}	Per cup
Men									
All cancers	18,383	1.00 (ref.)	0.98 (0.91–1.06)	0.99 (0.93–1.05)	0.97 (0.93–1.03)	0.98 (0.93–1.03)	0.95 (0.89–1.02)	0.30	0.99 (0.98–1.00)
Colorectum	2,144	1.00 (ref.)	0.92 (0.73–1.15)	0.90 (0.75–1.08)	0.90 (0.77–1.04)	0.98 (0.84–1.14)	1.07 (0.88–1.31)	0.12	1.02 (0.99–1.06)
Lung	2,167	1.00 (ref.)	0.84 (0.64–1.11)	0.91 (0.74–1.12)	1.05 (0.88–1.24)	1.08 (0.91–1.29)	1.05 (0.85–1.29)	0.15	1.02 (0.99–1.06)
NHL	1,357	1.00 (ref.)	0.95 (0.71–1.26)	0.98 (0.79–1.23)	1.10 (0.91–1.32)	1.04 (0.86–1.26)	1.24 (0.97–1.59)	0.13	1.04 (1.00–1.09)
Stomach	676	1.00 (ref.)	1.26 (0.85–1.87)	1.10 (0.80–1.53)	0.86 (0.65–1.15)	1.07 (0.80–1.43)	1.12 (0.77–1.65)	0.40	1.02 (0.96–1.09)
Pancreas	520	1.00 (ref.)	1.20 (0.77–1.88)	1.16 (0.81–1.66)	1.05 (0.76–1.44)	0.97 (0.70–1.34)	1.02 (0.67–1.55)	0.49	0.99 (0.92–1.06)
Melanoma	542	1.00 (ref.)	0.89 (0.59–1.33)	0.75 (0.53–1.06)	0.93 (0.70–1.22)	0.64 (0.48–0.86)	0.76 (0.52–1.12)	0.01	0.93 (0.87–1.00)
Kidney	511	1.00 (ref.)	0.62 (0.38–1.02)	1.19 (0.86–1.66)	0.90 (0.67–1.21)	0.82 (0.60–1.12)	0.97 (0.66–1.44)	0.55	0.97 (0.90–1.04)
Liver	418	1.00 (ref.)	1.32 (0.84–2.09)	0.96 (0.65–1.42)	0.87 (0.62–1.23)	0.63 (0.44–0.91)	0.58 (0.35–0.95)	<0.001	0.85 (0.78–0.93)
Bladder	477	1.00 (ref.)	1.01 (0.59–1.71)	1.15 (0.77–1.73)	1.13 (0.80–1.61)	1.21 (0.85–1.73)	0.89 (0.56–1.43)	0.86	1.00 (0.93–1.08)
Thyroid	84	1.00 (ref.)	0.53 (0.17–1.68)	0.87 (0.38–1.96)	0.92 (0.45–1.89)	0.84 (0.40–1.74)	0.58 (0.20–1.69)	0.47	0.94 (0.78–1.13)
Gallbladder[b]	136	1.00 (ref.)	1.73 (0.66–4.50)	1.31 (0.57–2.97)	1.40 (0.68–2.88)	1.47 (0.70–3.08)	2.11 (0.89–5.05)	0.20	1.08 (0.94–1.23)
Esophagus	207	1.00 (ref.)	2.41 (1.21–4.82)	1.36 (0.72–2.57)	1.26 (0.72–2.21)	1.23 (0.70–2.17)	1.18 (0.59–2.36)	0.54	0.96 (0.86–1.07)
Women									
All cancers	15,648	1.00 (ref.)	1.03 (0.95–1.11)	1.03 (0.96–1.11)	1.02 (0.97–1.08)	0.99 (0.93–1.05)	0.97 (0.89–1.06)	0.15	0.99 (0.98–1.00)
Colorectum	1,952	1.00 (ref.)	1.17 (0.94–1.44)	1.10 (0.91–1.33)	1.06 (0.91–1.24)	1.14 (0.97–1.35)	1.10 (0.85–1.43)	0.34	1.02 (0.97–1.06)
Lung	1,787	1.00 (ref.)	0.87 (0.65–1.16)	0.91 (0.72–1.16)	1.03 (0.86–1.24)	1.03 (0.85–1.25)	1.12 (0.88–1.43)	0.15	1.04 (1.00–1.09)
NHL	1,223	1.00 (ref.)	1.39 (1.07–1.81)	1.19 (0.94–1.50)	1.23 (1.01–1.49)	1.19 (0.97–1.47)	1.06 (0.77–1.47)	0.80	0.99 (0.94–1.04)
Stomach	480	1.00 (ref.)	0.90 (0.57–1.42)	0.82 (0.55–1.23)	0.98 (0.72–1.35)	0.86 (0.61–1.22)	1.18 (0.70–1.99)	0.88	1.00 (0.91–1.09)
Pancreas	616	1.00 (ref.)	1.36 (0.94–1.98)	1.20 (0.87–1.67)	1.05 (0.80–1.39)	1.22 (0.91–1.64)	1.20 (0.76–1.88)	0.43	1.04 (0.96–1.12)
Melanoma	379	1.00 (ref.)	0.54 (0.29–1.01)	1.07 (0.69–1.66)	1.05 (0.75–1.49)	0.74 (0.51–1.06)	0.58 (0.31–1.09)	0.05	0.89 (0.80–0.98)
Kidney	327	1.00 (ref.)	1.04 (0.61–1.79)	1.23 (0.79–1.91)	1.19 (0.82–1.72)	0.94 (0.62–1.41)	0.70 (0.37–1.36)	0.12	0.94 (0.85–1.04)
Liver	252	1.00 (ref.)	0.78 (0.41–1.46)	1.03 (0.62–1.71)	0.90 (0.59–1.36)	0.60 (0.37–0.97)	0.57 (0.26–1.25)	0.02	0.83 (0.73–0.95)
Bladder	174	1.00 (ref.)	0.96 (0.45–2.07)	1.04 (0.54–2.01)	0.99 (0.58–1.69)	1.00 (0.57–1.75)	0.84 (0.34–2.08)	0.76	1.00 (0.86–1.15)
Thyroid	236	1.00 (ref.)	0.80 (0.42–1.51)	1.04 (0.64–1.71)	1.01 (0.67–1.52)	0.68 (0.43–1.08)	0.37 (0.15–0.91)	0.009	0.85 (0.75–0.97)
Gallbladder[b]	156	1.00 (ref.)	1.38 (0.65–2.96)	0.97 (0.47–1.98)	1.30 (0.73–2.32)	1.11 (0.59–2.08)	1.34 (0.55–3.22)	0.76	1.01 (0.88–1.17)
Esophagus	65	1.00 (ref.)	0.57 (0.09–3.70)	0.21 (0.04–0.99)	1.15 (0.47–2.81)	0.44 (0.15–1.30)	1.20 (0.30–4.89)	0.70	1.02 (0.77–1.33)

Abbreviation: NHL, non-Hodgkin lymphoma.

[a]HR (95% CI). The following variables were included to rigorously control for the effects of smoking: ethnicity, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time-dependent), number of years since quitting (time-dependent), and interactions between ethnicity and smoking status, average number of cigarettes, squared average number of cigarettes, and number of years smoked. The models were further adjusted for age at cohort entry, body mass index, education, alcohol intake, physical activity, history of diabetes, family history of corresponding cancer, and menopausal status and menopausal hormone therapy for women only.

[b]Excluding participants who reported cholecystectomy at baseline.

Because the positive association with lung cancer could be due to residual confounding by smoking, we performed stratified analysis by smoking status. There was no positive association between coffee drinking and lung cancer among never smokers (HR = 0.84; 95% CI, 0.45–1.58; P_{trend} = 0.61; Supplementary Table S1).

The inverse association observed for ovarian, liver, and thyroid cancers and melanoma was present among participants who exclusively drank caffeinated coffee, but not in those who exclusively drank decaffeinated coffee (Supplementary Table S2). Further adjusting for soda intake did not change the association between coffee drinking and cancer risk (Supplementary Table S3).

In our study, coffee consumption contributed to the majority of total caffeine intake (77.4% overall, ranging from 70.2% in Native Hawaiians to 80.7% in Latinos). Tea and soda intake contributed to 7.6% and 13.4% of total caffeine intake, respectively. The associations between caffeine intake and cancer risk are shown in Supplementary Table S4. The results of caffeine analysis were similar to the total coffee consumption analyses (i.e., inverse association with liver, melanoma, ovarian cancer, and melanoma), with the exception of significant inverse associations with overall cancer and prostate cancer.

In racial/ethnic–specific analyses (Table 4), we found no indication that the association between coffee consumption and liver cancer varied by race/ethnicity ($P_{heterogeneity}$ = 0.15). The HR for per cup of coffee ranged from 0.45 in Native Hawaiians to 0.93 in Latinos. Similarly, there was no evident of heterogeneity in the ethnic specific association of coffee intake with melanoma ($P_{heterogeneity}$ = 0.35) and thyroid cancer ($P_{heterogeneity}$ = 0.67). The associations with these two cancers, however, were mainly observed in whites (melanoma HR = 0.89; 95% CI, 0.83–0.96 and thyroid HR = 0.73; 95% CI, 0.57–0.95).

In the BMI subgroup analysis, a heterogeneity in coffee intake and endometrial cancer association according to BMI categories was observed ($P_{heterogeneity}$ = 0.03; Table 5). A significant decrease in endometrial cancer risk was observed among women with a BMI higher than 30 kg/m^2 (HR = 0.31; 95% CI, 0.14–0.72 for ≥4 cups/day vs. none; P_{trend} = 0.04). No association was observed in women with a BMI <30 kg/m^2. No heterogeneity of effect by BMI was observed in other cancer sites ($P_{heterogeneity} \geq 0.07$; Supplementary Table S5).

In this study, 18% participants reported drinking ≥1 cup of tea/day at baseline (ranged from 10% in African Americans to 29% in Japanese Americans). Tea consumption was not associated with risk of all cancers combined or any cancer site (Supplementary Table S6), which remained similar with further adjustment for coffee intake or after excluding coffee drinkers. In Japanese Americans, the most frequent tea drinkers in the cohort, no association with overall cancer or any cancer site was observed (Supplementary Table S7).

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Table 4. Coffee consumption and cancer risk by race/ethnicity in the Multiethnic Cohort Study, 1993–2012[a]

	African American		Native Hawaiian		Japanese American		Latino		White		
	Cases	Per cup	Cases	Per cup	Cases	Per cup	Cases	Per cup	Cases	Per cup	$P_{heterogeneity}$
All cancers	6,648	0.96 (0.93–0.99)	2,562	0.95 (0.90–1.00)	9,922	1.00 (0.98–1.02)	6,873	1.00 (0.98–1.02)	8,026	0.98 (0.96–1.00)	0.07
Prostate	1,662	0.94 (0.89–1.00)	384	1.01 (0.90–1.14)	2,103	1.00 (0.96–1.04)	1,797	0.98 (0.95–1.02)	1,562	0.99 (0.95–1.03)	0.91
Aggressive[b]	634	1.01 (0.92–1.11)	210	0.93 (0.79–1.09)	1,109	1.00 (0.95–1.06)	710	0.96 (0.91–1.02)	715	0.98 (0.92–1.04)	0.35
Female breast	1,009	1.04 (0.96–1.12)	523	0.93 (0.84–1.04)	1,627	1.01 (0.97–1.07)	835	1.02 (0.96–1.08)	1,246	1.03 (0.98–1.09)	0.60
Colorectum	802	1.01 (0.93–1.11)	256	0.92 (0.79–1.07)	1,506	1.03 (0.97–1.08)	756	1.04 (0.98–1.10)	776	1.03 (0.96–1.10)	0.74
Lung	964	0.95 (0.88–1.02)	389	1.03 (0.91–1.16)	1,023	1.08 (1.02–1.15)	539	1.00 (0.93–1.08)	1,039	1.03 (0.97–1.09)	0.11
NHL	500	1.02 (0.92–1.14)	181	1.09 (0.93–1.29)	654	1.02 (0.95–1.10)	601	0.98 (0.92–1.05)	644	1.03 (0.96–1.10)	0.62
Stomach	147	1.18 (0.98–1.42)	83	0.62 (0.41–0.94)	522	0.96 (0.88–1.05)	285	1.02 (0.93–1.13)	119	0.97 (0.81–1.15)	0.09
Pancreas	234	1.09 (0.92–1.28)	91	1.01 (0.76–1.33)	394	0.93 (0.84–1.03)	204	1.05 (0.94–1.17)	213	1.03 (0.91–1.17)	0.39
Melanoma	39	0.92 (0.64–1.33)	38	1.33 (0.85–2.08)	89	1.02 (0.83–1.25)	77	0.92 (0.76–1.13)	678	0.89 (0.83–0.96)	0.35
Kidney	134	0.89 (0.72–1.10)	76	0.90 (0.68–1.18)	216	0.98 (0.86–1.13)	236	0.97 (0.87–1.08)	176	0.93 (0.82–1.06)	0.77
Endometrium[c]	179	0.86 (0.70–1.07)	78	0.67 (0.46–0.97)	210	0.99 (0.85–1.14)	158	1.02 (0.89–1.18)	213	0.94 (0.81–1.08)	0.11
Liver	93	0.75 (0.54–1.03)	43	0.45 (0.24–0.82)	213	0.85 (0.72–0.99)	236	0.93 (0.83–1.04)	85	0.88 (0.72–1.07)	0.15
Bladder	111	0.96 (0.77–1.20)	43	1.14 (0.73–1.79)	191	0.97 (0.85–1.12)	111	1.15 (0.99–1.32)	195	1.06 (0.94–1.20)	0.57
Ovary[d]	70	0.72 (0.47–1.10)	35	0.59 (0.26–1.36)	115	0.85 (0.69–1.06)	87	0.90 (0.72–1.13)	97	0.86 (0.69–1.08)	0.79
Thyroid	42	0.85 (0.55–1.30)	41	0.95 (0.69–1.31)	89	0.96 (0.78–1.18)	92	0.85 (0.70–1.04)	56	0.73 (0.57–0.95)	0.67
Gallbladder[e]	46	1.12 (0.79–1.58)	18	1.53 (0.60–3.93)	94	1.05 (0.87–1.27)	97	1.01 (0.86–1.19)	37	1.12 (0.85–1.47)	0.87
Esophagus	45	0.81 (0.55–1.19)	15	0.00 (0.00–.)	84	1.05 (0.88–1.26)	57	1.04 (0.85–1.29)	71	1.07 (0.87–1.32)	0.47

Abbreviation: NHL, non-Hodgkin lymphoma.

[a]HR (95% CI). The following variables were included to rigorously control for the effects of smoking: smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time-dependent), and number of years since quitting (time-dependent). The models were further adjusted for sex, age at cohort entry, BMI, education, alcohol intake, physical activity, history of diabetes, family history of corresponding cancer, and menopausal status and menopausal hormone therapy for women only.

[b]Advanced stage or high grade.

[c]Excluding female participants who reported hysterectomy at baseline.

[d]Excluding female participants who reported oophorectomy at baseline.

[e]Excluding participants who reported cholecystectomy at baseline.

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Table 5. Coffee consumption and endometrial cancer risk by BMI in the Multiethnic Cohort Study, 1993–2012[a]

Body mass index	No. of cases	Coffee consumption						P_{trend}	Per cup
		None	1–3 cups/month	1–6 cups/week	1 cup/day	2–3 cups/day	≥4 cups/day		
<30 kg/m^2	500	1.00 (ref.)	0.94 (0.62–1.43)	1.00 (0.70–1.41)	0.95 (0.71–1.26)	1.00 (0.75–1.34)	0.82 (0.51–1.32)	0.75	0.99 (0.92–1.07)
≥30 kg/m^2	311	1.00 (ref.)	0.64 (0.38–1.07)	0.87 (0.59–1.30)	0.82 (0.57–1.17)	0.76 (0.52–1.13)	0.31 (0.14–0.72)	0.04	0.87 (0.78–0.97)
$P_{heterogeneity}$		0.03							

[a]HR (95% CI). The following variables were included to rigorously control for the effects of smoking: smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time-dependent), and number of years since quitting (time-dependent). The models were further adjusted for age at cohort entry, education, alcohol intake, physical activity, history of diabetes, family history of corresponding cancer, and menopausal status and menopausal hormone therapy. Female participants who reported hysterectomy at baseline and those with missing or invalid BMI have been excluded.

Discussion

In this large multiethnic population, we found that a higher coffee intake was associated with lower risk of ovarian and thyroid cancers and of melanoma, in addition to liver cancer for which we previously reported an inverse association. We observed an inverse association with endometrial cancer but only among women with a BMI greater than 30 kg/m^2. The inverse associations were limited to caffeinated coffee and were consistent across racial/ethnic groups. Tea consumption was not associated with either cancer overall or with specific cancer sites.

A large number of previous studies have investigated associations of coffee drinking and cancer, although relatively few studies of non-white populations have been conducted. On the basis of current evidence, the WCRF/AICR Continuous Update Project (CUP) concluded that coffee intake probably decreases the risks of endometrial and liver cancers (15, 16). Our findings strongly support an inverse association for liver cancer as did our previous report (17). While we did not find an association with overall endometrial cancer in our multiethnic populations, we observed coffee drinking to be protective against endometrial cancer among women with high BMI (≥30 kg/m^2), consistent with previous reports (23–25). The IARC Working Group recently concluded that based on available evidence it was no longer possible to determine whether drinking coffee causes bladder cancer (5). Our results also showed no association between coffee consumption and risk of bladder cancer.

We found a decreased risk of melanoma associated with high coffee intake, which is consistent with recent meta-analyses (26–29). A recent meta-analysis of 7 prospective studies showed that the pooled relative risk (RR) of melanoma was 0.82 (95% CI, 0.69–0.97) for the highest versus lowest quantity of caffeinated coffee intake (29). Our results in the multiethnic U.S. populations were consistent with the meta-analyses which also reported a decreased risk with caffeinated coffee, but not with decaffeinated coffee (26–29).

In the CUP, the evidence for an association between coffee intake and ovarian cancer was judged to be too limited to draw a conclusion (11). A meta-analysis of 9 cohort studies in the CUP showed that the summary RR for ovarian cancer per 200 mL/day of coffee (~1 cup/day) was 1.02 (95% CI, 0.98–1.06; ref. 30). Since the CUP, and unlike our finding of an inverse association with ovarian cancer, two cohort studies reported no association between coffee consumption and this cancer (31, 32), while one case–control study found that coffee consumption was associated with a modest decreased risk of ovarian cancer (33). These previous reports were from studies conducted in mainly white populations. In our study, none of the ethnic specific association with ovarian cancer, including in whites, was statistically significant.

In this study, higher coffee consumption was associated with a lower risk of thyroid cancer. Reports that oxidative stress is involved in the development of thyroid cancer (34, 35) suggest that coffee consumption may reduce the risk of thyroid cancer through its antioxidant property (36). However, two cohort studies (32, 36) and two meta-analyses of case–control studies (37, 38) reported no association between coffee consumption and thyroid cancer.

Although tea and/or tea polyphenols have been shown to have anticancer properties in laboratory conditions (39, 40), the results of human studies have been inconclusive (6, 41). A study in the PLCO cohort found a decreased risk with tea drinking for all cancers combined but not with cancer specific sites (32). Our findings do not support a cancer preventive effect of tea and are consistent with results from a recent systematic review and meta-analysis of 57 papers from prospective studies (41).

Caffeine appears to be one of the contributors to the inverse association of certain cancers with coffee consumption that we found in the MEC, as the inverse association was present in exclusive drinkers of caffeinated coffee but not in exclusive drinkers of decaffeinated coffee. A recent study showed that caffeine and its own metabolites may counter age-related inflammation that contributes to the etiology of many cancers (42). However, our findings should be interpreted with caution because only 13% of coffee drinkers consumed decaffeinated coffee exclusively, while 59% were exclusive drinkers of caffeinated coffee and 28% drank both.

Our study has several important strengths including a prospective, population-based, design, a large number of participants, inclusion of a diverse population of five different racial/ethnic groups, a long follow-up period, and a capability to comprehensively control for potential confounding factors. However, there are also limitations to consider. Coffee intake was estimated by food frequency questionnaire at baseline and prone to measurement error. Coffee intake may also have changed over time during the follow-up. Nevertheless, among the participants who completed a follow-up food frequency questionnaire between 2003 and 2007 (average 11 years since baseline), the intraclass correlation coefficient between the two questionnaires was 0.60 (17). Using data from the baseline and the follow-up questionnaire, which about 46% of participants completed, the analysis with coffee consumption as a time-dependent variable yielded stronger inverse associations with ovarian, liver, and thyroid cancers and melanoma. However, when we limited the analysis to a subset who completed both questionnaires, incident cases especially of less common cancers as the follow-up survey were too small for meaningful analysis. Also, for less common cancers, the numbers of cases were limited for racial/ethnic-specific analyses. In addition, multiple testing may have accounted for some of the associations that we found. When considering Bonferroni

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correction for multiple comparison (significance level of 0.003 = 0.05/16 sites), trend tests for melanoma and liver cancer still met the stringent criteria.

In summary, in this large multiethnic prospective study we observed lower risk of liver, ovarian, thyroid and endometrial cancers, and melanoma with higher intake of coffee. The lower risk of endometrial cancer associated with coffee consumption was observed only among heavy women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Le Marchand, L.R. Wilkens
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Le Marchand
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