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Research Article

Coffee Intake and Gastric Cancer Risk: The Singapore Chinese Health Study

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Abstract

Background: Despite experimental evidence showing chemopreventive effects of coffee-related compounds on gastric carcinogenesis, epidemiologic studies generally do not support coffee–gastric cancer associations. Observational data are lacking among high-risk populations with sufficient regular coffee consumption.

Methods: We examined the association between caffeinated coffee intake and gastric cancer risk in a population-based cohort that enrolled 63,257 Chinese men and women ages 45 to 74 years between 1993 and 1998 in Singapore. Incident gastric cancer cases ($n = 647$) were identified after a mean follow-up of 14.7 years. Biomarkers of *Helicobacter pylori* (*H. pylori*) infection were measured in a subset of gastric cancer cases with blood collected before cancer diagnosis and their matched controls.

Results: In the total cohort, daily versus nondaily coffee intake was associated with a statistically nonsignificant decrease in gastric cancer risk [HR = 0.85; 95% confidence interval (CI), 0.69–1.04]. In women, the inverse association strengthened and reached statistical significance (HR = 0.63; 95% CI, 0.46–0.87). In analyses restricted to never smokers and nondrinkers of alcohol, inverse associations strengthened in the total cohort (HR = 0.69; 95% CI, 0.52–0.91) and in women (HR = 0.52; 95% CI, 0.37–0.74). There was no coffee–gastric cancer risk association among men, regardless of smoking status or alcohol consumption. Similar results were observed in the nested case–control study after adjustment for *H. pylori* infection.

Conclusion: Daily coffee consumption may reduce the risk of gastric cancer in high-risk populations, especially among women.

Impact: Research aimed at identifying the compounds in coffee that may protect against gastric carcinogenesis is warranted. *Cancer Epidemiol Biomarkers Prev; 23(4); 638–47. ©2014 AACR.*

Introduction

Gastric cancer is the third leading cause of cancer-related deaths in men and the fifth in women worldwide (1). The incidence of gastric cancer is especially high in East Asian populations due in part to diets rich in salt and fermented foods as well as a high prevalence of *Helicobacter pylori* (*H. pylori*) infection (2). In Singapore Chinese, gastric cancer is the fourth most common cause of cancer-related deaths (3). The average annual incidence rates (world-age standardized per 100,000) of gastric cancer from 2006 to 2010 were 14.3 and 7.9 in Singapore Chinese men and women, respectively (3). Established risk factors for gastric cancer worldwide include male gender, cigarette smoking, and larger body mass index (BMI; refs. 4, 5). Infection of the stomach with *H. pylori* is a strong risk factor for gastric cancer and was classified as a group 1 human carcinogen by the International Agency for Research on Cancer in 1994 (6). In addition to *H. pylori* infection, chronic atrophic gastritis, a condition of loss of glandular differentiation in the stomach tissue is also associated with an increased risk of gastric cancer (7).

Although *H. pylori* infection is a strong risk factor for noncardia gastric cancer, certain dietary factors also play a role in gastric cancer development. Epidemiologic studies have shown that high salt intake interacts synergistically with *H. pylori* infection to increase the risk of noncardia gastric cancer, while a few studies demonstrated a statistically significant protective effect of vitamin C or fresh fruit for all gastric cancers regardless of *H. pylori* status (6, 8). In addition, consumption of allium vegetables, such as garlic and onions, has been inversely associated with risk of gastric cancer (8). However, there are limited data

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addressing gastric cancer risk modulation by beverage sources of antioxidants, such as coffee.

Coffee is one of the most frequently consumed beverages worldwide (9). Singaporeans are among the only Asian population that consumes coffee on a regular basis (10). Kahweol and cafestol (diterpenes) are polyphenols in coffee that have demonstrated chemopreventive properties in cell and animal models of various cancers (11–13). In addition to providing diterpenes and antioxidants such as chlorogenic acids, coffee is a source of melanoidins, a heterogeneous group of compounds that has shown antimicrobial effects against *H. pylori in vitro* (14–16).

In Singapore, coffee grounds are typically boiled in water and then filtered through a muslin bag, a process that results in brewed coffee that has similar concentrations of the diterpenes kahweol and cafestol relative to the use of a paper filter, as in most Western populations (10, 17). In a meta-analysis of 6 cohort and 16 case–control studies, Botelho and colleagues (18) concluded that coffee consumption was not associated with gastric cancer risk, but nearly all of the prospective studies included were conducted in low-risk, Western populations and without consideration of *H. pylori* infection status. To explore whether there are associations between coffee consumption and the risk of gastric cancer in a Chinese population, we conducted prospective analyses with the Singapore Chinese Health Study database, a population-based prospective cohort of Chinese men and women living in Singapore. Furthermore, the availability of prediagnostic biospecimens from this cohort allowed for testing of and adjusting for *H. pylori* infection and atrophic gastritis status in evaluating the coffee–gastric cancer associations.

Materials and Methods

Study population

The design and inclusionary and exclusionary criteria for participation in the Singapore Chinese Health Study have been previously described (19). Members of the cohort were selected from permanent residents or citizens of Singapore ages 45 to 74 years living in government housing estates and belonging to one of the two major Chinese dialect groups (Cantonese and Hokkien; ref. 20). At baseline, all cohort members completed an in-person interview with a trained study staff member that included a validated 165-item food frequency questionnaire (FFQ) that assessed coffee intake at 9 predefined levels: never or hardly ever, 1–3 times per month, once per week, 2–3 times per week, 4–6 times per week, once per day, 2–3 times per day, 4–5 times per day, and 6 or more times per day (20). Because of the infrequent consumption of decaffeinated coffee among Singapore Chinese, only caffeinated coffee intake was assessed during the baseline interview. In concert with the FFQ validation, the Singapore Food Composition Database was developed using food composition data from China, Malaysia, Taiwan, and Hawaii; from this database, mean daily consumption values for 96 dietary components, including caffeine, were ascertained for each cohort member (20).

We collected biospecimens from 3% of random samples of cohort participants beginning in 1994 and the sample collection was extended to all consenting cohort participants in 2000. By April 2005, biospecimens were obtained from 32,543 subjects, representing a consent rate of approximately 60% after excluding deaths. The various components of blood, buccal, and urine samples have been stored at −80°C freezers since their collection. The Singapore Chinese Health Study was approved by the Institutional Review Boards at the National University of Singapore and the University of Pittsburgh (Pittsburgh, PA).

Identification of cancer cases

Cancer diagnoses and deaths from cancer were identified by linkage analysis for all cohort members with the Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases (21). We used data from the 27,293 men and 34,028 women who did not have a history of cancer diagnosis at baseline, based on self-report and computer-assisted record linkage analysis with the Singapore Cancer Registry. To date, only 49 cohort participants were lost to follow-up due to migration out of Singapore. As of December 31, 2011 (an average follow-up of 14.7 years), 647 of these cohort members had been diagnosed with gastric adenocarcinoma (ICD-10, 16.0–16.9). Of these cases, 629 were diagnosed based on histopathologic confirmation, while 18 were clinically confirmed. There were 90 gastric cardia cases, 424 noncardia cases and 133 unspecified cases.

H. pylori and chronic atrophic gastritis testing

All patients with incident gastric cancer diagnosed before December 31, 2008 and who donated a blood sample before cancer diagnosis were included in a nested case–control study for *H. pylori* infection in relation to gastric cancer risk. For each case, we randomly selected 3 individual subjects among the cohort participants who donated a blood sample at baseline. The eligible subjects were those alive and free of cancer at the time of gastric cancer diagnosis of the index case. All three chosen subjects were individually matched to the index case on age at study enrollment (within 3 years), sex, dialect, and date of sample collection (within 6 months). A total of 133 cases and 389 controls were available for the present study.

Plasma samples were tested for *H. pylori* antibodies by Western blot analysis using a qualitative assay (Helico Blot 2.1, MP Biomedicals, Singapore; F. Zhu). Subjects were classified as *H. pylori*-positive according to kit specifications, which have been validated with 96% sensitivity and 95% specificity by the manufacturer based on differentiation of reactivity to each of the various *H. pylori* antigens, including CagA, VacA, and UreA (22). Plasma pepsinogen I (PG I) and II (PG II) were measured with a latex agglination turbidimetric immunoassay kit (LZ Test "Eiken" Pepsinogen I and II) and an automated analyzer (Siemens Advia 2400). Subjects were classified as positive

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for atrophic gastritis if PG I <70 ng/mL and PG I:II <3, as recommended by the manufacturer. In a recent analysis of a prospective cohort study conducted in Japan, the sensitivity and specificity of these biomarkers for gastric cancer were 71.0% and 69.2%, respectively, among individuals over 40 years of age with no prior history of gastric cancer or gastrectomy (23). All assays were conducted by personnel who were blinded to the case–control status of all test samples.

Statistical analyses

Person-years of follow-up were computed from the recruitment date to the date of gastric cancer diagnosis, death, migration, or December 31, 2011, whichever occurred first. A series of Cox proportional hazards regression models were performed to test the associations between coffee and gastric cancer incidence. The proportional hazards assumption was investigated by including an interaction term for coffee intake and time (i.e., person-years of follow-up) in the adjusted model and evaluating whether the covariate was a statistically significant predictor of gastric cancer risk. Defined categories of coffee intake frequencies (e.g., cups/day) were evaluated as exposure variables. Quartiles of caffeine exposure were derived from the intake distribution among the entire cohort. To control for confounding, the following were included as covariates: sex, dialect group (Cantonese, Hokkien), age (years), interview year (1993–1995, 1996–1998), education level (no formal education/primary, secondary or higher), cigarette smoking status (never, former, current), number of cigarettes smoked per day (never, 1–12, ≥13), years smoked (never, 1–39, ≥40), BMI (<20, 20–<24, 24–<28, ≥28 kg/m^2), and total energy intake (kcal/day). In addition, daily caffeine intake (mg/day) was included as a covariate in the final coffee–gastric cancer models to assess if compounds other than caffeine have an independent association with gastric cancer risk. Adjustment for history of diabetes, alcohol consumption, or selected dietary factors (i.e., dairy, protein, fruit and vegetable, and preserved meat and fish intakes) did not materially change the HRs for coffee intake and gastric cancer risk in the entire cohort or in men and women separately. For women, further adjustment for reproductive factors (i.e., age at first period, number of live births, and menopausal status) in the proportional hazards model did not alter the association between coffee intake and gastric cancer risk.

Separate parallel statistical analyses were performed for the overall cohort as well as for men and women separately. In addition, we examined whether the association between coffee intake and gastric cancer risk varied by smoking status, alcohol consumption, and BMI by stratified analyses and assessing the fitness of interaction terms in adjusted models. All HRs and 95% confidence intervals (CI) reported were computed relative to the lowest exposure category. The linear tests for coffee/caffeine–gastric cancer trends were computed on the basis of ordinal values for the quartile or ordered categories (e.g., 0, 1, 2, 3).

The objective of the nested case–control study was to examine the association between coffee and gastric cancer risk after taking into account *H. pylori* infection and chronic atrophic gastritis status. We performed these statistical analysis using both conditional and unconditional logistic regression methods and obtained similar results. Therefore, all results presented in this report were based on unconditional logistic regression method to maximize the number of subjects included in the analysis. In addition to variables for *H. pylori* infection and atrophic gastritis status, all matching factors forming the case–control set were included in the unconditional logistic regression models. ORs and their corresponding 95% CIs were used to assess the association between coffee intake and gastric cancer risk.

All statistical computing was carried out using SAS 9.2 (SAS Institute, Inc.). All *P* values reported were two-sided. The *P* value of <0.05 was considered statistically significant.

Results

The distribution of demographic characteristics of cohort members by coffee intake frequency is presented for the total cohort (Supplementary Table S1) and for men and women separately (Table 1). The percentage of never coffee drinkers in the total cohort and in men and women was 18.5, 17.1, and 19.6, respectively. The proportion of current smokers and alcohol consumption increased, while the proportion with higher education and a history of diabetes decreased with increasing coffee intake in both men and women. Compared with individuals consuming less than one cup of coffee per day, men who drank more than 4 cups of coffee per day had lower levels of BMI. Among women, the distributions of reproductive factors (i.e., age at first menstrual period, number of live births, and menopausal status) were similar across different categories of coffee intake (data not shown). Those who drank more coffee were more likely to add sugar to their coffee and also consumed more total energy but less fruit and vegetables than nondrinkers or those consuming <1 cup of coffee per day.

In the total cohort, higher education level was associated with decreased risk of gastric cancer and higher BMI and current smoking were associated with increased risk (Table 2). The positive association with BMI was observed in men, but not women. No associations were observed with diabetes, history of ulcer or alcohol intake in the total cohort or in men or women (Table 2). Fruit intake was inversely associated with gastric cancer risk in the total cohort, with similar associations in men and women. Vegetable intake was not associated with gastric cancer risk.

In women, daily coffee intake was associated with a statistically significant decrease in gastric cancer risk, compared with nondaily intake (Table 3). Conversely, there was no association between coffee intake and gastric cancer risk in men ($P_{\text{interaction}}$ with sex = 0.184). The inverse association between daily coffee drinking and gastric cancer risk in women remained after removing

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Table 1. Distribution of selected baseline characteristics stratified by sex and coffee intake frequency

	Men Coffee intake				Women Coffee intake			
Characteristic	**<1 cup/day**	**1 cup/day**	**2–3 cups/day**	**≥4 cups/day**	**<1 cup/day**	**1 cup/day**	**2–3 cups/day**	**≥4 cups/day**
Person years of follow-up	108,838	118,655	136,914	22,002	155,252	207,347	140,411	13,742
Mean age, y (SD)	57 (8)	57 (8)	56 (8)	55 (7)	56 (8)	56 (8)	56 (8)	56 (8)
Body mass index, kg/m^2 (%)								
<20	13.6	15.6	17.0	20.1	15.9	14.1	14.4	15.3
20–<24	51.8	53.0	54.2	54.2	54.6	54.7	55.2	56.2
24–<28	27.5	25.3	23.1	20.5	21.5	23.3	22.5	20.3
≥28	7.1	6.2	5.8	5.2	8.0	7.9	7.9	8.2
Education, ≥secondary level (%)	43.1	37.8	34.9	33.9	26.1	19.4	17.0	15.3
Smoking status (%)								
Never	53.4	44.1	35.0	19.4	94.7	91.6	88.4	76.7
Former	23.5	22.4	19.9	14.4	2.1	2.7	2.6	3.4
Current	23.1	33.5	45.1	66.2	3.2	5.8	9.1	20.0
Alcohol use, ≥1 drink/week (%)	18.5	24.1	24.8	24.2	3.6	4.5	5.9	8.5
History of ulcer (% yes)	6.6	4.1	3.7	5.6	3.3	1.8	1.8	3.0
History of diabetes (% yes)	10.9	8.9	7.0	6.0	10.8	9.3	7.5	5.0
Additions to coffee or tea (% yes)								
Sugar	48.1	71.7	78.5	83.2	36.9	64.5	74.5	84.7
Milk	50.9	50.7	48.1	38.3	42.3	47.4	45.1	34.6
Mean daily intake (SD)								
Total energy, kcal	1,697 (584)	1,702 (599)	1,816 (618)	1,929 (674)	1,369 (465)	1,366 (451)	1,466 (493)	1,568 (558)
Caffeine, mg/1,000 kcal	45.6 (46.9)	81.3 (43.2)	151.4 (59.3)	255.8 (105.0)	33.8 (42.8)	86.1 (40.7)	173.3 (65.4)	306.1 (114.8)
Fruit, g/1,000 kcal	132.8 (96.8)	129.0 (91.6)	110.5 (83.1)	92.6 (75.3)	146.8 (108.7)	143.0 (102.8)	121.9 (92.6)	97.3 (93.2)
Vegetables, g/1,000 kcal	67.3 (32.5)	65.9 (30.3)	61.5 (29.5)	56.5 (27.6)	82.5 (39.0)	80.9 (36.0)	74.4 (34.2)	70.2 (34.3)

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Table 2. HR and 95% CIs for baseline characteristics in relation to gastric cancer risk

	Overall		Men		Women	
	Cases, *n*	HR (95% CI)	Cases, *n*	HR (95% CI)	Cases, *n*	HR (95% CI)
N	647		394		253	
Education						
No formal education	224	1.00[a]	64	1.00[a]	160	1.00[a]
Primary level	309	0.87 (0.72–1.05)	243	1.11 (0.84–1.47)	66	0.61 (0.45–0.82)
≥Secondary level	114	0.63 (0.49–0.81)	87	0.74 (0.53–1.04)	27	0.59 (0.38–0.90)
P_{trend}		<0.001		0.032		0.001
Body mass index, kg/m^2						
<20	80	1.00[a]	45	1.00[a]	35	1.00[a]
20–<24	367	1.26 (0.99–1.60)	224	1.46 (1.06–2.02)	143	1.00 (0.69–1.45)
24–<28	144	1.24 (0.94–1.63)	93	1.51 (1.06–2.16)	51	0.92 (0.59–1.42)
≥28	56	1.71 (1.21–2.42)	32	2.24 (1.41–3.53)	24	1.20 (0.71–2.02)
P_{trend}		0.012		0.002		0.774
Self-reported diabetes						
No	588	1.00[a]	366	1.00[a]	222	1.00[a]
Yes	59	1.01 (0.77–1.33)	28	0.84 (0.57–1.23)	31	1.27 (0.86–1.85)
History of ulcer						
No	619	1.00[a]	375	1.00[a]	244	1.00[a]
Yes	28	1.03 (0.71–1.51)	19	0.93 (0.58–1.48)	9	1.42 (0.73–2.77)
Smoking status						
Never	351	1.00[b]	134	1.00[b]	217	1.00[b]
Former	90	1.16 (0.84–1.62)	79	1.00 (0.70–1.44)	11	2.32 (0.99–5.42)
Current	206	1.70 (1.33–2.17)	181	1.64 (1.25–2.15)	25	1.82 (0.95–3.47)
Alcohol use						
Nondrinker	547	1.00[a]	305	1.00[a]	242	1.00[a]
<7 drinks/week	68	1.21 (0.94–1.57)	60	1.25 (0.95–1.65)	8	1.06 (0.52–2.15)
≥7 drinks/week	32	1.13 (0.78–1.62)	29	1.16 (0.79–1.71)	3	0.99 (0.32–3.09)
P_{trend}		0.208		0.169		0.936
Fruit intake						
Quartile 1	209	1.00[c]	115	1.00[c]	94	1.00[c]
Quartile 2	175	1.02 (0.83–1.25)	109	1.10 (0.84–1.43)	66	0.91 (0.66–1.26)
Quartile 3	140	0.88 (0.70–1.10)	86	0.88 (0.66–1.18)	54	0.90 (0.63–1.28)
Quartile 4	123	0.80 (0.63–1.03)	84	0.83 (0.60–1.13)	39	0.78 (0.52–1.19)
P_{trend}		0.053		0.128		0.265
Vegetable intake						
Quartile 1	198	1.00[c]	108	1.00[c]	90	1.00[c]
Quartile 2	167	0.98 (0.80–1.21)	103	1.10 (0.83–1.44)	64	0.86 (0.62–1.19)
Quartile 3	151	0.98 (0.78–1.23)	101	1.18 (0.89–1.57)	50	0.76 (0.52–1.09)
Quartile 4	131	0.98 (0.72–1.21)	82	0.98 (0.70–1.37)	49	0.91 (0.60–1.37)
P_{trend}		0.627		0.845		0.408

[a]HRs are adjusted for age (years), gender (in overall model only), interview year (1993–1995, 1996–1998), dialect (Hokkien, Cantonese), cigarette smoking status (never, former, current), number of cigarettes smoked per day (never, 1–12, ≥13), years smoked (never, 1–39, ≥40), and body mass index (<20, 20–<24, 24–<28, ≥28 kg/m^2).

[b]HRs are adjusted for same covariates as listed above (a), excluding cigarette smoking status.

[c]HRs are adjusted for same covariates as listed above (a), including total energy intake (kcal/day).

the first 2 years of follow-up (HR = 0.62; 95% CI, 0.43–0.91; P_{trend} = 0.01; comparing daily to nondaily intake). The inverse relationship between coffee and gastric cancer in women did not differ by duration of follow-up (data not shown) or by subsite (HR = 0.82; 95% CI, 0.30–2.25 for cardia, and HR = 0.68; 95% CI, 0.46–1.01 for noncardia). Caffeine intake was not associated with gastric cancer risk in either men or women or both sexes combined (Table 3).

We conducted stratified analyses by factors that were correlated with coffee intake in our data (i.e., smoking, alcohol intake, and BMI) to further reduce the potential confounding effect of these factors on the observed coffee–gastric cancer risk associations. Among never smokers,

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Table 3. Coffee and caffeine intake and gastric cancer risk

	Overall		Men		Women	
	Cases, *n*	HR (95% CI)	Cases, *n*	HR (95% CI)	Cases, *n*	HR (95% CI)
Coffee intake						
Never/monthly	132	1.00[a]	75	1.00[a]	57	1.00[a]
Weekly	61	1.06 (0.78–1.44)	32	0.95 (0.62–1.43)	29	1.22 (0.78–1.92)
1 cup/day	199	0.84 (0.66–1.07)	118	0.98 (0.72–1.33)	81	0.66 (0.45–0.97)
2–3 cups/day	223	1.00 (0.71–1.40)	147	1.12 (0.74–1.69)	76	0.81 (0.45–1.47)
≥4 cups/day	32	0.93 (0.49–1.79)	22	1.06 (0.48–2.32)[b]	10	0.76 (0.23–2.53)[b]
P_{trend}		0.449		0.719		0.068
Nondaily	193	1.00[a]	107	1.00[a]	86	1.00[a]
Daily	454	0.85 (0.69–1.04)	287	1.03 (0.79–1.34)[c]	167	0.63 (0.46–0.87)[c]
Caffeine intake[d]						
Q1 (lowest)	161	1.00[d]	85	1.00[e]	76	1.00[e]
Q2	134	0.78 (0.62–0.98)	86	0.89 (0.66–1.21)	48	0.66 (0.46–0.94)
Q3	157	0.86 (0.69–1.07)	108	1.02 (0.76–1.36)	49	0.65 (0.45–0.94)
Q4 (highest)	195	0.98 (0.79–1.22)	115	1.02 (0.75–1.37)[f]	80	0.98 (0.71–1.36)[f]
P_{trend}		0.869		0.685		0.902

[a]HRs are adjusted for age (years), gender (in overall model only), interview year (1993–1995, 1996–1998), dialect (Hokkien, Cantonese), education (less than secondary, secondary or greater), cigarette smoking status (never, former, current), number of cigarettes smoked per day (never, 1–12, ≥13), years smoked (never, 1–39, ≥40), body mass index (<20, 20–<24, 24–<28, ≥28 kg/m^2), caffeine (mg/day), and total energy intake (kcal/day).

[b]*P* for sex interaction = 0.733.

[c]*P* for sex interaction = 0.184.

[d]The following are the cutpoints for first through fourth quartiles of caffeine intake (mg/day): <71.2, 71.2–114.0, 114.1–224.1, >224.1.

[e]HRs are adjusted for same covariates as listed above ([a]), excluding caffeine and with the addition of alcohol consumption (never, ever).

[f]*P* for sex interaction = 0.948.

the inverse association between daily coffee drinking and gastric cancer risk in the total cohort strengthened and became statistically significant ($P_{interaction} = 0.0495$; Table 4). In women the statistically significant association strengthened ($P_{interaction} = 0.026$), but in men there remained no association ($P_{interaction} = 0.827$). The inverse association with daily coffee intake and gastric cancer risk in women was most evident among nondrinkers of alcohol, although alcohol intake in women was infrequent ($P_{interaction} = 0.692$). In men who drank alcohol, there was a statistically nonsignificant inverse association with coffee ($P_{interaction} = 0.325$). When we further restricted analyses among men to those who were never smokers and nondrinkers of alcohol, there remained no association between daily versus nondaily coffee intake and gastric cancer risk (HR = 1.13; 95% CI, 0.70–1.83). In the analyses restricted to never smokers and nondrinkers of alcohol, there were statistically significant inverse associations with daily versus nondaily coffee intake and gastric cancer risk in the total cohort (HR = 0.69; 95% CI, 0.52–0.91) and in women (HR = 0.52; 95% CI, 0.37–0.74). There was no evidence of effect modification by BMI level on the association between coffee intake and gastric cancer risk in the total cohort, or among men and women separately (all *P* values for coffee by BMI interaction > 0.050; Table 4).

We further examined the association between coffee intake and gastric cancer risk after adjustment for *H. pylori* infection in a subset of the cohort study. In this study population, the seroprevalence of *H. pylori* (i.e., CagA) was 96.2% in cases and 84.6% in controls. The corresponding figure for positive atrophic gastritis (i.e., PG I <70 ng/mL and PG I:II <3) was 35.3% in cases and 12.6% in controls. There was no relationship between coffee drinking and *H. pylori* seroprevalence or atrophic gastritis status among controls (Supplementary Table S2). Compared with nondaily coffee drinkers, those who drank at least 1 cup per day had a 50% lower risk of gastric cancer in both men and women combined after adjustment for CagA and other serologic biomarkers of *H. pylori* infection (Table 5). The *H. pylori*-adjusted inverse association between coffee intake and gastric cancer risk was stronger for women than for men (*P* for coffee by sex interaction = 0.287). Further adjustment for serologic biomarker of atrophic gastritis status did not materially alter the association between coffee intake and gastric cancer risk. The pepsinogen-adjusted OR (95% CIs) of gastric cancer for daily coffee drinkers was 0.47(0.27–0.83) in total subjects, 0.72 (0.35–1.49) in men, and 0.20 (0.07–0.54) in women, compared with their counterparts who drank less than 1 cup of coffee per day.

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Table 4. Coffee intake and gastric cancer risk by smoking status, alcohol use, and body mass index

	Overall		Men		Women	
Coffee intake	**Cases, *n***	**HR (95% CI)**	**Cases, *n***	**HR (95% CI)**	**Cases, *n***	**HR (95% CI)**
Never smokers						
Nondaily	132	1.00[a]	48	1.00[a]	84	1.00[a]
Daily	219	0.71 (0.54–0.92)	86	1.06 (0.69–1.63)	133	0.54 (0.38–0.76)
Ever smokers						
Nondaily	61	1.00[b]	59	1.00[b]	2	1.00[b]
Daily	235	1.10 (0.79–1.52)	201	1.00 (0.72–1.41)	34	3.36 (0.75–15.03)
Alcohol nondrinkers						
Nondaily	167	1.00[a]	83	1.00[a]	84	1.00[a]
Daily	380	0.84 (0.67–1.05)	222	1.09 (0.80–1.47)	158	0.61 (0.44–0.84)
Alcohol drinkers						
Nondaily	26	1.00[a]	24	1.00[a]	2	1.00[a]
Daily	74	0.84 (0.5–1.42)	65	0.80 (0.46–1.38)	9	1.41 (0.24–8.18)
BMI (<23.1 kg/m^2)						
Nondaily	87	1.00[c]	51	1.00[c]	36	1.00[c]
Daily	226	0.91 (0.68–1.23)	163	1.13 (0.78–1.64)	63	0.59 (0.35–0.99)
BMI (≥23.1 kg/m^2)						
Nondaily	106	1.00[c]	56	1.00[c]	50	1.00[c]
Daily	228	0.79 (0.60–1.05)	124	0.90 (0.62–1.32)	104	0.66 (0.43–0.99)

[a]HRs are adjusted for age (years), gender (in overall model only), interview year (1993–1995, 1996–1998), dialect (Hokkien, Cantonese), education (less than secondary, secondary or greater), cigarette smoking status (never, former, current), number of cigarettes smoked per day (never, 1–12, ≥13), years smoked (never, 1–39, ≥40), body mass index (<20, 20–<24, 24–<28, ≥28 kg/m^2), caffeine (mg/day), and total energy intake (kcal/day).

[b]HRs are adjusted for same covariates as listed above ([a]), excluding cigarette smoking status.

[c]HRs are adjusted for same covariates as listed above ([a]), excluding body mass index.

Discussion

Using the extensive database of The Singapore Chinese Health Study, a population-based cohort study with a mean follow-up of more than 14 years, inverse associations were reported for daily coffee intake and gastric cancer risk in women, but not in men. Singapore Chinese women who drank coffee at least one cup a day had a statistically significant 37% decreased risk of gastric cancer. Our novel findings suggest that coffee may decrease the risk of gastric cancer among women in high-risk populations, where *H. pylori* infection is common.

Our main finding for an inverse association with daily coffee intake and gastric cancer risk among women appears to be inconsistent with the majority of epidemiologic findings. In a meta-analysis that included epidemiologic studies among mostly low-risk populations, no association was observed between coffee intake and gastric cancer risk (OR = 0.97; 95% CI, 0.86–1.09; ref. 18). None of the six prospective cohort studies in the meta-analysis observed statistically significant associations between coffee intake and gastric cancer risk, regardless of sex (18). In a recent U.S. cohort, more than 3 cups per day versus less than 1 cup per day was associated with a statistically significant 57% increase in risk of gastric cardia cancer, but no association was observed with noncardia cancer risk (24). It is plausible that the differences in etiology between gastric cardia and noncardia cancers may explain this disparity. We did not observe a positive association between coffee and gastric cardia cancer risk (HR = 0.78; 95% CI, 0.46–1.33 for daily versus nondaily consumption). These analyses were based on only 90 cases and thus too imprecise for meaningful interpretation.

The populations of Sweden and Finland are among the highest coffee consumers in the world (9). In a recent publication from a Finnish cohort, where the average intake in men and women was 5.2 cups per day and 4.5 cups per day, respectively, a statistically nonsignificant inverse association was reported, comparing ≥10 cups per day versus none (HR = 0.75; 95% CI, 0.40–1.41; P_{trend} = 0.19; ref. 25). In a Swedish cohort of women, a positive association for an increase of 1 cup per day was reported (HR = 1.22; 95% CI, 1.05–1.42; ref. 26). However, after adjusting for smoking status among a smaller subset of the cohort with available smoking data (n = 55 cases), the association remained, but lost statistical significance (HR = 1.21; 95% CI, 0.96–1.54).

Infection with *H. pylori* is a necessary, but not sufficient factor for the development of gastric cancer (27). The bacterium colonizes in the gastric mucosa, eliciting an inflammatory response that increases oxidative stress and

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Table 5. Coffee intake and gastric cancer risk among cases and controls nested within the Singapore Chinese Health Study

Coffee intake	Cases/controls, *n*	Multivariable-adjusted OR (95% CI)[a]	*H. pylori*–adjusted OR (95% CI)[b]
Overall			
Nondaily	45/107	1.00	1.00
Daily	88/282	0.54 (0.31–0.91)	0.50 (0.29–0.86)
Men			
Nondaily	25/72	1.00	1.00
Daily	60/178	0.84 (0.43–1.65)	0.76 (0.38–1.52)
Women			
Nondaily	20/35	1.00	1.00
Daily	28/104	0.22 (0.08–0.56)	0.21 (0.08–0.56)

[a]ORs are adjusted for age (years), gender (in overall model only), interview year (1993–1995, 1996–1998), dialect (Hokkien, Cantonese), education (less than secondary, secondary or greater), cigarette smoking status (never, former, current), number of cigarettes smoked per day (never, 1–12, ≥13), years smoked (never, 1–39, ≥40), body mass index (<20, 20–<24, 24–<28, ≥28 kg/m^2), caffeine (mg/day), total energy intake (kcal/day), and date of biospecimen collection.

[b]ORs are adjusted for the same covariates as in model (a), in addition to *H. pylori* serology status.

gastric epithelial cell proliferation during in the initiating stages of gastric carcinogenesis (28, 29). A high prevalence of *H. pylori* infection is a characteristic of populations in regions with intermediate and high gastric cancer rates, such as Singapore, China, and South America (30, 31).

A mechanism by which coffee may reduce the risk of developing gastric cancer, especially in stomach mucosa with chronic *H. pylori* infection, is that the phenolic compounds present in coffee, such as chlorogenic acid and the diterpenes cafestol and kahweol decrease oxidative stress and inflammation (32–34), thereby reducing the likelihood of mutagenesis and cancer initiation (14, 35). In fact, it is the attenuation of subclinical inflammation as well as reduction of oxidative stress that are the hypothesized underlying mechanisms responsible for the inverse associations that we and others have observed for coffee intake and development of type II diabetes (36, 37). In a recent human trial, consumption of 4 or 8 cups of coffee per day, compared with none, showed statistically significant reduced serum levels of inflammatory cytokines (e.g., interleukin 18), increased anti-inflammatory biomarkers (e.g., adiponectin), and oxidative stress biomarkers (e.g., 8-isoprostane; ref. 38).

Under a hypothesis of a protective effect of coffee consumption against the development of gastric cancer through an anti-inflammatory/oxidative stress mechanism, one would expect to observe a stronger inverse association between coffee intake and gastric cancer risk in a population with high prevalence of *H. pylori* as well as sufficient level of coffee consumption. Our study population has both of these characteristics, in which a modest, statistically significant inverse association was observed. Similar results were reported in different populations with similar characteristics, i.e., with high-risk of gastric cancer and sufficient coffee consumption. High coffee consumption was associated with a significantly reduced risk of gastric cancer in a population-based case–control study in Venezuela (OR = 0.58; 95% CI, 0.37–0.92; P_{trend} = 0.01; for fourth versus first quartile; ref. 39), and in a hospital-based case–control study in Uruguay (OR = 0.42; 95% CI, 0.25–0.68; $P_{trend} < 0.001$; for third versus first tertile; ref. 40). On the other hand, largely null results or statistically nonsignificant coffee–gastric cancer associations have generally been reported from epidemiologic studies in low-risk populations with high coffee intake, as well as those in high-risk populations with low coffee intake. For example, no association was reported from a large population-based case–control study in Shanghai, China, where regular coffee consumption was rare (41). Similarly, no association was observed in a prospective cohort in Japan, where coffee consumption was low (42).

It is interesting that the present study shows an inverse association between daily coffee intake and gastric cancer risk among women only. The reasons for stomach cancer excess in males over females worldwide are not completely understood (43–45). One hypothesis is that female sex hormones may offer some protection against the development of gastric cancer (46). In a rat model of carcinogen-induced gastric cancer, sex-associated differences in estrogen receptor (ER)-β mRNA expression were observed, where higher ER-β levels in cancer versus normal tissues were reported for female, but not male rats (47). ER-β blocks ER-α transcriptional activity, and ER-α induction is implicated in the malignant transformation and progression of a number of epithelial tumors (48, 49). Dietary phytoestrogens may protect against gastric cancer (50), given their structural and functional similarity to 17β-estradiol and their particular affinity for binding to ER-β (51). Coffee, as a source of dietary phytoestrogens (52), such as trigonelline (53), has demonstrated weak

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estrogenic activity *in vitro* (54). Phytoestrogens are considered estrogen agonists in postmenopausal women, due to the significantly reduced production of natural estrogens after menopause. Seventy-two percent of women in our study population were postmenopausal at baseline. There was no difference in the association with daily coffee intake when analyses were restricted to postmenopausal women (HR = 0.63; 95% CI, 0.44–0.88). Although adjustment for reproductive factors did not alter the HR for coffee and gastric cancer risk, it seems biologically plausible that coffee, as a source of phytoestrogens, may be inversely related to gastric cancer risk through an estrogen-dependent mechanism.

There were a number of strengths of our analyses. The prospective nature of the Singapore Chinese Health Study allowed for the ascertainment of coffee intake, as well as important covariate exposures before diagnosis of cancer, thereby eliminating the opportunity for differential recall bias. There was also no potential bias due to loss of follow-up given the virtually complete follow-up for incidence of gastric cancer among the cohort participants (<0.1% loss to follow-up). Finally, the inclusion of biomarkers benefits the analysis by providing information about the important risk factors *H. pylori* infection and chronic atrophic gastritis. There were limitations inherent in relying on only a baseline assessment of self-reported coffee intake. Nondifferential misclassification due to changes in coffee drinking behavior during follow up may have attenuated the observed association in the total cohort. Another limitation was the reduced precision of the HRs for coffee–gastric cancer associations in analyses among women, given the lower number of female versus male gastric cancer cases. It remains possible that the gender-specific results are spurious and thus should be interpreted cautiously.

In conclusion, consumption of at least one cup of coffee per day was associated with a statistically significant reduction in gastric cancer risk among Singapore Chinese women, especially never smokers or nondrinkers of alcohol. Our finding is consistent with previous findings from smaller, cross-sectional studies conducted among populations at high risk of gastric cancer and with sufficient regular coffee consumers. Additional prospective data from studies conducted in high-risk populations are needed to confirm our finding. Experimental research is needed to elucidate the specific anti-inflammatory, antioxidative stress, and phytoestrogenic mechanisms by which coffee-related compounds may play a role in reducing gastric cancer development.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.E. Ainslie-Waldman, J.-M. Yuan, L.M. Butler
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.-P. Koh, J.-M. Yuan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.E. Ainslie-Waldman, A. Jin, K.G. Yeoh, F. Zhu, R. Wang, L.M. Butler
Writing, review, and/or revision of the manuscript: C.E. Ainslie-Waldman, W.-P. Koh, K.G. Yeoh, F. Zhu, J.-M. Yuan, L.M. Butler
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.E. Ainslie-Waldman
Study supervision: W.-P. Koh

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