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Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies

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Specific beverage intake may be associated with the risk of renal cell cancer through a diluting effect of carcinogens, alterations of hormone levels, or other changes in the renal tubular environment, but few prospective studies have examined these associations. We evaluated the associations between coffee, tea, milk, soda and fruit and vegetable juice intakes and renal cell cancer risk in a pooled analysis of 13 prospective studies (530,469 women and 244,483 men). Participants completed a validated food-frequency questionnaire at baseline. Using the primary data, the study-specific relative risks (RRs) were calculated and then pooled using a random effects model. A total of 1,478 incident renal cell cancer cases were identified during a follow-up of 7–20 years across studies. Coffee consumption was associated with a modestly lower risk of renal cell cancer (pooled multivariate RR for 3 or more 8 oz (237 ml) cups/day versus less than one 8 oz (237 ml) cup/day = 0.84; 95% CI = 0.67–1.05; *p* value, test for trend = 0.22). Tea consumption was also inversely associated with renal cell cancer risk (pooled multivariate RR for 1 or more 8 oz (237 ml) cups/day versus nondrinkers = 0.85; 95% CI = 0.71–1.02; *p* value, test for trend = 0.04). No clear associations were observed for milk, soda or juice. Our findings provide strong evidence that neither coffee nor tea consumption increases renal cell cancer risk. Instead, greater consumption of coffee and tea may be associated with a lower risk of renal cell cancer.

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Key words: renal cell cancer; coffee; tea; milk; juice; soda; prospective study

Renal cell cancer incidence rates have been increasing steadily over the past 3 decades.¹ However, the etiology of renal cell cancer remains unclear. Given that the main functions of the kidneys are to regulate water and inorganic-ion balance, and to excrete waste

products and foreign chemicals,² the risk of renal cell cancer may be affected by the quantity and type of beverages consumed. More specifically, beverages containing caffeine and/or antioxidants may reduce renal cell cancer risk because caffeine has a diuretic effect by blocking anti-diuretic hormone,² and antioxidants alleviate oxidative damage to DNA, proteins and other molecules.³ Moreover, coffee and tea intake may reduce the risk of renal cell cancer by improving insulin sensitivity.^{4,5} Beverages high in protein, such as milk, may increase the risk of renal cell cancer because high protein intakes may cause renal hypertrophy or renal damage.⁶

Inconsistent associations with risk of renal cell cancer have been observed in several case-control studies for intakes of coffee and tea,^{7–18} soda,^{7–9,11,16,18} juice¹⁹ and milk.^{9–11,17,19–21} However, very few prospective studies^{22–25} have examined these relationships because many prospective studies have a relatively small number of incident renal cell cancer cases. We therefore examined the associations between intakes of coffee, tea, milk, soda and juice and risk of incident renal cell cancer in a pooled analysis of 13 prospective studies including 1,478 renal cell cancer cases. We previously reported a modest inverse association between alcohol intake and renal cell cancer risk.²⁶

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Material and methods

Study population

The Pooling Project of Prospective Studies of Diet and Cancer (referred to as the Pooling Project) has been described elsewhere.²⁷ For the renal cell cancer analyses, each included study met the following prespecified criteria: at least one publication on a diet and cancer association, identification of at least 25 incident renal cell cancer cases, assessment of long-term dietary intake, and validation of the dietary assessment method or a closely related instrument. Studies including both men and women were treated as 2 separate cohorts (1 of men and 1 of women) and the inclusion criteria were applied to each gender-specific cohort. Overall, the renal cell cancer analyses included 530,469 women and 244,483 men from 13 prospective studies. The Canadian National Breast Screening Study and the Netherlands Cohort Study were each analyzed as case-cohort studies.²⁸ In the Pooling Project, we have divided the person-time of the Nurses' Health Study into 2 segments corresponding to the 1980–1986 follow-up period (part a) and follow-up beginning in 1986 (part b) to take advantage of the increased comprehensiveness of the food-frequency questionnaire (FFQ) completed in 1986 ($n = 131$ food items) compared to the FFQ completed in 1980 ($n = 61$ food items). In the renal cell cancer analyses, we only used data from the Nurses' Health Study (part b) because fewer than 25 cases were identified between 1980 and 1986.

Case ascertainment

Cases were ascertained by follow-up questionnaires and subsequent review of medical records,^{22,29} linkage to cancer registries,^{23,24,30–34} or both.^{35–37} Some studies also used linkage to mortality registries to identify outcomes.^{22–24,29,30,33–37} We defined renal cell cancer cases as those with histologically confirmed renal cell cancer (ICD-O-2 code = C64.9; ICD-9 = 189.0) using histological codes based on the International Classification of Diseases for Oncology^{38,39} or the morphological classification provided by the study investigators. The majority (62%) of cases were classified as renal cell carcinoma, NOS (morphology code = 8312) and clear cell carcinoma was the second most frequent (20%) histologic subgroup. The proportion of renal cell carcinoma, NOS in our database is higher than that reported in surgical series which have reported clear cell carcinoma as the most common type of renal cell cancer.⁴⁰ This may be due to, in part, the large number of renal cell cancer cases in our data that were ascertained before a 1997 workshop on the diagnosis and prognosis of renal cell cancer held by the World Health Organization,⁴⁰ which prompted more widespread use of the currently used classification system. We have combined all histologically confirmed renal cell cancers together in our analyses due to the insufficient number of cases for histology-specific analyses.

Assessment of beverage and other dietary intake

Each study assessed baseline consumption of several beverages using a validated FFQ or diet history. Each study provided food and beverage intake data as either the number of servings consumed per day or grams consumed per day. For those studies that quantified intake in servings per day, the intake of each beverage was converted to grams per day based on the frequency reported and study-specific serving sizes. Intake of each beverage group was calculated by summing the intake of the related individual beverages listed on each study's FFQ. We excluded from the analyses of coffee and tea 2 studies (Breast Cancer Detection Demonstration Project Follow-Up Study and Cancer Prevention Study II Nutrition Cohort) that did not inquire about coffee and tea consumption at baseline and 1 study (California Teachers Study) that asked a combined question on coffee and tea intake. We were not able to separate caffeinated, decaffeinated and herbal tea because most studies did not assess intakes of specific types of tea. The FFQ used in the Melbourne Collaborative Cohort Study⁴¹ did not assess overall milk consumption and therefore, this study was

excluded for the milk analyses. Each study also provided intake data for several nutrients.

Although each study in this analysis conducted a validation study for their diet assessment method,²⁷ the results for beverage consumption were reported in only a few of the validation studies. In these studies, the correlation coefficients comparing beverage intake from the FFQs to diet records generally exceeded 0.6 for coffee, tea, milk, soda and juice,^{42–44} or nonalcoholic beverages.⁴⁵

Assessment of nondietary factors

Information on nondietary factors was collected at baseline in each study using self-administered questionnaires. Age, height and weight were asked in all studies; body mass index (BMI, weight (kg)/height (m²)) was calculated using height and weight at the start of the follow-up period. All the cohort studies including women assessed parity and age at first birth. Three studies did not measure history of hypertension, and 1 study had a large proportion of missing data on history of hypertension. One study did not measure smoking habits.

Statistical analysis

After applying the study-specific exclusion criteria, we further excluded participants if they consumed an unreasonable energy intake (± 3 SDs from the study-specific log_e-transformed mean energy intake), had a history of cancer except for nonmelanoma skin cancer at baseline, or had missing data on specific beverage intake (if applicable). Each study was analyzed using the Cox proportional hazards model.⁴⁶ Age at baseline (in days) and the year that the baseline questionnaire was returned were used as stratification variables, thereby creating a time metric, which simultaneously accounted for age, calendar time and time since entry into the study. Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of renal cell cancer diagnosis, death, loss to follow-up, if applicable, or end of follow-up, whichever came first.

We categorized the intake of each beverage using uniform cut-points across studies. We defined 1 serving as 237 g (8 oz) for coffee and tea, 245 g (8 oz) for milk, 186 g (6 oz) for juice and 355 g (12 oz) for soda. If there were no cases in the highest intake category in a study, the relative risk (RR) for the highest category could not be estimated in that study and the noncases in the highest category were included in the second highest category. To calculate the p -value for the test for trend, participants were assigned the median value of their intake category and this variable was treated as a continuous term in the model. In the multivariate analyses, we further adjusted for BMI (continuous), history of hypertension (yes, no), pack-years of smoking (continuous), energy intake (continuous), fruit and vegetable consumption (tertiles), alcohol intake (continuous), and, among women, parity and age at first birth (1 or 2 children and age at first birth <25 years old, 1 or 2 children and age at first birth ≥ 25 years old or nulliparous, ≥ 3 children and age at first birth <25 years old, and ≥ 3 children and age at first birth ≥ 25 years old). Among studies that measured covariates included in the analyses, mean proportion of missing data across studies ranged from 0.2 to 5% for BMI, history of hypertension, pack-years of smoking, and among women, parity and age at first birth. Alcohol intake, and fruit and vegetable intake generally did not have missing responses. For each measured covariate in a study, an indicator variable was used for missing responses, if needed.

After calculating study- and gender-specific RRs for each category, we combined the log_e RRs using a random effects model.^{47,48} The individual study estimates were weighted by the inverse of their variance. We tested for heterogeneity between studies using the Q statistic.^{49,50} Two-sided 95% confidence intervals (CIs) were calculated.

To assess whether the associations between intakes of coffee and tea and risk of renal cell cancer were linear, we examined non-parametric regression curves using restricted cubic splines^{51,52}. To

TABLE I – BASELINE CHARACTERISTICS OF THE COHORT STUDIES INCLUDED IN THE POOLED ANALYSES OF BEVERAGE INTAKES AND RENAL CELL CANCER RISK

| Study (Sex ²) | Follow-up period | Baseline cohort size | No. of cases ³ | Median intake among drinkers (g/day) (% of nondrinkers) ¹ | | | | |
|---|------------------|----------------------|---------------------------|---|-------------|---------------|-------------|-------------|
| | | | | Coffee | Tea | Milk | Juice | Soda |
| Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (M) | 1985–1999 | 26,987 | 187 | 600 (2) | 157 (64) | 654 (0.01) | 16 (51) | 47 (58) |
| Breast Cancer Detection Demonstration Project Follow-up Study (W) | 1987–1999 | 42,007 | 49 | – | – | 200 (4) | 89 (21) | 47 (61) |
| California Teachers Study (W) | 1995–2001 | 100,036 | 35 | 231 ⁴ (14) | 141 (23) | 141 (18) | 57 (18) | 50 (66) |
| Canadian National Breast Screening Study (W) | 1980–2000 | 49,613 | 81 | 448 (15) | 384 (22) | 244 (15) | 147 (14) | 39 (43) |
| Cancer Prevention Study II Nutrition Cohort (W) | 1992–2001 | 74,138 | 86 | – | – | 215 (3) | 78 (19) | 29 (64) |
| Cancer Prevention Study II Nutrition Cohort (M) | 1992–2001 | 66,166 | 220 | – | – | 232 (3) | 91 (16) | 77 (45) |
| Health Professionals Follow-up Study (M) | 1986–2000 | 47,780 | 116 | 237 (30) | 102 (42) | 196 (15) | 159 (8) | 202 (17) |
| Iowa Women's Health Study (W) | 1986–2000 | 34,588 | 117 | 597 (10) | 102 (42) | 245 (12) | 149 (9) | 104 (28) |
| Melbourne Collaborative Cohort Study (M) | 1990–2003 | 14,908 | 50 | 500 (11) | 500 (19) | – | 79 (20) | 86 (37) |
| Netherlands Cohort Study (W) | 1986–1993 | 62,573 | 68 | 500 (4) | 375 (11) | 180 (7) | 25 (41) | 29 (54) |
| Netherlands Cohort Study (M) | 1986–1993 | 58,279 | 134 | 500 (3) | 375 (15) | 179 (7) | 23 (55) | 54 (47) |
| New York State Cohort (M) | 1980–1987 | 30,363 | 62 | 710 (12) | 237 (64) | 207 (10) | 158 (4) | 370 (82) |
| Nurses' Health Study (W) | 1986–2000 | 68,523 | 86 | 592 (26) | 102 (37) | 210 (12) | 152 (9) | 159 (19) |
| Swedish Mammography Cohort (W) | 1987–2004 | 60,604 | 138 | 443 (4) | 181 (29) | 345 (14) | 24 (37) | 23 (60) |
| Women's Health Study (W) | 1993–2004 | 38,387 | 49 | 592 (14) | 102 (33) | 196 (12) | 111 (11) | 284 (13) |
| Total | | 774,952 | 1,478 | | | | | |

¹For coffee and tea, an 8 oz. serving/day is equivalent to 237 g/day. For milk, an 8 oz. serving/day is equivalent to 245 g/day. For juice, a 6 oz. serving/day is equivalent to 186 g/day. For soda, a 12 oz. serving/day is equivalent to 355 g/day. ²W, Women; M, Men. ³Histologically confirmed renal cell cancer cases. ⁴One question on coffee and tea consumption was asked.

test for nonlinearity, the model fit including the linear and cubic spline terms selected by a stepwise regression procedure was compared to the model fit with only the linear term using the likelihood ratio test, and by visual inspection of the restricted cubic spline graphs. For these analyses, all studies were combined into a single dataset, and then stratified by age, the year that the questionnaire was returned, and study, and were adjusted for other covariates in the model. For analyses of each beverage, individuals reporting extremely high intake (top 1% of participants in the aggregated dataset) of that beverage were excluded from the analysis to reduce the influence of extreme values.

We examined whether the associations between each beverage and renal cell cancer varied by gender, median age at diagnosis (<68, ≥68 years), smoking status (never, past, current smoker), and parity (nulliparous or 1 child, 2 children, ≥3 children) using a mixed effects meta-regression model.⁵³ For evaluation of whether BMI (<25, ≥25 kg/m²), history of hypertension (no, yes), alcohol intake (nondrinkers, drinkers), hormone replacement therapy (ever, never) and oral contraceptive use (user, nonuser) modified the association for each beverage, we used a Wald test of the pooled cross-product term of beverage intake as a continuous variable with the specific modifier variable modeled as a dichotomous variable.

Results

During maximum follow-up periods of 7–20 years across studies, 1,478 incident renal cell cancer cases (709 women and 769 men) were diagnosed among 530,469 women and 244,483 men (Table I).

Consumption of each beverage varied across studies. There were 3- to 5-fold differences in the median intakes of coffee, tea

and milk across studies. Coffee was consumed more frequently and in higher quantities than tea. There was more than a 10-fold variation in median soda and juice intake across studies.

Coffee consumption was associated, but not significantly, with a lower risk of renal cell cancer overall (Table II). Inverse association was observed in women, although the difference in the results between women and men was not statistically significant (*p* value, test for between-studies heterogeneity due to gender for the ≥ three 8 oz servings/day category = 0.13). When we alternatively adjusted for smoking habits using categories of never smokers, 2 categories of years smoked among past smokers (<30 years, ≥30 years), and 3 levels of amount smoked among current smokers (<15 cigarettes/day, 15 to <25 cigarettes/day, ≥25 cigarettes/day), the results (data not shown) did not differ from the multivariate results presented in Table II. The nonparametric regression curve and a formal test showed that the relations between coffee consumption and renal cell cancer risk were consistent with linear associations (*p*-values, test for curvature = 0.25 for women, 0.55 for men). When coffee consumption was modeled as a continuous variable, an increment of 237 g/day (8 oz or 237 ml) was associated with a 5% lower risk of renal cell cancer among women (pooled multivariate RR = 0.95; 95% CI = 0.90–1.01), but not among men (pooled multivariate RR = 1.00; 95% CI = 0.94–1.06). The multivariable RRs obtained in the aggregated dataset were not different from the pooled multivariable RRs (data not shown). We could not examine the association for regular coffee and decaffeinated coffee separately because too few studies asked separate questions.

For tea, the pooled age-adjusted RRs were similar to the pooled multivariate RRs (Table II). In the multivariate analyses, we found a nonsignificant 15% lower risk of renal cell cancer among participants who consumed 1 or more 8 oz (237 ml) cups of tea per day

TABLE II – POOLED RELATIVE RISKS¹ (RR) AND 95% CONFIDENCE INTERVALS (CI) OF RENAL CELL CANCER ACCORDING TO CATEGORIES OF INTAKE FROM SPECIFIC BEVERAGES

| Beverage, serving size (weight) | Categories | | | | | | Per one serving/day | |
|--|--------------------------|---------------------------------------|----------------------------------|-----------------------------------|---------------------------------|---|--------------------------|--|
| | RR | RR (95% CI) | RR (95% CI) | RR (95% CI) | <i>p</i> -value, test for trend | <i>p</i> -value, test for between-studies heterogeneity due to sex ² | RR (95% CI) ³ | <i>p</i> -value, test for between-studies heterogeneity due to sex |
| Coffee, 8 oz (237 g) ^{4,5} No. of cases (W, M) ⁷ | <1/d (148, 119) | 1-<2/d ⁶ (124, 94) | 2-<3/d (174, 174) | ≥3/d ³ (76, 157) | | | | |
| Age-adjusted | | | | | | | | |
| Women | 1.00 | 0.86 (0.67–1.11) | 1.00 (0.79–1.27) | 0.73 (0.54–0.98) | 0.08 | | 0.95 (0.90–1.01) | |
| Men | 1.00 | 0.92 (0.58–1.45) | 1.25 (0.82–1.91) | 1.15 (0.83–1.61) | 0.21 | | 1.04 (0.98–1.01) | |
| Combined | 1.00 | 0.86 (0.70–1.06) | 1.07 (0.89–1.28) | 0.91 (0.74–1.12) | 0.78 | 0.04 | 1.00 (0.96–1.04) | 0.03 |
| Multivariate | | | | | | | | |
| Women | 1.00 | 0.89 (0.69–1.16) | 1.03 (0.81–1.31) | 0.71 (0.53–0.97) | 0.07 | | 0.95 (0.90–1.01) | |
| Men | 1.00 | 0.84 (0.55–1.28) | 1.17 (0.75–1.83) | 1.00 (0.73–1.37) | 0.83 | | 1.00 (0.94–1.06) | |
| Combined | 1.00 | 0.86 (0.70–1.06) | 1.05 (0.87–1.27) | 0.84 (0.67–1.05) | 0.22 | 0.13 | 0.97 (0.93–1.01) | 0.29 |
| Tea, 8 oz (237 g) ^{4,5} No. of cases (W, M) ⁷ | Nondrinker (151, 256) | 1/mo-<1/d ⁸ (207, 136) | ≥1/d ³ (164, 152) | | | | | |
| Age-adjusted | | | | | | | | |
| Women | 1.00 | 1.14 (0.92–1.41) | 0.99 (0.78–1.27) | | 0.47 | | 1.00 (0.92–1.09) | |
| Men | 1.00 | 0.93 (0.74–1.17) | 0.70 (0.54–0.91) | | 0.08 | | 0.90 (0.77–1.03) | |
| Combined | 1.00 | 1.04 (0.89–1.21) | 0.84 (0.71–1.01) | | 0.05 | 0.06 | 0.96 (0.70–1.03) | 0.15 |
| Multivariate | | | | | | | | |
| Women | 1.00 | 1.15 (0.93–1.42) | 0.98 (0.77–1.26) | | 0.33 | | 0.99 (0.91–1.08) | |
| Men | 1.00 | 0.98 (0.77–1.23) | 0.72 (0.55–0.94) | | 0.10 | | 0.89 (0.77–1.04) | |
| Combined | 1.00 | 1.07 (0.91–1.25) | 0.85 (0.71–1.02) | | 0.04 | 0.09 | 0.96 (0.89–1.03) | 0.24 |
| Milk, 8 oz (245 g) ⁹ No. of cases (W, M) ⁷ | <2/wk (183, 127) | 2/wk-<4/wk (91, 106) | 4/wk-<1/d (103, 134) | ≥1/d ^{3,8} (320, 352) | | | | |
| Age-adjusted | | | | | | | | |
| Women | 1.00 | 0.92 (0.70–1.20) | 0.93 (0.72–1.20) | 0.97 (0.80–1.18) | 0.82 | | 1.00 (0.93–1.07) | |
| Men | 1.00 | 1.03 (0.79–1.35) | 0.91 (0.70–1.17) | 1.02 (0.80–1.28) | 0.89 | | 1.01 (0.95–1.08) | |
| Combined | 1.00 | 0.97 (0.81–1.17) | 0.92 (0.77–1.09) | 0.99 (0.85–1.15) | 0.79 | 0.78 | 1.00 (0.96–1.05) | 0.81 |
| Multivariate | | | | | | | | |
| Women | 1.00 | 0.91 (0.69–1.19) | 0.92 (0.70–1.19) | 0.95 (0.78–1.16) | 0.99 | | 0.98 (0.90–1.06) | |
| Men | 1.00 | 1.05 (0.81–1.38) | 0.92 (0.70–1.21) | 1.03 (0.81–1.31) | 0.73 | | 1.02 (0.94–1.11) | |
| Combined | 1.00 | 0.98 (0.81–1.18) | 0.92 (0.76–1.10) | 0.98 (0.84–1.14) | 0.82 | 0.61 | 1.00 (0.94–1.06) | 0.45 |
| Soda, 12 oz (355 g) ¹⁰ No. of cases (W, M) ⁷ | Nondrinker (299, 352) | 1/mo-<3/wk ⁸ (259, 280) | ≥3/wk ³ (140, 136) | | | | | |
| Age-adjusted | | | | | | | | |
| Women | 1.00 | 1.15 (0.97–1.37) | 1.17 (0.85–1.62) | | 0.09 | | 1.01 (0.95–1.07) | |
| Men | 1.00 | 1.08 (0.91–1.28) | 1.23 (0.86–1.76) | | 0.31 | | 1.05 (0.99–1.10) | |
| Combined | 1.00 | 1.12 (0.99–1.26) | 1.21 (0.95–1.51) | | 0.06 | 0.80 | 1.04 (1.00–1.08) | 0.76 |
| Multivariate | | | | | | | | |
| Women | 1.00 | 1.11 (0.93–1.32) | 1.05 (0.78–1.41) | | 0.42 | | 1.01 (0.95–1.07) | |
| Men | 1.00 | 1.10 (0.93–1.31) | 1.17 (0.83–1.64) | | 0.45 | | 1.03 (0.97–1.09) | |
| Combined | 1.00 | 1.11 (0.98–1.25) | 1.11 (0.89–1.38) | | 0.24 | 0.48 | 1.02 (0.98–1.06) | 0.56 |
| Juice, 6 oz (186 g) ¹¹ No. of cases (W, M) ⁷ | Nondrinker (145, 221) | 1/mo-<4/wk (281, 307) | 4/wk-<1/d (119, 148) | ≥1/d ^{3,12} (143, 93) | | | | |

TABLE II – POOLED RELATIVE RISKS¹ (RR) AND 95% CONFIDENCE INTERVALS (CI) OF RENAL CELL CANCER ACCORDING TO CATEGORIES OF INTAKE FROM SPECIFIC BEVERAGES (CONTINUED)

| Beverage, serving size (weight) | Categories | | | | | RR (95% CI) ³ | p-value, test for between-studies heterogeneity due to sex ² | p-value, test for between-studies heterogeneity due to sex |
|---------------------------------|-------------|------------------|------------------|-------------------------|---|--------------------------|---|--|
| | RR (95% CI) | RR (95% CI) | RR (95% CI) | p-value, test for trend | p-value, test for between-studies heterogeneity due to sex ² | | | |
| Age-adjusted | | | | | | | | |
| Women | 1.00 | 0.99 (0.80–1.21) | 0.89 (0.64–1.23) | 1.08 (0.78–1.50) | 0.62 | 1.00 (0.89–1.13) | | |
| Men | 1.00 | 0.97 (0.74–1.28) | 0.89 (0.68–1.15) | 1.05 (0.69–1.60) | 0.51 | 1.07 (0.93–1.22) | | |
| Combined | 1.00 | 0.99 (0.85–1.16) | 0.89 (0.74–1.08) | 1.07 (0.85–1.35) | 0.61 | 1.03 (0.94–1.12) | 0.50 | |
| Multivariate | | | | | | | | |
| Women | 1.00 | 1.00 (0.81–1.24) | 0.91 (0.66–1.25) | 1.09 (0.78–1.53) | 0.68 | 1.00 (0.89–1.13) | | |
| Men | 1.00 | 1.00 (0.76–1.33) | 0.92 (0.71–1.20) | 1.09 (0.68–1.74) | 0.40 | 1.09 (0.94–1.25) | | |
| Combined | 1.00 | 1.01 (0.86–1.20) | 0.92 (0.76–1.11) | 1.10 (0.85–1.43) | 0.47 | 1.03 (0.95–1.13) | 0.38 | |

¹Multivariate models were adjusted for age, history of hypertension (yes/no), body mass index (continuous), pack-years of smoking (continuous), combination of parity and age at first birth (age at first birth <25 years and parity of 1 or 2; age at first birth ≥25 years and parity of ≥3), or nulliparous; age at first birth <25 years and parity of ≥3, fruit and vegetable consumption (tertiles), alcohol intake (continuous) and total energy intake (continuous).—²For the highest category.—³p value, test for between-studies heterogeneity > 0.1.—⁴The Breast Cancer Detection Demonstration Project Follow-Up Study, the Cancer Prevention Study II Nutrition Cohort, and the California Teachers Study were excluded from the analyses of coffee and tea because coffee and tea intake was not assessed in the Breast Cancer Detection Demonstration Project Follow-Up Study and the Cancer Prevention Study II Nutrition Cohort, and one combined question on coffee and tea was asked in the California Teachers Study. In the remaining studies, participants who did not report coffee and tea intake were excluded (n = 22).—⁵Further adjusted for tea (continuous) for the coffee analysis and coffee (continuous) for the tea analysis.—⁶The Melbourne Collaborative Cohort Study was excluded from this category because there was no one in this category due to the way that frequency of intake was assessed on this study's FFQ.—⁷Women (M); Men.—⁸The New York State Cohort was excluded from this category because there was no one in this category due to the way that frequency of intake was assessed on this study's FFQ.—⁹The Melbourne Collaborative Cohort Study did not assess overall milk consumption and was excluded from this analysis. In the remaining studies participants who did not report milk intake were excluded (n = 12).—¹⁰Participants who did not report soda intake were excluded (n = 12).—¹¹The model did not include fruit and vegetable consumption. Participants who did not report juice intake were excluded (n = 21).—¹²The Breast Cancer Detection Demonstration Project Follow-Up Study was excluded from the highest category because no cases were included in this category. The participants who would have been in the highest category were included in the next highest category.

TABLE III – POOLED MULTIVARIATE RELATIVE RISKS (RRS) AND 95% CONFIDENCE INTERVALS (CIS) OF RENAL CELL CANCER FOR AN INCREMENT OF ONE 8 oz. (237 g) CUP OF COFFEE AND TEA PER DAY STRATIFIED BY BODY MASS INDEX, SMOKING STATUS AND HISTORY OF HYPERTENSION

| Beverages | Body mass index ¹ | | | Smoking Status ² | | History of hypertension ^{3,4} | |
|--|------------------------------|-----------------------|--------------------|-----------------------------|------------------------|--|------------------|
| | <25 kg/m ² | ≥25 kg/m ² | Never ⁵ | Past ¹ | Current ^{1,6} | No | Yes |
| Coffee | | | | | | | |
| No. of cases (W, M) ⁷ | (217, 208) | (296, 330) | (216, 69) | (97, 175) | (69, 285) | (195, 335) | (115, 147) |
| Women | 0.99 (0.85–1.14) | 0.96 (0.89–1.03) | 0.89 (0.82–0.98) | 1.00 (0.88–1.13) | 0.97 (0.81–1.15) | 0.92 (0.84–1.02) | 1.01 (0.90–1.13) |
| Men | 0.98 (0.86–1.11) | 1.00 (0.92–1.09) | 0.95 (0.80–1.13) | 0.96 (0.86–1.08) | 1.00 (0.89–1.12) | 1.04 (0.96–1.12) | 0.99 (0.87–1.12) |
| Combined | 0.98 (0.89–1.07) | 0.98 (0.93–1.04) | 0.91 (0.84–0.98) | 0.98 (0.90–1.06) | 0.98 (0.90–1.08) | 0.99 (0.92–1.06) | 1.00 (0.92–1.09) |
| p value, test for interaction (W, M, C) ⁷ | (0.89, 0.85, 0.95) | | | (0.34, 0.78, 0.40) | | (0.10, 0.59, 0.84) | |
| Tea | | | | | | | |
| No. of cases (W, M) ⁷ | (217, 208) | (296, 330) | (216, 69) | (97, 175) | (69, 285) | (195, 335) | (115, 147) |
| Women | 1.00 (0.88–1.13) | 1.00 (0.89–1.13) | 1.00 (0.87–1.14) | 0.80 (0.54–1.20) | 1.05 (0.89–1.25) | 0.89 (0.75–1.06) | 1.08 (0.90–1.29) |
| Men | 0.95 (0.77–1.18) | 0.84 (0.66–1.06) | 0.73 (0.40–1.32) | 0.89 (0.65–1.21) | 0.97 (0.81–1.15) | 0.95 (0.82–1.10) | 0.93 (0.76–1.13) |
| Combined | 0.99 (0.90–1.09) | 0.94 (0.84–1.06) | 0.97 (0.83–1.12) | 0.87 (0.70–1.09) | 1.01 (0.90–1.14) | 0.93 (0.84–1.03) | 1.01 (0.88–1.15) |
| p value, test for interaction (W, M, C) ⁷ | (0.98, 0.41, 0.57) | | | (0.86, 0.47, 0.66) | | (0.10, 0.92, 0.30) | |

¹Models were adjusted for age, history of hypertension (yes/no), body mass index (continuous), pack-years of smoking (continuous), combination of parity and age at first birth (age at first birth <25 years and parity of 1 or 2; age at first birth ≥25 years and parity of ≥3), or nulliparous; age at first birth <25 years and parity of ≥3, and age at first birth ≥25 years and parity of ≥3, fruit and vegetable consumption (tertiles), alcohol intake (continuous) and total energy intake (continuous). Coffee intake and tea intake were mutually adjusted in the models.—²The Swedish Mammography Cohort was excluded from these analyses because data on smoking habit were not available at baseline. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was included in only the current smoking group status because the cohort included only current smokers.—³Models were adjusted for all covariates listed in footnote 1 except history of hypertension.—⁴The Breast Cancer Detection Demonstration Project Follow-Up Study, the Canadian National Breast Screening Study, the New York State Cohort, and the Swedish Mammography Cohort were excluded from these analyses because history of hypertension was not available at baseline.—⁵Models were adjusted for all covariates listed in footnote 1 except pack-years of smoking. The Netherlands Cohort Study was excluded from the analysis of never smoker due to small case numbers (n < 10).—⁶The Women's Health Study was excluded from the analysis of current smoker due to small case numbers (n < 10).—⁷W, Women; M, Men; C, Combined.

compared with nondrinkers (pooled multivariate RR = 0.85; 95% CI = 0.71–1.02) (Table II). The inverse association was limited to men (pooled multivariate RR = 0.72; 95% CI = 0.55–0.94), and the difference in the results between women and men was marginally significant (p value, test for between-studies heterogeneity due to gender = 0.09). When we additionally adjusted for multivitamin use (user, nonuser) and physical activity (low, medium, high), the results did not differ (data not shown). The multivariable RRs obtained in the aggregated dataset were not different from the pooled multivariable RRs (data not shown). For both women and men, the nonparametric regression curve and a formal test showed that the relations between tea consumption and renal cell cancer risk were consistent with linear associations (p -values, test for curvature = 0.36 for women, 0.66 for men). In the continuous analyses, we found a nonsignificant 4% lower risk of renal cell cancer for an increment of one 8 oz (237 ml) cup of tea per day (pooled multivariate RR = 0.96; 95% CI = 0.89–1.03), but the inverse association was limited to men.

No significant associations with renal cell cancer risk were observed for intakes of milk, soda and fruit and vegetable juice (Table II). When we examined whole milk and reduced fat milk separately in the 11 studies that assessed the intake of these items separately, there were no clear associations for either type of milk but the consumption of whole milk was uncommon in most studies (data not shown). Neither fruit juice (13 studies) nor vegetable juice (7 studies) was associated with risk of renal cell cancer (data not shown). We were not able to examine artificially sweetened and sugar-sweetened soda consumption separately because only a few studies asked separate questions for these beverages.

Overall, the associations between coffee or tea intakes and renal cell cancer risk were not significantly modified by BMI, history of hypertension, smoking habits (Table III), alcohol intake (nondrinkers, drinkers; data not shown) or age at diagnosis (<68, and \geq 68 years old, the median age at diagnosis; data not shown). Because there were suggestions that associations for coffee and tea consumption varied by gender, we also examined whether the associations for coffee and tea intake varied by hormone-related variables. We found a marginally significant difference by oral contraceptive use (user, nonuser; p value, test for interaction = 0.09) in women, but no clear differences in risk of renal cell cancer by parity (\leq 1 child, 2 children, \geq 3 children), and hormone replacement therapy use (ever, never) (p values, test for interaction \geq 0.11).

Discussion

In our pooled analysis of 13 prospective studies, we found that neither coffee nor tea intake was associated with increased renal cell cancer risk, but rather our results suggest that frequent coffee or tea consumption may be associated with a modestly lower risk of renal cell cancer. Consumption of milk, soda and fruit and vegetable juice was not associated with the risk of renal cell cancer. We found suggestive differences in the apparent benefits of coffee and tea consumption on risk of renal cell cancer between women and men which were unexpected. These gender-differences could be due to chance but it is possible that associations between lifestyle factors such as diet and renal cell cancer risk vary by hormone-related variables. The incidence of renal cell cancer is more than twice as common in men compared to women, but it remains uncertain whether this difference in the association observed is due to differences in endogenous estrogen levels, smoking habits or some other factors. Caffeine metabolism has been shown to be slower among women who received exogenous estrogens compared to women who did not^{54,55} partly because estrogens and caffeine compete for the CYP1A2 isoenzyme of the P450 family.⁵⁴ Although we did not find clear differences in the association between coffee and tea intake and renal cell cancer risk by several hormone-related variables, we had a limited number of cases for these analyses.

Ecological studies have found strong positive correlations between per capita consumption of coffee and renal cell cancer mortality⁵⁶ and incidence.⁵⁷ Because coffee drinking is positively correlated with smoking, a positive correlation between coffee consumption and renal cell cancer risk at the ecological level could be confounded by smoking habits. In our data, the inverse association for coffee was stronger among never smokers compared to past or current smokers, which may suggest that residual confounding by smoking habits could obscure an inverse association of coffee intake if the effects of smoking are not completely controlled for. The majority of case-control studies of renal cell cancer have found no significant associations^{9–14,16,17} for coffee consumption. Only a few prospective studies,^{22,24,58,59} 3 of which^{22,24} (2 studies were reported in 1 paper; Lee *et al.*²²) are included in our analysis, have examined the association between coffee intake and risk of renal cell cancer. In the 2 cohort studies that were not included in our analysis because they did not meet the prespecified criteria (described in Material and Methods section), significant association in women and men combined⁵⁸ or non-significant inverse association in men⁵⁹ were found for coffee consumption. Our data suggested the inverse association was limited to women, although the difference in the risk estimates between women and men was not statistically significant.

For tea, most, but not all^{16,17} case-control studies have found no significant association with renal cell cancer risk in men,^{7,12,13} women^{7,12,13} or both genders combined.^{7,9–11,14,15,18} Among 4 prospective studies^{22,24,25} (2 studies were reported in Lee *et al.*²²) that examined the association between tea consumption and renal cell cancer risk, 3^{22,24} were included in our analyses. The prospective study that was not included in our analyses found that black tea consumption appeared to increase the risk of kidney cancer death, but that green tea did not.²⁵ However, the authors postulated that, in this Japanese population, drinking black tea may be a surrogate for a westernized diet, which may be associated with an increased risk of renal cell cancer. In contrast, the studies in our analysis, tea consumption was positively correlated with healthy behaviors. Inadequate control for these healthy behaviors could result in a spurious inverse association. However, we found little difference between our age-adjusted results and those adjusted for smoking habits, history of hypertension, BMI, physical activity and multivitamin use.

Milk consumption has been associated with an increased risk of renal cell cancer in some case-control studies^{9–11,20}, but, as observed in our prospective analysis, other case-control studies have not seen an association for milk intake.^{17,19,21} Our finding of no association between soda intake and renal cell cancer risk agrees with the results from the few case-control studies that have examined associations with either total soda intake^{7,11,18} or low calorie soda intake.⁷ Information on intakes of milk, soda and juice in relation to renal cell cancer risk from prospective studies is limited.

There are several possible mechanisms by which coffee and tea consumption might reduce the risk of renal cell cancer. First, coffee and tea may improve insulin sensitivity. A possible link between insulin sensitivity and renal cell cancer risk is suggested by the strong positive association between obesity and renal cell cancer risk.⁶⁰ Furthermore, renal cell cancer incidence rates have been shown to be higher in individuals with diabetes,^{61,62} which is usually characterized by impaired insulin sensitivity, and in individuals with elevated fasting glucose levels.⁶³ Coffee consumption has been associated with improved insulin sensitivity,⁴ inversely associated with the risk of diabetes,⁶⁴ and inversely correlated with C-peptide levels, a marker of insulin secretion.⁶⁵ Tea consumption also has been shown to improve insulin sensitivity in experimental studies,^{5,66} but has not been associated with risk of Type 2 diabetes mellitus in prospective cohort studies.^{67,68}

Second, the diluting effect caused by coffee and tea could reduce the risk of renal cell cancer by decreasing the time that carcinogenic solutes are in contact with renal epithelial cells.

However, a pooled analysis of the Nurses' Health Study and the Health Professionals Follow-up Study, both of which were included in our analyses, reported that total fluid intake was not associated with a lower risk of renal cell cancer.²² In this pooled analysis, we were not able to examine if total fluid intake was associated with risk of renal cell cancer because the FFQs of 7 of the 13 studies did not assess water consumption, an important contributor to total fluid intake.

Third, coffee and tea also contain phenolic compounds and bioactive flavonoids,^{69,70} which may reduce the risk of renal cell cancer by removing oxidized carcinogenic agents, reducing lipid peroxidation, reducing cell proliferation, or promoting apoptosis.^{3,71}

This pooled analysis has limitations. We used only a baseline measure of beverage intake for each study therefore we could not investigate the effects of changes in beverage intake during follow-up, or consumption of specific beverages during earlier age periods or over the lifetime. Also, we only had a baseline measure for confounding factors and potential effect modifiers, so that changes in these variables during follow-up could not be taken into consideration in our analyses. Even though our study included a large number of cases, we could not examine the effects of high intake of each beverage due to the small number of cases with high intakes. Also, we could not examine regular or decaffeinated coffee separately, types of tea, or types of soda. We were not able to examine if the associations differed by ethnicity because over 90% of the participants in our study were Caucasian. We did not have sufficient power to examine associations separately by histological type of renal cell cancer. Smoking habits or history of hypertension, important risk factors for renal cell cancer, were measured in most studies, but not in all. However, in those studies that measured smoking habits and history of hypertension, the

pooled RRs from the multivariate model presented were similar to the pooled RRs where we did not adjust for smoking habits and history of hypertension (data not shown).

Our analysis has several strengths. Because of the prospective design of the studies, recall bias and selection bias do not account for our findings. In addition, because of the large number of cases in our study, which has not been possible in any single prospective study, we were able to achieve better precision in our risk estimates relative to the individual prospective studies. Although we did not have information on some risk factors for renal cell cancer, including family history of renal cell cancer, environmental exposures such as asbestos, medications such as phenacetin, or advanced kidney disease, and thus were not able to control for these factors in our analyses, the associations that we observed are not likely to be fully explained by these factors because these factors would need to be both common and strongly associated with each beverage intake. Because we analyzed the primary data from each study, we were able to model beverage intake and confounding factors uniformly across studies to remove potential sources of heterogeneity in the results across studies.

In conclusion, our results suggest that coffee and tea consumption may be associated with a modestly lower risk of renal cell cancer, whereas intakes of milk, juice and soda were not associated with risk. Further studies are needed to explore possible mechanisms and the suggestive gender-difference in risk for coffee and tea.

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