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Coffee Consumption and Risk of Renal Cell Carcinoma

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Abstract

Background—Studies have suggested an inverse association between coffee consumption and risk of renal cell carcinoma (RCC); however, data regarding decaffeinated coffee are limited.

Methods—We conducted a case-control study of 669 incident RCC cases and 1,001 frequency-matched controls. Participants completed identical risk factor questionnaires that solicited information usual coffee consumption habits, and they were categorized as non-coffee, caffeinated coffee, decaffeinated coffee, or both caffeinated and decaffeinated coffee drinkers. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression, adjusting for multiple risk factors for RCC.

Results—Compared with no coffee consumption, we found an inverse association between caffeinated coffee consumption and RCC risk (OR=0.74; 95% CI=0.57–0.99), whereas we observed a trend toward increased risk of RCC for consumption of decaffeinated coffee (OR=1.47; 95% CI=0.98–2.19). Furthermore, decaffeinated coffee consumption was associated with

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increased risk of the clear cell RCC (ccRCC) subtype, particularly the aggressive form of ccRCC (OR=1.80; 95%CI=1.01–3.22).

Conclusions—Consumption of caffeinated coffee is associated with reduced risk of RCC, while decaffeinated coffee consumption was associated with an increase in risk of aggressive ccRCC. Further inquiry is warranted in large prospective studies and should include assessment of dose-response associations.

Keywords

coffee; decaffeinated coffee; kidney cancer; renal cell carcinoma; RCC; clear cell renal cell carcinoma

Introduction

Incidence rates for renal cell carcinoma (RCC) have been rising over the last several decades, while mortality rates have remained fairly stable [1–3]. The etiology of RCC is not completely understood and while understanding the underlying biology of RCC remains an area of active inquiry, there is a pressing need to work in parallel to identify modifiable risk factors to better inform strategies for prevention of this increasingly common malignancy. Few modifiable predisposing factors for RCC have been well-established, namely cigarette smoking, obesity, and hypertension; however, these factors have been reported to account for only about one-half of all RCC cases diagnosed each year in the United States [4, 5]. Further research is therefore needed to identify additional contributing risk factors for RCC cases, particularly modifiable risk factors for the most aggressive forms of RCC.

Based on suggestions that caffeine or other antioxidants in coffee (e.g., phenolic acids [6]) may reduce cancer risk, several groups have examined the association between coffee consumption and RCC risk, with varying results [7–14]. These mixed findings may be due, in part, to the inability of investigators to separate caffeinated coffee from decaffeinated coffee consumption, which are thought to have varying health effects because of differing levels of caffeine, and possibly other antioxidants [15, 16]. There is also the longstanding hypothesis that historical methods used for decaffeinating coffee (i.e., exposing coffee beans to a variety of chemical solvents) may have detrimental health effects [17, 18].

The largest study on coffee consumption and RCC risk conducted to date, a pooled analysis of 13 prospective studies, reported that overall coffee consumption was associated with a modest reduction in RCC risk [19]. However, the true association appeared to have been masked in that study by the mixing of caffeinated and decaffeinated coffee consumption into one group [19]. More recently, a case-control study conducted in Italy reported a null association between overall coffee consumption and RCC risk, but the investigators observed a suggestion of an increase in RCC risk associated with decaffeinated coffee consumption (odds ratio [OR] = 1.38, 95% confidence interval [CI] = 0.94–2.03, coffee drinker vs. non-drinkers) [20]. Due to the absence of a centralized pathology review, they were unable to explore associations with specific histologic subtypes of RCC or with the more aggressive forms of RCC. Therefore, we analyzed data from a large case-control study to determine the relationship between decaffeinated and caffeinated coffee consumption and

RCC risk. We further investigated associations of decaffeinated and caffeinated coffee intake with the clear cell subtype of RCC [5]. In addition, we examined associations between these forms of coffee consumption and several known and accepted prognostic factors for cancer-specific death from clear cell RCC (ccRCC), as determined by the externally validated, Mayo Clinic SSIGN (tumor stage, size nuclear grade, and necrosis) scoring algorithm [21–23].

Methods

Case and Control Ascertainment

Following Mayo Clinic Institutional Review Board approval, we ascertained RCC cases from the Renal Cancer Registry, housed in the Departments of Urology at Mayo Clinic in Rochester, MN, and Mayo Clinic in Jacksonville, FL. As part of the Registry efforts, patients undergoing surgery for newly diagnosed, clinically localized RCC provide written informed consent for data and specimen collection. This study utilized the registry databases to identify RCC patients treated at each of the two sites between May 2003 and July 2012, who have completed risk factor questionnaire at enrollment. At each site, approximately 70% of RCC patients consented and completed the risk factor questionnaires. Non-cancer control patients were recruited from each site using site-specific resources.

In Jacksonville (FL), controls were identified through review of appointment calendars of the Department of Family and Community Medicine ahead of patient visit for a regular wellness check-up. Potential control patients were approached on their appointment dates for recruitment and asked to complete risk factor questionnaires identical to those completed by the RCC cases. Among the potential controls approached, 73% completed and returned the questionnaires. The cases and controls in Jacksonville completed the risk factor questionnaires at enrollment. The Florida controls were frequency-matched to the Florida cases on age (± 5 -years), sex, and state of residence. In Rochester (MN), controls were recruited through collaboration with the Mayo Clinic Biobank [24]. In brief, Mayo Clinic patients who were (1) 18 years or older, (2) of sound mind and memory and able to consent, and (3) US residents were eligible to participate in the Mayo Clinic Biobank in Rochester. Individuals recruited to the Biobank were asked to complete a health history questionnaire and to provide consent for future contact for additional data collection. We leveraged this resource by pooling a random sample of potential controls from the Biobank who reported no personal history of kidney cancer. The potential controls were mailed the same risk factor questions completed by the cases to obtain information that was not originally collected as part of the Biobank health history questionnaire (i.e., history of alcohol and coffee consumption). Of the potential Biobank controls invited to participate, 76% completed and returned the risk factor questionnaires. The Rochester controls also were frequency-matched to the Rochester cases on age (± 5 years), sex, and state of residence.

Centralized Pathology Review on RCC Cases

As part of the Registry efforts at both Rochester and Jacksonville, H&E slides from RCC patients undergo a centralized pathology review by genitourinary pathologists from our investigative team (J.C.C. and K.J.W., respectively). This process establishes the diagnosis

of RCC, verifies the histological subtype (e.g., clear cell or papillary), and provides confirmation of tumor stage, size, nuclear grade and necrosis—the components of the SSIGN scoring algorithm [21]. In brief, the Mayo Clinic SSIGN score is an externally validated [22, 23] scoring system that is used clinically to determine which ccRCC patients are at greater risk of dying from the disease after surgical excision of the primary tumor. In this study, the SSIGN scores were used to categorize ccRCC patients as having less aggressive or moderate/high aggressive disease, as described below.

Assessment of Coffee Intake and Covariates

The RCC cases and controls completed a self-administered, identical risk factor questionnaire that solicited information on a variety of environmental and lifestyle risk factors, including usually intake of caffeinated and decaffeinated coffee (i.e., cups per day). The same questions were used to solicit information on coffee consumption at each site for both cases and controls. The questionnaire asked participants, “how often have you usually drank coffee as an adult (18 years old or older), please exclude dietary changes within the last two years.” Response options included usual number of cups consumed per day of caffeinated coffee, decaffeinated coffee, both, or rarely/never. To maximize sample sizes for coffee consumption categories, information on cups per day were used to categorize participants into four groups: non-coffee drinkers, regular consumers of caffeinated coffee only, regular consumers of decaffeinated coffee only, or both. Other information obtained from the risk factor questionnaire included demographics (age, sex, race/ethnicity, marital status, and the highest level of education), smoking history, adult height, usual adult weight, self-reported history of hypertension, and alcohol consumption habits. Data on usual adult weight and height collected at enrollment were used to calculate body mass index (BMI) as the ratio of weight to height in kilograms per meter squared (kg/m^2). Smoking history was categorized as never, former, and current. Data on coffee consumption and covariates were available for 669 RCC cases and 1,001 controls (Supplementary Table 1).

Statistical Analysis

Means and proportions were used to compare demographic, lifestyle, and anthropometric measures between cases and controls. Unconditional logistic regression was used to calculate ORs and 95% CIs. In examining the association between coffee consumption and RCC risk, non-coffee drinkers were used as the referent group to estimate ORs and corresponding 95% CIs for the other coffee consumption categories, adjusting for various known risk factors for RCC. The most comprehensively adjusted (i.e., fully-adjusted) model included age (continuous), sex, institutional site (Jacksonville, Rochester), smoking history (never, former, current), BMI (continuous), self-reported history of hypertension (no, yes) and alcohol consumption (never, ever) to account for potential confounding by these factors. To examine whether the association between coffee consumption and RCC is modulated by known risk factors for RCC, we performed stratified analyses by age (< 64 vs. 64 years; the median age among controls), sex, BMI (< 30 vs. 30 kg/m^2), smoking history (ever [former + current], never), history of hypertension (yes, no), alcohol consumption (yes, no), and study site (Rochester vs. Jacksonville) in fully-adjusted models. We further examined interaction between each of these factors and the coffee consumption variable using likelihood ratio chi-square test nested in multivariable-adjusted logistic regression models

with and without multiplicative interaction terms (i.e., age group*coffee consumption). In assessing interaction, chi-square tests were used to determine statistical significance of difference between -2 log-likelihood values from the full model (with interaction) and the reduced model using appropriate degrees of freedom (i.e., difference in degrees of freedom between the two models).

Because of the heterogeneous nature of RCC, we performed separate analyses between coffee consumption and ccRCC; the most common subtype (>80% of all RCC) [25]. Among the 669 RCC cases included in the study, 516 were determined through the centralized pathologic review as ccRCC. We compared these ccRCC cases with the same set of controls used in the larger analysis (n=1, 001). Further, we explored associations of coffee consumption with the extent of ccRCC aggressiveness. The Mayo Clinic SSIGN score was used to classify the ccRCC cases into low aggressive (SSIGN score 0–3) and moderate or high aggressive (SSIGN score 4) disease groups [21] and exploratory analyses were performed using polychotomous logistic regression. All statistical tests herein reported were two-sided and p-values lower than 0.05 were considered statistically significant. Analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the 669 RCC cases and 1,001 controls included in the study are presented in Table 1. Given the frequency-matched design, the cases and controls did not differ by age or sex and were similar in self-identified race and marital status. Compared to controls, cases were less likely to have college or graduate level education (54% vs. 36%). A greater proportion of cases than controls had a BMI >30 kg/m² (56% vs. 46%), and the cases were also more likely than controls to reported being a current smoker (7% vs. 3%), report a personal history of hypertension (62% vs. 46%) or reported never consuming alcohol (20% vs. 15%). While the proportion of caffeinated coffee only drinkers was higher among controls than cases (53% vs. 45%), there was a slightly higher proportion of decaffeinated coffee only drinkers among cases than controls (13% vs. 8%). Differences in age, institutional site, race, smoking history, history of hypertension, and alcohol consumption were observed between the four coffee exposure groups (i.e., non-drinkers, caffeinated coffee drinks, non-caffeinated coffee drinks, and both) (Supplementary Table 2).

Table 2 shows results for associations between coffee consumption and RCC risk. In the age-adjusted model, regular consumption of caffeinated coffee was associated with a 27% reduced risk of RCC (OR = 0.73, 95% CI = 0.58–0.93), whereas regular consumption of decaffeinated coffee was associated with a 50% increase in risk of RCC (OR = 1.50, 95% CI = 1.04–2.17), compared with non-coffee consumption. After adjusting for age, institutional site, sex, smoking, BMI, hypertension, and alcohol consumption, caffeinated coffee consumption remained inversely associated with RCC risk (OR = 0.74, 95% CI = 0.57–0.97) and decaffeinated coffee consumption remained positively related to RCC risk (OR = 1.48, 95% CI = 0.99–2.21). Of note, we did not observe significant associations in the age- or multivariable-adjusted models for overall consumption of both caffeinated and decaffeinated coffee, which reflects the masking of associations in studies that combined caffeinated with decaffeinated coffee (Table 2).

In Table 3, we present results of stratified analyses stratified by known risk factors for RCC. There was a consistent pattern of lower ORs for RCC risk with caffeinated coffee consumption and elevated ORs for decaffeinated coffee consumption both among individuals < 64 years and those ≥ 64 years. No statistically significant interaction was observed by sex, BMI category, smoking status, or study site. However, compared to non-coffee drinkers, decaffeinated coffee consumption was associated with increased RCC risk among females (OR = 2.19, 95% CI = 1.16–4.13) and among never smokers (OR = 1.83, 95% CI = 1.06–3.15), whereas caffeinated coffee was associated with decreased RCC risk among individuals with BMI ≥ 30 kg/m² (OR = 0.67, 95% CI = 0.46–0.94) and among ever smokers (OR = 0.61, 95% CI = 0.40–0.94). Significant interactions were observed by alcohol consumption and history of hypertension (interaction p-values < 0.001), such that among non-alcohol users, caffeinated coffee was associated with decreased RCC risk (OR = 0.44, 95% CI = 0.23–0.83), while decaffeinated coffee consumption was associated with increased risk (OR = 3.72, 95% CI = 1.49–9.29). Among individuals both with and without a personal history of hypertension, there was a suggestion of lower RCC risk associated with caffeinated coffee intake, whereas there was a trend toward increased risk associated with decaffeinated coffee intake.

Table 4 shows results from analyses that limited the RCC cases to those with the clear cell subtype (ccRCC). In fully-adjusted models, ORs for ccRCC risk associated with caffeinated coffee and decaffeinated coffee consumption were 0.77 (95% CI = 0.58–1.02) and 1.40 (95% CI = 0.90–2.17), respectively, compared with no coffee consumption. Results from the exploratory polychotomous regression analyses showed some interesting associations with the extent of ccRCC aggressiveness (Table 4). Compared with no coffee consumption, caffeinated coffee intake was associated with reduced risk of the less aggressive form of ccRCC (OR = 0.62, 95% CI = 0.44–0.88), and no association was observed between decaffeinated coffee and less aggressive ccRCC. In contrast, decaffeinated coffee consumption was associated with higher risk of the moderate or high aggressive forms of ccRCC (OR = 1.80, 95% CI = 1.01–3.22), and no association was observed with caffeinated coffee consumption. As with overall RCC risk, no association was observed between consumption of both caffeinated and decaffeinated coffee with ccRCC or the extent of ccRCC aggressiveness.

Discussion

In this large case-control study we observed an inverse association between caffeinated coffee intake and RCC risk. Our results also suggest a positive association between decaffeinated coffee consumption and RCC risk. The increased RCC risk associated with decaffeinated coffee consumption was most pronounced among females, never smokers, and non-alcohol users. For the clear cell subtype of RCC, there were suggestions of an increased risk associated with decaffeinated coffee and decreased risk associated with caffeinated coffee consumption. We further found that decaffeinated coffee consumption was associated with an increase in risk of the moderate or highly aggressive form of ccRCC, whereas caffeinated coffee consumption was associated with lower risk of the less aggressive form of ccRCC. Together, these findings suggest that caffeinated coffee intake may play a protective

role against RCC development, while regular consumption of decaffeinated coffee may increase RCC risk.

Because of the kidney's function as the body's primary filtration system, several investigators have examined the hypothesis that consumption of certain fluids and their subsequent clearance by the kidney may be associated with RCC risk [5]. In this context, overall coffee consumption has been examined in relation to RCC in many studies [7–14]; however, the possibility that the effect of decaffeinated coffee may differ from that of caffeinated coffee has not been investigated thoroughly. In 2007, Lee *et al.* provided the most definitive evaluation of overall coffee consumption (caffeinated and decaffeinated combined) and RCC risk to date.[19] Their pooled analysis of 13 prospective studies, reported that consumption of >3 cups of coffee per day (compared to <1 per day) is associated with a modestly lower risk of RCC (pooled RR=0.84; P=0.22), particularly among women (pooled RR=0.71; P=0.07) [19]. These authors proposed explanations that centered on improved insulin sensitivity and lower C-peptide levels for coffee drinkers [26–28] and antioxidant effects of caffeine [29, 30]. For the gender-specific effect, the authors noted published evidence of differences in metabolism of caffeine between men and women [31]. Germane to the present study, Lee *et al.* could not evaluate the risk associated with caffeinated and decaffeinated coffee separately because of data limitations [19]. We are aware of only one other study that reported evidence of a possible association of decaffeinated coffee and RCC risk. In 2009, Montella *et al.* reported from a case-control study in Italy (767 cases, 1534 controls) that found a multivariable-adjusted OR for “ever” consuming decaffeinated coffee of 1.38 (95% CI: 0.94–2.03) [20]. Given the relatively novel nature of the finding and the lack of a statistical significance, the authors did not conduct further exploration analyses (e.g., stratified analyses) or comment on potential mechanisms supporting this putative association. The current study is, therefore, the first study to provide more compelling evidence that decaffeinated coffee consumption increases RCC risk.

While we cannot completely rule out the role of chance or bias as a possible explanation for the association with decaffeinated coffee, it is worth noting that historical methods of decaffeinating coffee involved exposure of coffee beans to a variety of toxic solvents (e.g., benzene, chloroform, dichloromethane, ethyl acetate, methylene chloride) [15, 17]. Therefore, it is reasonable to suggest that residual chemicals could be ingested from the consumption of decaffeinated coffee and that kidney would be at specific risk of any possible carcinogenic effects of these chemicals given its function as the primary fluids filtration organ of the body. Another explanation could be an indirect effect, in that, antioxidant contents of decaffeinated coffee have been reported to be generally lower than that of caffeinated coffee [15, 16]. Further, habitual decaffeinated coffee consumers would potentially not benefit from the improved insulin sensitivity or lower C-peptide levels that have been associated with caffeinated coffee consumption [26–28] and suggested to offer some protection against RCC [19]. These explanations require further verification in studies that would account for means of caffeine consumption (e.g. tea, energy drinks, etc.) and dose-response associations. Moreover, the observed interactions, particularly with sex, alcohol consumption, and hypertension may be too preliminary to definitive conclusions to be drawn. Further investigations are needed to validate our findings and unravel the mechanisms underlying the observed associations.

Limitations of the present study included those inherent to all case-controls studies, such as recall and participation biases. Differential recall between cases and controls, wherein cases had better recall of coffee drinking habits than controls, would either inflate or attenuate the true associations. However, because of lack of widespread public knowledge of the association between coffee consumption and RCC risk, it is less likely that the cases considered their diagnosis or the extent of the disease aggressiveness when responding to questions about coffee intake. Non-differential recall of coffee consumption among cases and controls is more likely to have occurred, which generally tends to attenuate effect estimates. Nevertheless, we noticed that questions about decaffeinated coffee were not answered by more of the cases than controls (33% vs. 11%) and presumed that those who skipped questions about decaffeinated coffee drinking habits did so because they did not drink this type of coffee. If true, we would have underrepresented the percentage of “never” coffee consumers in the cases and this would have led to an overestimation of the ORs. However, because we are unable to assign a specific reason why some subjects skipped questions on decaffeinated coffee and it is unlikely that all of these subjects would be non-decaffeinated coffee users, we restricted the analysis to those with complete information on coffee consumption. Other limitations include limited generalizability of our findings given that our analytic sample consisted predominantly of self-identified Caucasians (>90%) recruited from a tertiary referral center. Furthermore, we were unable to assess quantity of intake and therefore restricted analyses to drinkers of different coffee types versus non-drinkers. Residual confounding by poorly measured factors or confounding by unmeasured factors cannot be ruled out. Moreover, self-reported coffee intake may not necessarily reflect bioavailable levels of caffeine or constituents of coffee owing to individual differences in metabolisms and absorption. Strengths of the study include its large size, the centralized pathology review of malignancy among cases, availability of data on multiple confounders, and the ability to explore associations with the aggressive forms of RCC using a clinically validated scoring algorithm for RCC prognosis (i.e., the Mayo clinic SSIGN score).

In conclusion, the results of the present study suggest that caffeinated coffee consumption is associated with reduced risk of RCC, whereas consumption of decaffeinated coffee may increase RCC risk. Decaffeinated coffee consumption was associated also with increased risk of the aggressive forms of ccRCC. Further studies are needed to validate these findings and explore possible mechanisms underlying the associations, particularly the suggestive interactions with alcohol consumption and hypertension status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
OR	odds ratio
RCC	renal cell carcinoma
SSIGN	stage, size, grade, and necrosis

References

1. Lipworth L, et al. Renal cancer paradox: higher incidence but not higher mortality among African-Americans. *Eur J Cancer Prev.* 2011; 20(4):331–3. [PubMed: 21633203]
2. King SC, et al. Continued increase in incidence of renal cell carcinoma, especially in young patients and high-grade disease: United States 2001 to 2010. *J Urol.* 2014; 191(6):1665–70. [PubMed: 24423441]
3. Sun M, et al. Age-adjusted incidence, mortality, and survival rates of stage-specific renal cell carcinoma in North America: a trend analysis. *Eur Urol.* 2011; 59(1):135–41. [PubMed: 21035250]
4. Benichou J, et al. Population attributable risk of renal cell cancer in Minnesota. *Am J Epidemiol.* 1998; 148(5):424–30. [PubMed: 9737554]
5. Ljungberg B, et al. The epidemiology of renal cell carcinoma. *Eur Urol.* 2011; 60(4):615–21. [PubMed: 21741761]
6. Svilaas A, et al. Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. *J Nutr.* 2004; 134(3):562–7. [PubMed: 14988447]
7. Maclure M, Willett W. A case-control study of diet and risk of renal adenocarcinoma. *Epidemiology.* 1990; 1(6):430–40. [PubMed: 2090280]
8. McCredie M, Ford JM, Stewart JH. Risk factors for cancer of the renal parenchyma. *Int J Cancer.* 1988; 42(1):13–6. [PubMed: 3391702]
9. Talamini R, et al. A case-control study of risk factor for renal cell cancer in northern Italy. *Cancer Causes Control.* 1990; 1(2):125–31. [PubMed: 2102282]
10. Benhamou S, et al. Risk factors for renal-cell carcinoma in a French case-control study. *Int J Cancer.* 1993; 55(1):32–6. [PubMed: 8344750]
11. Kreiger N, et al. Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes Control.* 1993; 4(2):101–10. [PubMed: 8481488]
12. Yuan JM, et al. Cruciferous vegetables in relation to renal cell carcinoma. *Int J Cancer.* 1998; 77(2):211–6. [PubMed: 9650554]
13. Yu MC, et al. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *J Natl Cancer Inst.* 1986; 77(2):351–6. [PubMed: 3461197]
14. McLaughlin JK, et al. A population--based case--control study of renal cell carcinoma. *J Natl Cancer Inst.* 1984; 72(2):275–84. [PubMed: 6582315]
15. Niseteo T, et al. Bioactive composition and antioxidant potential of different commonly consumed coffee brews affected by their preparation technique and milk addition. *Food Chemistry.* 2012; 134(4):1870–1877. [PubMed: 23442632]
16. Preedy, VR. *Processing and Impact on Antioxidants in Beverages.* First. Academic Press; San Diego: 2014.
17. Schapira, J., Schapira, K., Schapira, D. *The Book of Coffee and Tea: A Guide to the Appreciation of Fine Coffees, Teas, and Herbal Beverages.* 2. New York: St. Martin's Press; 1982.

16. Schapira, J., Schapira, K., Schapira, D. The Book of Coffee and Tea: A Guide to the Appreciation of Fine Coffees, Teas, and Herbal Beverages. 2. New York: St. Martin's Press; 1982.
18. Page BD, Charbonneau CF. Headspace gas chromatographic determination of methylene chloride in decaffeinated tea and coffee, with electrolytic conductivity detection. *J Assoc Off Anal Chem.* 1984; 67(4):757–61. [PubMed: 6469909]
19. Lee JE, et al. Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies. *Int J Cancer.* 2007; 121(10):2246–53. [PubMed: 17583573]
20. Montella M, et al. Coffee, decaffeinated coffee, tea intake, and risk of renal cell cancer. *Nutr Cancer.* 2009; 61(1):76–80. [PubMed: 19116877]
21. Frank I, et al. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol.* 2002; 168(6):2395–400. [PubMed: 12441925]
22. Fujii Y, et al. External validation of the Mayo Clinic cancer specific survival score in a Japanese series of clear cell renal cell carcinoma. *J Urol.* 2008; 180(4):1290–5. discussion 1295–6. [PubMed: 18707704]
23. Zigeuner R, et al. External validation of the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score for clear-cell renal cell carcinoma in a single European centre applying routine pathology. *Eur Urol.* 2010; 57(1):102–9. [PubMed: 19062157]
24. Olson JE, et al. The Mayo Clinic Biobank: a building block for individualized medicine. *Mayo Clin Proc.* 2013; 88(9):952–62. [PubMed: 24001487]
25. Leibovich BC, et al. Histological Subtype is an Independent Predictor of Outcome for Patients With Renal Cell Carcinoma. *Urology.* 2010; 183(4):1309–1316.
26. Arnlov J, Vessby B, Riserus U. Coffee consumption and insulin sensitivity. *JAMA.* 2004; 291(10):1199–201. [PubMed: 15010440]
27. Van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA.* 2005; 294(1):97–104. [PubMed: 15998896]
28. Wu T, et al. Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. *Diabetes Care.* 2005; 28(6):1390–6. [PubMed: 15920057]
29. Leon-Carmona JR, Galano A. Is caffeine a good scavenger of oxygenated free radicals? *J Phys Chem B.* 2011; 115(15):4538–46. [PubMed: 21438616]
30. Anissi J, et al. A comparative study of the antioxidant scavenging activity of green tea, black tea and coffee extracts: a kinetic approach. *Food Chem.* 2014; 150:438–47. [PubMed: 24360473]
31. Arnaud, M. Metabolism of caffeine and other components of coffee. In: Garattini, S., editor. *Caffeine, Coffee and Health.* New York: Raven Press; 1993. p. 43-95.1993, *Raven Press*, New York

Table 1Characteristics of renal cell carcinoma cases and controls ($N = 1,670$)

	Cases (N = 669)	Controls (N = 1,001)
Age, years ^a		
Mean (SD)	61.5 (11.4)	63.4 (11.9)
Median (min, max)	62 (28, 88)	64 (20, 90)
Sex		
Male	434 (65%)	601 (60%)
Female	235 (35%)	400 (40%)
Institutional Site		
MCF	174 (26%)	215 (21%)
MCR	495 (74%)	786 (79%)
Race		
Caucasian	612 (92%)	941 (95%)
Non-Caucasian	50 (8%)	47 (5%)
Marital Status		
Married/Cohabitation	547 (82%)	856 (86%)
Widowed	33 (5%)	28 (3%)
Divorced/Separated	46 (7%)	52 (5%)
Single, never married	38 (6%)	61 (6%)
Education		
< High School	23 (3%)	14 (1%)
High School graduate/GED	152 (23%)	152 (15%)
Vocational or some College	217 (33%)	270 (27%)
College graduate	119 (18%)	266 (27%)
Graduate school	119 (18%)	267 (27%)
Other	32 (5%)	24 (2%)
BMI Category ^a		
<25 kg/m ²	74 (12%)	161 (17%)
25–30 kg/m ²	196 (32%)	356 (37%)
>30 kg/m ²	349 (56%)	448 (46%)
Smoking Status		
Never	320 (49%)	551 (56%)
Former	284 (44%)	412 (42%)
Current	48 (7%)	25 (3%)
Missing	17	13
Pack Years		
0 pack years	321 (53%)	551 (59%)
>0 to <20 pack years	134 (22%)	239 (25%)
20 to <40 pack years	90 (15%)	86 (9%)
40+ pack years	63 (10%)	65 (7%)

	Cases (N = 669)	Controls (N = 1,001)
Missing	61	60
History of Hypertension		
No	252 (38%)	537 (54%)
Yes	408 (62%)	455 (46%)
Alcohol consumption		
No	133 (20%)	155 (15%)
Yes	536 (80%)	846 (85%)
Coffee consumption		
None	207 (31%)	255 (25%)
Caffeinated coffee only	298 (45%)	535 (53%)
Decaffeinated coffee only	84 (13%)	81 (8%)
Both caffeinated and decaf coffee	80 (12%)	130 (13%)

^aAge at diagnosis (cases) or at the time of consent/recruitment (controls)

Abbreviation: BMI, body mass index

Table 2
Associations of caffeinated and decaffeinated coffee consumption and risk of renal cell carcinoma (N = 1,670).

	Non-coffee drinkers	Coffee Consumption Categories			
		Caffeinated coffee only	Decaffeinated coffee only	Both caffeinated and decaffeinated coffee	P-value
N, case : control	207 : 255	298 : 535	84 : 81	80 : 130	
Covariate Adjustment in Model:					
<i>Age (continuous)</i>	1.00 (ref) ^a	0.73 (0.58, 0.93)	1.50 (1.04, 2.17)	0.85 (0.61, 1.20)	0.36
<i>Age + Site (Florida, Rochester)</i>	1.00 (ref)	0.73 (0.58, 0.92)	1.46 (1.00, 2.11)	0.84 (0.60, 1.18)	0.31
<i>Age + sex</i>	1.00 (ref)	0.72 (0.57, 0.92)	1.52 (1.05, 2.19)	0.86 (0.61, 1.21)	0.37
<i>Age + Site + sex + Smoking status (never, former, current)</i>	1.00 (ref)	0.67 (0.53, 0.86)	1.42 (0.97, 2.07)	0.80 (0.56, 1.14)	0.21
<i>Age + Site + sex + BMI (continuous)</i>	1.00 (ref)	0.74 (0.58, 0.95)	1.53 (1.04, 2.25)	0.86 (0.60, 1.22)	0.40
<i>Age + Site + sex + History of hypertension (no, yes)</i>	1.00 (ref)	0.74 (0.58, 0.94)	1.40 (0.96, 2.06)	0.86 (0.60, 1.22)	0.39
<i>Age + Site + sex + Alcohol consumption (never, ever)</i>	1.00 (ref)	0.76 (0.60, 0.97)	1.52 (1.05, 2.21)	0.89 (0.63, 1.26)	0.52
<i>Age, Site, sex, Smoking status, BMI, History of hypertension, Alcohol consumption</i>	1.00 (ref)	0.74 (0.57, 0.97)	1.48 (0.99, 2.21)	0.87 (0.60, 1.27)	0.48
<i>Age, Site, sex, pack-years of smoking (0, >0-<20, 20-40, 40+), BMI, history of hypertension, alcohol consumption</i>	1.00 (ref)	0.74 (0.57, 0.97)	1.48 (0.98, 2.25)	0.90 (0.62, 1.32)	0.59
<i>Age, state of residence (MN, WI, IA, FL, GA, other), sex, Smoking status, BMI, History of hypertension, Alcohol consumption</i>	1.00 (ref)	0.74 (0.57, 0.96)	1.47 (0.98, 2.19)	0.88 (0.60, 1.28)	0.50

^aOdds ratios (95% confidence intervals)

Associations of caffeinated and decaffeinated coffee consumption and renal cell carcinoma risk, stratified by age, gender, BMI, smoking status, alcohol consumption, and history of hypertension (N = 1,670).

Table 3

	Non-coffee drinkers	Coffee Consumption Categories			P-value for interaction
		Caffeinated coffee only	Decaffeinated coffee only	Both caffeinated and decaffeinated coffee	
Age					
< 64 years					
N, case : control	130 : 161	145 : 248	28 : 17	51 : 33	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.66 (0.47, 0.92)	1.67 (0.85, 3.31)	0.70 (0.42, 1.18)	
64 years					
N, case : control	49 : 81	120 : 256	49 : 60	40 : 72	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.85 (0.55, 1.32)	1.36 (0.79, 2.33)	0.96 (0.55, 1.66)	P _{interaction} =0.86
Sex					
Male					
N, case : control	105 : 144	183 : 306	42 : 48	43 : 74	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.82 (0.59, 1.16)	1.19 (0.70, 2.02)	0.83 (0.51, 1.36)	
Female					
N, case : control	74 : 98	82 : 198	35 : 29	30 : 49	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.66 (0.43, 1.01)	2.19 (1.16, 4.13)	1.02 (0.57, 1.84)	P _{interaction} =0.13
BMI category					
< 30kg/m ²					
N, case : control	66 : 127	119 : 255	39 : 48	33 : 73	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.91 (0.61, 1.36)	1.63 (0.93, 2.86)	0.90 (0.52, 1.56)	
30 kg/m ²					
N, case : control	113 : 115	146 : 249	38 : 29	40 : 50	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.67 (0.46, 0.94)	1.51 (0.84, 2.74)	0.87 (0.51, 1.47)	P _{interaction} =0.47
Smoking status					
Ever (current + former)					
N, case : control	64 : 55	156 : 251	40 : 38	44 : 68	

	Non-coffee drinkers	Coffee Consumption Categories			P-value for interaction
		Caffeinated coffee only	Decaffeinated coffee only	Both caffeinated and decaffeinated coffee	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.61 (0.40, 0.94)	1.05 (0.57, 1.94)	0.65 (0.38, 1.14)	
Never					
N, case : control	115 : 187	109 : 253	37 : 39	29 : 55	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.81 (0.58, 1.13)	1.83 (1.06, 3.15)	1.07 (0.63, 1.83)	P _{interaction} =0.08
Alcohol Consumption					
Never					
N, case : control	52 : 63	24 : 62	26 : 9	16 : 11	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.44 (0.23, 0.83)	3.72 (1.49, 9.29)	1.70 (0.70, 4.16)	
Ever					
N, case : control	127 : 179	241 : 442	51 : 68	112 : 57	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.78 (0.58, 1.04)	1.11 (0.70, 1.76)	0.76 (0.50, 1.16)	P _{interaction} <0.001
History of hypertension					
No					
N, case : control	83 : 136	105 : 275	19 : 31	23 : 64	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.68 (0.47, 1.00)	1.30 (0.65, 2.57)	0.70 (0.39, 1.25)	
Yes					
N, case : control	96 : 106	160 : 229	58 : 46	50 : 59	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.82 (0.57, 1.19)	1.62 (0.98, 2.69)	1.06 (0.64, 1.75)	P _{interaction} <0.001
Study site					
Rochester					
N, case : control	137 : 194	189 : 411	53 : 50	53 : 92	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.74 (0.55, 1.01)	2.11 (1.30, 3.42)	1.01 (0.66, 1.56)	
Jacksonville					
N, case : control	42 : 48	76 : 93	24 : 27	20 : 31	
Multivariable-adjusted OR (95% CI) ^a	1.00 (ref)	0.88 (0.50, 1.55)	1.75 (0.35, 1.59)	0.92 (0.28, 1.35)	P _{interaction} =0.45

^a Adjusting for age, site, sex, smoking status, BMI, HTN, and alcohol in models not stratified by the respective factor.

Table 4

Associations of caffeinated and decaffeinated coffee consumption with clear cell renal carcinoma (ccRCC) risk, and stratified by level of disease aggressiveness (N = 1,517).

	Non-coffee drinkers	Coffee Consumption Categories			
		Caffeinated coffee only	Decaffeinated coffee only	Both caffeinated and decaffeinated coffee	P-value
Overall association					
N, case : control	162 : 255	234 : 535	58 : 81	62 : 130	
Minimally-adjusted OR (95% CI) ^a	1.00 (ref)	0.72 (0.56, 0.93)	1.32 (0.88, 1.98)	0.84 (0.58, 1.21)	0.35
N, case : control	138 : 242	209 : 504	53 : 77	57 : 123	
Fully-adjusted OR (95% CI) ^b	1.00 (ref)	0.77 (0.58, 1.02)	1.40 (0.90, 2.17)	0.88 (0.59, 1.33)	0.55
Level of ccRCC aggressiveness^c					
<i>Minimally-adjusted model</i>					
Low risk ccRCC, N	101 : 255	117 : 535	30 : 81	32 : 130	
OR (95% CI) ^a	1.00 (ref)	0.60 (0.44, 0.82)	1.18 (0.72, 1.95)	0.74 (0.46, 1.17)	0.19
Moderate/high risk ccRCC, N	59 : 255	108 : 535	26 : 81	29 : 130	
OR (95% CI) ^a	1.00 (ref)	0.89 (0.62, 1.27)	1.55 (0.90, 2.69)	1.04 (0.63, 1.71)	0.89
<i>Fully-adjusted model</i>					
Low risk ccRCC, N	89 : 242	105 : 504	26 : 77	31 : 123	
OR (95% CI) ^b	1.00 (ref)	0.62 (0.44, 0.88)	1.15 (0.67, 1.98)	0.78 (0.48, 1.29)	0.33
Moderate/high risk ccRCC, N	48 : 242	95 : 504	25 : 77	25 : 123	
OR (95% CI) ^b	1.00 (ref)	0.96 (0.65, 1.44)	1.80 (1.01, 3.22)	1.08 (0.62, 1.88)	0.80

^a Adjusted for age (continuous), site (Florida, Rochester), and gender.

^b Additional adjustment for smoking status (never, former, ever), BMI (continuous), history of hypertension (yes, no), and alcohol consumption (never, ever).

^c ORs and 95% confidence intervals were derived from derived from polychotomous logistic regression models with a three level outcome variable (i.e., modeled as control=0, 'low risk' case=1, 'moderate/high risk' case=2).