



Total Serum Calcium and Renal Cell Cancer Risk: Potential Additive Interactions in a High Risk Cohort

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Male smokers with both *hypertension and low total serum calcium* were at a *6.2-fold increased risk* of subsequent development of renal cell cancer (RCC). The interaction between hypertension and TSC was *super-additive* among those already at higher RCC risk.

BACKGROUND

- Circulating concentrations of calcium have been associated with DNA repair capacity and with risk of some cancers, including renal cell cancer (RCC)
- DNA repair capacity phenotypes in lymphocytes (e.g., γ H2AX and micronuclei) have been correlated with total serum calcium (TSC) among adults
- Smoking, male sex, and hypertension are well-recognized RCC risk factors
- Circulating TSC is influenced by 1) hypertension, 2) protein intake and 3) fat intake
- Interactions of public health importance are often additive
- Therefore, we investigated a potential additive influence of hypertension, protein intake and fat intake upon the association between TSC and renal cell cancer (RCC)

HYPOTHESES

- 1) *Male smokers with hypertension and lower serum calcium are at increased RCC risk, compared with male smokers having no hypertension and higher serum calcium (hypertension x TSC)*
- 2) *Additive interaction: Protein intake x TSC*
- 3) *Additive interaction: Total fat intake x TSC*

METHODS

- Nested case-control study design
- 154 newly diagnosed RCC cases and 308 cancer-free controls Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) cohort
- Matching on age at randomization (± 7 years), whole blood draw date (± 20 days within the same season), pack-years of smoking, and years of follow-up (± 2 years)
- TSC by colorimetric assay (BioVision, intra-assay CV=3.5%)
- Fasting blood samples, classified as above, below, or within the normal range (8.6-10.3 mg/dL)
- Hypertension (yes/no) defined according to the 2017 American Heart Association guidelines
- Dietary intakes assessed using a validated food frequency questionnaire, including portion size and intake frequency for 203 food items and 73 mixed dishes
- Multiple conditional logistic regression to adjust odds ratios (aOR) for potential confounding factors (hypertension, body mass index, whole blood lead (Pb), and alcohol intake) and calculate confidence intervals (CI)
- Synergy indexes (SI), with >1 indicating a super-additive interaction

Table 1. Time in years from study enrollment to RCC diagnosis and total serum calcium concentrations

Years from enrollment to cancer diagnosis	Total Serum Calcium (mg/dL)	95% Confidence Interval (CI)	p trend
5.0 - 8.9	9.48	9.18, 9.78	0.002
9.0 - 11.7	9.70	9.47, 9.93	
11.8 - 15.1	9.77	9.61, 9.94	
15.2 - 20.9	9.91	9.73, 10.09	

Table 2. Additive interaction between total serum calcium and hypertension status on risk of RCC, adjusted odds ratios (OR)

Risk Category	Adjusted OR*	95% CI	p value
High Serum Calcium with No Hypertension	Reference		
Low Serum Calcium with No Hypertension	3.0	0.57, 15.73	0.886
High Serum Calcium with Hypertension	3.4	0.76, 15.15	0.431
Low Serum Calcium with Hypertension	6.2	1.39, 27.44	0.001

RESULTS

- No difference between cases and controls for dietary fat intake (total, saturated, monounsaturated, nor polyunsaturated) or total dietary protein intake (all p-values > 0.05)
- Among cases, length of time (years) to RCC diagnosis and TSC were positively correlated (Pearson's rho = 0.25, p=0.002)
- Individuals with both hypertension and low TSC were at increased RCC risk (aOR = 6.2, 95% CI: 1.39-27.44, p=0.001, p-trend=0.008, SI=1.2), compared with those having no hypertension and higher TSC
- Conversely, high TSC was protective even among individuals with high combined fat and protein intake (aOR= 0.3; 95% CI: 0.11-0.79, SI=1.4), however no dose-response effect was identified (data not shown).

CONCLUSIONS

- Combined risk profiles may be important in development of RCC screening protocols
- RCC risks may be higher when investigated in cohorts with both high and low RCC risk groups

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