Glycemic index, glycemic load and renal cell carcinoma risk

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Background: The risk of renal cell carcinoma (RCC) has been related to refined cereals and starchy foods, but the association has not been studied in terms of glycemic index (GI) and glycemic load (GL). To provide information on this issue, we analyzed data from an Italian multicentric case–control study.

Materials and methods: Cases were 767 patients with histologically confirmed, incident RCC. Controls were 1534 subjects admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions, unrelated to known risk factors for RCC. Information on dietary habits was derived through a food-frequency questionnaire. Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) for GI and GL intake were adjusted for major relevant covariates.

Results: Compared with the lowest quintile, the ORs for the highest quintile were 1.43 (95% CI 1.05–1.95) for GI and 2.56 (95% CI 1.78–3.70) for GL, with significant trends in risk. Compared with the lowest quintile, the risk of RCC for all subsequent levels of GL was higher in never drinkers than in ever drinkers.

Conclusions: We found direct relations between dietary levels of GI and GL and RCC risk. This can be related to mechanisms linked to insulin resistance and sensitivity.

Key words: cancer risk, case–control studies, diet, glycemic index, glycemic load, renal cell carcinoma

introduction

Cigarette smoking, obesity and family history of kidney cancer are established risk factors for renal cell carcinoma (RCC), the major histologic type of kidney cancer, but they explain only part of cases [1]. There are some evidences that dietary factors typically associated with a Western lifestyle, such as high intake of proteins [2] and refined carbohydrates [3, 4], as well as lack of physical activity might be detrimental on RCC risk. Carbohydrates are the main dietary component affecting insulin secretion and postprandial glycemia and may be involved also in the etiology of RCC, as postulated for other chronic diseases including cancer [3–5].

The glycemic index (GI) and glycemic load (GL) have been proposed to measure potential of carbohydrates to modulate insulin sensitivity [6]. The overall GI, a ranking system for carbohydrates according to their effect on blood glucose concentrations, reflects the average quality of carbohydrates consumed. The total dietary GL, the sum of the GLs for the total serving of all carbohydrate-containing foods consumed per day, reflects both the average quantity and quality of carbohydrates [7]. Numerous epidemiological studies have investigated GI and GL as potential risk factors for chronic diseases, such as diabetes, cardiovascular disease, obesity and cancer [5, 8, 9]. A meta-analysis found that both GL and GI were directly associated with risk of colorectal [relative risk (RR) = 1.26, 95% confidence interval (CI) 1.11–1.44 and RR = 1.18, 95% CI 1.05–1.34, respectively], upper aerodigestive tract [11] and stomach [12] found a direct association with intake of GI and GL.

To our knowledge, no study has investigated the role of dietary GI and GL on RCC. To provide information on this issue, we analyzed data from a multicentric case–control study conducted in Italy, one of the largest studies of diet and RCC to date [13].
A case–control study on RCC was conducted from 1992 to 2004 in four Italian areas, including the greater Milan area and the provinces of Udine and Pordenone in northern Italy, the province of Latina in central Italy and the Puglia region in southern Italy. The study population included 533 cases aged 20 years and older who were admitted to major teaching and subject’s hospital stay and included information on personal characteristics, anthropometric measures and lifestyle habits, including alcohol drinking and cigarette smoking, a problem-oriented medical history and history of morbidity. The FFQ included 78 foods, food groups or dishes divided into six sections: (i) bread, cereals and first courses; (ii) second courses (i.e. meat, fish and other main dishes); (iii) side dishes (i.e. vegetables); (iv) fruits; (v) sweets, desserts and soft drinks and (vi) milk, hot beverages and sweeteners. The FFQ allowed to estimate the intake of total energy as well as of selected nutrients, using Italian food composition databases integrated with other sources when needed. The FFQ was satisfactorily reproducible [15] and valid [16]. To compute the GI and GL for each subject, we assigned a GI value to the average number of servings of that food consumed by the subject per week, multiplied by the average GI of one serving of each of these 50 foods times the average GI of the food consumed. The average GI of a subject’s diet was computed by summing up the products of the GI value of one serving of each of these 50 foods times the average number of servings of that food consumed by the subject per week, divided by the subject’s weekly available carbohydrate intake [18]. A score for the average GI was computed as the GI, but without dividing by the total amount of available carbohydrates.

Odds ratios (OR) and the corresponding 95% CIs, for quintiles of GI and GL, were computed using conditional multiple logistic regression models. We considered two models, all conditioned on study center, sex and quinquennia of age and adjusted for period of interview and education, smoking habit, alcohol drinking, body mass index, occupational physical activity, treated hypertension, diabetes mellitus, family history of kidney cancer and nonalcohol–noncarbohydrate energy intake. ORs from multiple conditional logistic regression models, conditioned on study center, sex and quinquennia of age and adjusted for period of interview and education.

Table 1. ORs and 95% CIs of renal cell carcinoma according to glycemic index and glycemic load (Italy, 1992–2004)

<table>
<thead>
<tr>
<th>Glycemic index</th>
<th>Quintile of intakea</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>P for trend</th>
<th>Continuous OR (95% CI)b/c/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (median)</td>
<td>56.8 (49.2)</td>
<td>53.8 (46.3)</td>
<td>50.8 (43.6)</td>
<td>47.8 (40.6)</td>
<td>44.8 (37.6)</td>
<td>69.7 (66.7)</td>
<td>69.8–73.5 (71.8)</td>
<td>73.6–76.6 (75.1)</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>1,693/3,066</td>
<td>1,693/3,066</td>
<td>1,693/3,066</td>
<td>1,693/3,066</td>
<td>1,693/3,066</td>
<td>1,693/3,066</td>
<td>1,693/3,066</td>
<td>1,693/3,066</td>
</tr>
<tr>
<td>OR (95% CI)b/d</td>
<td>1.16 (0.86–1.55)</td>
<td>1.16 (0.86–1.58)</td>
<td>1.16 (0.86–1.58)</td>
<td>1.16 (0.86–1.58)</td>
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<td>1.16 (0.86–1.58)</td>
</tr>
</tbody>
</table>

aQuintiles were computed on the distribution of controls.

bThe unit is the difference between the 80th and 20th percentile, i.e. between the upper cut point of the fourth and first quintile.

cReference category.

dORs from multiple conditional logistic regression models, conditioned on study center, sex and quinquennia of age and adjusted for period of interview and education.
cigarettes/day, and ≥20 cigarettes/day), alcohol drinking (never drinkers, ex-drinkers and current drinkers of <21 drinks/week, and ≥21 drinks/week), nonalcohol–noncarbohydrate energy intake (in quintiles, calculated among distribution of controls: <735, 755 to <911, 911 to <1071, 1071 to <1312 and ≥1312 kcal/day), family history of kidney cancer in first-degree relatives, body mass index (in tertiles, calculated among distribution of controls: <24.6, 24.6 to <27.6 and ≥27.6 kg/m²), occupational physical activity at age 30 years (low, mainly standing/sitting; medium, intermediate and high, heavy/strenuous), history of treated hypertension and history of diabetes mellitus. GI and GL were also introduced as continuous variables, and the unit of measurement was the difference between the 80th and the 20th percentile, i.e. between the upper cut point of the fourth and the first quintiles, computed on the distribution of controls.

results

Table 1 shows the distribution of cases and controls and the multivariate ORs of RCC according to GI and GL. Compared with the lowest quintile, the ORs for the highest quintile were 1.43 (95% CI 1.05–1.95) for GI and 2.56 (95% CI 1.78–3.70) for GL. There were significant positive trends in risk for both GI and GL. When considering dietary GI and GL as continuous variables, the multivariate ORs for an increase in intake equal to the difference between the 80th and the 20th percentile were 1.23 (95% CI 1.05–1.44) for GI and 1.39 (95% CI 1.17–1.64) for GL. Table 2 considers the relationship between GI and GL and RCC risk in separate strata of sex, age, waist-to-hip ratio, smoking habit, energy intake and history of treated hypertension and intake of fiber. Neither appreciable nor significant heterogeneity emerged across these strata, although the ORs of RCC according to GI appeared to be, if anything, higher in women (OR = 1.48, 95% CI 1.06–2.07) than in men (OR = 1.34, 95% CI 1.11–1.62), in subjects with age ≥60 years (OR = 1.51, 95% CI 1.19–1.92) than in those with age <60 years (OR = 1.29, 95% CI 1.02–1.64) and in subjects with waist-to-hip ratio above median (OR = 1.74, 95% CI 1.18–2.56) than in those with waist-to-hip ratio below median (OR = 1.40, 95% CI 1.05–1.86). The ORs of RCC in relation with GI and GL were 1.26 (95% CI 1.03–1.54) and 1.36 (95% CI 1.12–1.67), respectively, among cases with clear cell histological type of cancer; 1.62 (95% CI 1.16–2.27) and 1.28 (95% CI 0.94–1.73), respectively, among cases with other histological subtypes of cancer; 1.00 (95% CI 0.76–1.31) and 1.46 (95% CI 1.12–1.93), respectively, among cases with unknown histological type of cancer.

The multivariate ORs of RCC for intake quintiles of GI in stratum of alcohol drinking are reported in Table 3. Compared with the lowest quintile, the risk of RCC for all subsequent levels of GI was higher in never drinkers than in ever drinkers. The continuous OR was 2.04 (95% CI 1.25–3.32) in never drinkers and 1.30 (95% CI 1.08–1.55) in ever drinkers.

We examined the combined effect of GI and waist-to-hip ratio by cross-classifying patients according to both variables (Figure 1). The OR for the combination of the highest levels of GI and waist-to-hip ratio, compared with the opposite extreme, was 2.1 (95% CI 1.4–3.0).

discussion

In this Italian study, conducted on one of the populations with the highest intake of starches among Western countries [19], we observed direct associations between GI and GL and RCC risk. For GI, the risk was somewhat higher in alcohol abstainers and subjects with high waist-to-hip ratio, indicating that mechanisms related to insulin resistance and sensitivity might explain the association.

In our previous articles, using the same dataset, we found a direct trend in risk of RCC for high intake of starch (OR = 1.9 for the highest versus the lowest intake quintile, 95% CI 1.4–2.6) [4] and for its major sources, i.e. white bread (OR = 1.9, 95% CI 1.4–2.7), pasta and rice (OR = 1.3, 95% CI 1.0–1.8) [13]. Refined grains are characterized by rapid digestion and absorption of their glucose component, resulting in higher postprandial blood glucose and insulin peaks. Conditions that are affected by hyperinsulinemia, such as obesity and diabetes, as well as its determinants, low physical activity and excess energy intake, have also been associated with

### Table 2. Continuous ORs* and 95% CIs of renal cell carcinoma according to GI and GL in separate strata of selected covariates (Italy, 1992–2004)

<table>
<thead>
<tr>
<th>Sex</th>
<th>GI, continuous OR (95% CI)</th>
<th>GL, continuous OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.29 (1.05–1.57)</td>
<td>1.34 (1.11–1.62)</td>
</tr>
<tr>
<td>Female</td>
<td>1.16 (0.89–1.51)</td>
<td>1.48 (1.06–2.07)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.40 (1.08–1.82)</td>
<td>1.29 (1.02–1.64)</td>
</tr>
<tr>
<td>≥60</td>
<td>1.13 (0.92–1.38)</td>
<td>1.51 (1.19–1.92)</td>
</tr>
<tr>
<td>Waist-to-hip ratio&lt;</td>
<td>1.31 (0.96–1.80)</td>
<td>1.40 (1.05–1.86)</td>
</tr>
<tr>
<td>Median value</td>
<td>1.68 (1.15–2.46)</td>
<td>1.74 (1.18–2.56)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>0.98 (0.76–1.27)</td>
<td>1.30 (0.99–1.70)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.59 (1.16–2.18)</td>
<td>1.40 (1.02–1.95)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.24 (0.92–1.67)</td>
<td>1.37 (1.01–1.85)</td>
</tr>
<tr>
<td>Energy intake&lt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median value</td>
<td>1.22 (0.99–1.50)</td>
<td>1.40 (1.09–1.82)</td>
</tr>
<tr>
<td>Median value</td>
<td>1.22 (0.95–1.57)</td>
<td>1.28 (1.04–1.57)</td>
</tr>
<tr>
<td>Treated hypertension Yes</td>
<td>1.19 (0.99–1.45)</td>
<td>1.40 (1.14–1.70)</td>
</tr>
<tr>
<td>No</td>
<td>1.37 (1.02–1.84)</td>
<td>1.41 (1.01–1.98)</td>
</tr>
<tr>
<td>Intake of fiber&lt;</td>
<td>1.21 (0.97–1.52)</td>
<td>1.52 (1.10–2.12)</td>
</tr>
<tr>
<td>&lt;Median value</td>
<td>1.28 (1.01–1.64)</td>
<td>1.41 (1.13–1.75)</td>
</tr>
</tbody>
</table>

*ORs from multiple conditional logistic regression models, conditioned on study center, sex and quinquennia of age and adjusted for period of interview, education, smoking habit, alcohol drinking, body mass index, occupational physical activity, treated hypertension, diabetes mellitus, family history of kidney cancer and nonalcohol–noncarbohydrate energy intake, where appropriate. The unit of measurement was the difference between the 80th and the 20th percentile. Median cut point of distribution of controls for waist-to-hip ratio was 0.961 in males and 0.855 in females. Median cut point of distribution of controls was 987 kcal/day. OR, odds ratio; CI, confidence interval; GI, glycemic index; GL, glycemic load.
In this study, we found that elevated waist-to-hip ratio appeared to contribute in enhancing RCC risk when diet was high in GL. Overweight and obesity are accompanied by elevated levels of fasting serum and free insulin-like growth factor I (IGF-I), which contributes to cell growth and proliferation [21]. Hyperinsulinemia affects the production of sex hormones such as androgens and estrogens, which may be associated with cancer growth. There are indications for a role of estrogens and their receptors in the etiology of RCC in laboratory animals [22, 23]. In the Syrian hamster model, estrogen treatment resulted in kidney tumor, whereas antiestrogens reduced tumor formation [23]. However, there is little epidemiologic evidence supporting an association in humans [1].

Alcohol drinking has been inversely related to RCC [24, 25]. A mechanism by which alcohol may reduce the risk of RCC is by improving insulin sensitivity [26]. Moderate alcohol intake has beneficial effects of glycemic control, lowering postprandial glycemia [27] and has been also associated with reduced risk of diabetes [28]. This is consistent with a greater impact on risk of GL on RCC in alcohol abstainers, as compared with ever alcohol drinkers. In contrast, the associations with GI and GL were consistent in different strata of age, sex and various covariates, including total fiber intake, which has the property to flatten the glucose response [5]. Since obesity is a risk factor for RCC [20] and is strongly associated to diabetes, impaired insulin sensitivity appears to increase RCC risk. Diabetes mellitus has been positively associated to kidney cancer risk [29], but its relation with RCC is controversial. In this study, diabetes was related to RCC risk [30], and the combination of high GL diet and high waist-to-hip ratio led to an over twofold excess risk.

Among the possible limitations of the present study, there is the use of hospital controls, whose dietary habits and lifestyle may differ from those of the general population. However, we took great care in excluding from the control group all diagnoses that might have been associated to tobacco smoking or involved long-term modifications of diet. Further, in the present study, dietary intake was very similar across the four major diagnostic categories of controls (i.e. traumas and other orthopedic, surgical and miscellaneous conditions).

In the absence of population-based cancer registries, we had no information on total number of cases. The main cause of

![Figure 1. Odds ratio of renal cell carcinoma according to the joint effect of glycemic load (GL) and waist-to-hip (WTH) ratio. ORs from multiple conditional logistic regression models, conditioned on study center, sex and quinquennia of age and adjusted for period of interview, education, smoking habit, body mass index, occupational physical activity, treated hypertension, diabetes mellitus, family history of kidney cancer and nonalcohol–noncarbohydrate energy intake. The reference category was GL < median value calculated among distribution of controls (i.e. 205) and WTH ratio < median value calculated among distribution of controls (i.e. 0.96 in males and 0.85 in females).](https://academic.oup.com/annonc/article-abstract/20/11/1881/191056)
loss of subjects was absence of the patient from the ward at time of the visit of interviewer, while we had no physician refusal of interview. This is unlikely therefore to have introduced major selection bias. With reference to recall bias, it is likely that neither cases nor controls had any perception of a relation between dietary habits and RCC risk. The similar interview setting and catchment areas and the almost complete participation of cases and controls are reassuring against any relevant selection and recall bias. Among the strengths of the study, there are the large sample, which allowed analysis in subgroups of subjects, and the use of a validated [16] and reproducible [15] FFQ, which allowed a comprehensive assessment of major nutrient sources in the Italian diet. Further, nonalcohol–noncarbohydrate energy intake as well as major potential confounding factors—including tobacco smoking and anthropometric measures—were carefully accounted for in all the analyses.

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references