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Nutrition and renal cell cancer

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Epidemiologic evidence on the relation between nutrition and renal cell cancer is reviewed. Kidney cancer, comprising 1.7 percent of all malignant diseases diagnosed worldwide, shows about a 20-fold international variation in the incidence in men and 10-fold in women. This substantial variation indicates an important causal role of environmental factors. Renal cell (parenchymal) cancer (RCC) accounts for about 80 percent of all kidney cancers. While the etiology of RCC is incompletely understood, analytic epidemiologic studies provide consistent support for a positive association of obesity with risk of RCC; the dose-response observed supports a causal relationship. Only a few prospective studies, all of them limited in size, have been published, while ecologic and case-control studies suggest that diet may be important in the etiology of RCC. However, contradictory results and methodologic limitations in some case-control studies prevent definite conclusions concerning diet and RCC. A positive association of protein and fat intake, as well as their main food sources (meat, milk, fats), with risk of RCC – as suggested by ecologic studies – has no clear support in analytic epidemiologic studies. A protective effect of vegetables and fruits has been observed in most case-control studies, while the majority do not show an association between alcohol, coffee, and risk of RCC. Recent reports indicated an increased risk of RCC associated with consumption of fried/sautéed meat and low intakes of magnesium or vitamin E. An apparent positive association with total energy intake, perhaps due to bias, needs further investigation. *Cancer Causes and Control* 1996, 7, 5-18

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Introduction

It has been estimated that kidney cancer afflicted 127,000 individuals worldwide in 1985, thereby accounting for 1.7 percent of all malignant diseases.[1] In the same year, about 80,000 patients died from kidney cancer.[2] Incidence and mortality rates have been increasing slowly both in the United States[3] and in several,[4,5] but not all,[6] European countries. There have been no major advances in treatment of kidney cancer over the last decades, although the survival rates are increasing gradually, presumably due to earlier diagnosis.[4] Prevention, therefore, emerges as an increasingly important strategy in the combat of kidney cancer.

In adults, cancer of the kidney encompasses two major histopathologic entities, namely renal cell (parenchymal) cancer (RCC) and renal pelvic cancer. The latter arises in the transitional cell epithelium – in the same way as cancer of the ureter (usually grouped with cancer of the kidney) and urinary bladder. Renal pelvic cancer is associated strongly with tobacco smoking and with analgesics containing phenacetin, while data on dietary associations are sparse. This overview, therefore, will be confined—unless otherwise stated—to renal cell cancer, which accounts for about 80 percent of all kidney cancers in adults. In the literature, the distinction between renal cell cancer and renal pelvic cancer is not always explicit. This ambiguity pertains, in particular, to ecologic studies.

The international variation in the incidence of kidney cancer is about 20-fold in men and at least 10-fold in women. The highest rates are found in European populations – notably Scandinavian – and in North America.[7] Although part of the geographic variation could be due

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to differences in diagnostic intensity and autopsy rates, the importance of environmental factors in renal cell carcinogenesis is likely to be substantial. For many years, however, RCC attracted limited epidemiologic interest, with smoking and possibly obesity being the only reasonably well-documented risk factors.

During the last few years, research on the etiology of RCC has been expanded substantially. A recently published, large, international, collaborative case-control study[8-13] provided several new and important leads for future research. For instance, while analgesic use appeared to be unrelated to the risk of RCC, clear associations were found with certain occupational exposures[9] as well as with endocrine and reproductive factors in women.[10] There is also substantial evidence suggesting an association between hypertension and/or its treatment and RCC risk.[11] Most importantly, however, strong and complex associations were observed between obesity and risk of RCC, notably in women,[12] and further evidence was provided for a role of diet in the etiology of RCC. In the following, these recent findings are interpreted and discussed in the context of previous epidemiologic results from ecologic and analytic studies, as well as in the light of evidence from animal experiments.

Ecologic dietary studies

Several of the prevailing nutritional hypotheses concerning the etiology of renal cancer have been generated from ecologic studies.[14-17] A comparison has been made between incidence and mortality data for renal cancer and *per capita* food consumption data of the Food and Agriculture Organization (FAO) from different countries or, less commonly, within-country data. As with any correlational studies, the possibility of confounding by other risk factors exists, in particular, obesity and smoking, which are important risk factors for RCC. Armstrong and Doll[14] found a strong positive correlation between age-adjusted incidence of renal cancer in 23 countries and *per capita* consumption of animal protein ($r = 0.82$), total fat ($r = 0.76$), total protein ($r = 0.63$), and calories ($r = 0.60$). At the food level, the correlations were highest for milk ($r = 0.74$) and meat ($r = 0.72$); other correlations were below 0.6.

In a worldwide comparison of 18 countries, Wynder *et al*[15] found a positive correlation between mortality from kidney cancer and *per capita* consumption of milk ($r = 0.76$), fats and oils ($r = 0.67$), and sugar ($r = 0.67$). At the nutrient level, calories ($r = 0.85$), fat ($r = 0.83$), and protein from animal sources ($r = 0.80$) were correlated strongly positively with kidney cancer; in contrast, protein ($r = -0.79$) and calories ($r = -0.72$) from plant products were negatively associated. The plant foods most strongly correlated with kidney cancer mortality were cereals ($r = -0.67$, $r = -0.59$),[14,15] pulses ($r = -0.56$)[14] and vegetables ($r = -0.47$).[14]

Shennan[16] drew attention to a possible association between coffee consumption and kidney cancer by demonstrating a strong correlation ($r = 0.79$) between age-adjusted mortality rates and *per capita* consumption of coffee in 16 countries. The correlation of coffee with kidney cancer mortality, based on an analysis of 32 countries, was 0.62, while the correlation with incidence rates in 23 countries was lower ($r = 0.51$).[14] Correlations between *per capita* intake of different alcoholic beverages (spirits, wine, beer) and age-adjusted mortality rates for renal cancer in 41 states of the United States were significant only for beer, in both men (0.75) and women (0.42).[17] In another ecologic study among five ethnic groups in Hawaii (USA), statistically significant positive associations with age-adjusted incidence rates of kidney cancer were observed for beer but not for wine or liquor.[18]

Case-control dietary studies

Nutrients

Results from exploratory ecologic studies during the 1970s were tested subsequently in several case-control studies. In most of them, analyses were performed at the food level and only in two of the studies[19,20] were specific nutrients also investigated. Recently, a large multicenter study [13] on diet and RCC was performed with analyses of nutrients. Briefly, coordinated population-based case-control studies using the same protocol were carried out in five countries: Australia, Denmark, Sweden, USA, and Germany. Dietary data were collected by self-administered food-frequency questionnaires, with exception of in-person interviews in Sweden. A total of 1,185 incident, histopathologically confirmed cases (698 men, 487 women) and 1,526 controls (915 men, 611 women), frequency-matched to cases by gender and age, were included in the analyses. (Germany was excluded due to differences in the food questionnaire.) Results from pooled analyses[13] as well as from individual centers were published,[21,22] or submitted for publication.[23,24]

Case-control studies of macro- and micronutrients and risk of renal cell cancer are summarized in Table 1 and Table 2. The interpretation of the associations of any specific nutrient with the risk of RCC, especially energy and energy-deriving macronutrients, is hampered by high collinearity among the major nutrients. However, methods to separate the individual effects of protein, fat, carbohydrates, and total energy have been proposed,[25-31] which are satisfactory, if not perfect.

In two studies,[13,20] the association of energy intake with RCC was investigated and both reported a positive relation among incident cases, although this was signifi-

Table 1. Energy, protein, fat, carbohydrates, and renal cell cancer

Study (ref.) Year	Location Population	Number of cases	Energy	Protein	Fat	Carbohydrates
			Relative risks for high- *cf* low-intake categories[a]			
Maclure and Willett[20] 1990	Boston, MA, USA Men and women	203	1.3	1.3 animal 0.8 vegetable	1.5 animal 1.1 vegetable 1.3 saturated 0.9 cholesterol	— — — —
Wolk, *et al*[13] 1996	Multicenter study; Australia, Denmark, Sweden, USA Men and women	1,185	1.7	1.2 total	1.2 total 1.2 saturated 1.1 monounsaturated 0.9 polyunsaturated 1.1 cholesterol	1.1 — — — —
			Relative risks (95% confidence intervals) per 100 kcal[b]			
	All centers	1,185	1.03 (1.01- 1.04)	1.05 (0.93-1.18)	1.02 (0.97-1.02)	1.03 (0.99-1.07)
	Australia	208	1.04 —	1.07 —	1.02 —	1.05 —
	Denmark	345	1.04 —	0.88 —	1.10 —	1.06 —
	Sweden	372	1.01 —	1.12 —	0.98 —	1.00 —
	USA	260	1.02 —	1.19 —	0.97 —	1.02 —

[a] Energy-adjusted risk estimates.

[b] Risk estimates for protein, fat, and carbohydrates are from a model including all these macronutrients simultaneously as continuous variables (expressed as protein-kcal, fat-kcal, and carbohydrate-kcal).

Table 2. Vitamins and renal cell cancer

Study (ref) Year	Location Population	Number of cases	Relative risks for high- *cf* low-intake categories			
			Vitamin C	Carotene	Retinol	Vitamin E
McLaughlin, *et al*[19] 1984	Minnesota, USA Men and women	313 men 182 women	0.7 (men) 1.2 (women)	0.8 (men) 1.3 (women)	1.2 (men) 1.3 (women)	—
Maclure and Willett[20] 1990	Boston, MA, USA Men and women	203	—	0.6[a]	0.9[a,b]	—
Wolk, *et al*[13] 1995	Multicenter study: Australia, Denmark, Sweden, USA Men and women	1,185	0.9[a]	0.9[a]	1.2[a]	0.9[a]

[a] Energy-adjusted risk estimates.
[b] Preformed vitamin A.

cant only in one [13] of these studies. We cannot exclude a potential risk for differential misclassification in dietary self-reports in these studies, *i.e.*, cases might under- or overreport their remote food intake. Indeed, differential misclassification was suspected in the earlier study,[20] where energy intake was associated with risk of RCC among incident but not among 'prevalent' cases interviewed more than one year after diagnosis.[20] Analysis of subset data from the US in the multicenter study, however, did not reveal any difference in risk estimates for energy between short-term (dietary self-reports <1 year after diagnosis) and long-term reports ≥ 1 year); the relative risk (RR) per 100 kcal increase in total energy intake was RR = 1.02 in both case series.[13]

Protein intake was associated positively with risk of RCC in the case-control study by Maclure and Willett[20] for incident and for prevalent cases, and in the study from Minnesota[21] based on 415 cases (260 incident and 155 prevalent). However, results from the multicenter study (including 260 incident cases from the Minnesota [USA] study) did not clearly support this hypothesis.[13] There was an intricate problem of separating the effect of protein *per se* from protein-calories. The situation was similar for fat intake. Although Maclure and Willett[20] suggested a weak positive association of saturated fat and animal fat with RCC, results from the multicenter study neither confirmed nor refuted this hypothesis. In a model including, simultaneously, all macronutrients expressed in calories (Table 1: the multicenter study – all centers and each center separately), the RR (all centers) for 100 protein-kcal was slightly higher than for 100 fat-kcal and for 100 carbohydrate-kcal or 100 kcal *per se*. However, due to the wide confidence interval for protein-kcal, the hypothesis about a positive relation of protein (independently of calories) to RCC was not confirmed. Although the US center revealed a higher risk estimate for protein-kcal than other centers, in a random effects model using data from all centers, the risk estimate for the highest protein quartile was RR = 1.0 (95 percent confidence interval [CI] = 0.7-1.6). The hypothesis about positive association of RCC with protein, although biologically plausible,[21] has no clear support from the limited number of analytical epidemiologic studies. Wynder *et al*[15] hypothesized a role for cholesterol in the development RCC. However, neither of the studies[13,20] corroborated this hypothesis.

The hypothesis that β-carotene has a protective effect was tested in three studies;[13,19,20] however, none of them reported a significant negative association with RCC (Table 2). Vitamin A and retinol were not associated with a risk of RCC in any of the studies.[13,19,20] No effect of vitamin C was observed in the study by McLaughlin *et al*.[19] In the multicenter study, the protective effect of vitamin C was significant only in the subgroup of nonsmokers, RR = 0.6 (CI = 0.4-0.9).[13] In the multicenter study, low levels of vitamin E (below the lowest 10 percent of intake in the studied populations) increased the risk significantly, by about 40 percent. In the same study, a significant positive association with RCC was observed for the lowest 10 percent of magnesium intake, with an approximately 60 percent increase in risk. Although various models of action have been proposed for vitamin E, its role as an antioxidant or modulator of immune functions has been emphasized most.[32] The epidemiologic finding for magnesium has support in animal studies.[33] It has been postulated that the higher incidence of renal cancer in experimental animals deficient in magnesium is due to an impairment of humoral and cellular immunity. Also, magnesium deficiency has been reported to alter the fidelity of DNA replication, which could trigger a carcinogenic process.[34] Calcium, potassium, and iron were not associated with renal cell cancer risk.[13]

Foods

All case-control studies on diet and renal cell cancer,[13,19,20,35-41] had been analyzed at the food level (Table 3). It was concluded in the multicenter study that food results could be confounded by energy. After adjustment for energy, positive significant associations with some food (milk, eggs, foods rich in animal protein, cereal/bread) were no longer significant and the protective effect of vegetables and fruit became more pronounced.[13] In the context of these new results, previously reported positive associations of meat and milk with RRC may have been confounded by energy intake.

In the Minnesota study,[21] no association was observed for degree of 'doneness' and method of cooking of red meat (baked/roasted/boiled/stewed/broiled/grilled or fried/sautéed). In the multicenter study (including 260 incident cases from the Minnesota study comprising 415 cases), fried meats were associated with a significantly increased risk of RCC (RR = 1.5,CI = 1.2-1.8); the degree of 'doneness' of meat showed a significant dose-response (P trend < 0.05).[13] Pan frying/sautéing of meat induces the formation of heterocyclic amines, which appear to be absorbed rapidly and distributed to the kidneys. In feeding experiments in primates, DNA adducts have been observed in different organs, including the kidneys.[43] It is probable, therefore, that human populations who consume large amounts of meat also ingest large quantities of carcinogens derived from fried meats. This provides an alternative explanation for the international correlations between *per capita* meat consumption and rates of kidney cancer, a relation widely ascribed to animal protein and fat. Despite experimental evidence that nitrosamines can induce renal cell carcinoma,[44] no association with preserved meat was found in the multicenter study[13] and in the Minnesota study,[21] suggesting that intake of nitrites and nitrates may not be an important risk factor for RCC.

The majority of case-control studies reported a negative association of vegetables and fruits with RCC (Table 3). In detailed analyses of vegetables and fruits in the multicenter study,[13] orange/dark-green vegetables seemed to have the strongest inverse association, with RR = 0.7 (CI = 0.5-0.9) for the highest quartile (> 3.4 times/wk); P trend = 0.04. Significant negative associations with RCC were even more clear in nonsmokers: more frequent consumption of cruciferous (> 1.7 times/wk) or orange/dark-green vegetables (> 3.4 times/wk) or total fruits (> 16 times/wk) was associated with RR = 0.6 (CI = 0.4-0.9) for all these three foods. Orange/dark-green vegetables – a rich source of β-carotene – also contain plant phenols, with an antipromotive effect *in vivo* and *in vitro*.[45] Vegetables from the *Brassicacae* family (cruciferous) – a rich source of vitamin C–contain organic isothiocyanates, substances with antitumorigenic effects in experimental studies, notably in the initiation stage of the tumorigenesis.[46] Allium vegetables, which showed a slightly weaker association in nonsmokers for consumption > 1.9 times/wk (RR = 0.7,CI = 0.4-1.1) than cruciferous and orange/dark-green vegetables, may lower risk for several forms of cancer in humans,[47] perhaps due to free radical scavenging activity, immune system modulation, or a direct cytotoxic effect on cancer cells.[48]

Coffee and tea

The findings in case-control studies concerning coffee and tea consumption are conflicting. Most studies of coffee showed no association,[15,37,38,40,49,50] or a weak nonsignificant increase,[19,20,35,51] or decrease[41,52] in the risk of RCC. The study in France[53] based on 196 cases, showed a nonsignificant twofold increased risk in men and a fourfold increased risk in women, when comparing ever- *cf* never-drinkers of coffee. In the study of 160 cases from Los Angeles (California, USA),[36] drinking five or more cups of coffee per day gave a nonsignificant, twofold risk in women but not in men. The results from the large multicenter study – where adjustments were made for age, study center, smoking, and body mass index (BMI)(wt/ht^2) – indicated a twofold significant increase in the risk in women (but not in men) drinking more than six cups of coffee per day; however, no dose-response was observed.[13] Two studies of tea and RCC[36,53] reported decreased risk in both genders with the strongest negative association (70 percent reduction in risk) observed in women drinking tea daily in comparison with never-drinkers.[36] However, most case-control studies,[20,37,38,40,49] including the large multicenter study,[13] reported no association, or increased risk only in women,[19,52] or only in men[41] Despite the numerous studies, there has been no convincing evidence linking RCC and consumption of coffee or tea.

Alcohol

A hypothesized positive association between alcohol intake and risk of RCC has not been corroborated in case-control studies; only one[54] of 16 studies reported a nonsignificantly increased risk among ever- *cf* never-drinkers and a majority[15,19,20,35,36,40,41,50,53,55] reported no association. Indeed, there is even some suggestion of a negative association which seems to be more pronounced in women than in men and possibly associated with wine consumption.[13,38,52,56,57] In the multicenter study,[13] drinking of three or more glasses of wine per week was associated with 80 percent decreased risk in women (RR = 0.2,CI = 0.1-0.4); consumption of wine in men was generally lower and the RR for men in the highest

quartile (drinking 1.3 or more glasses per week) was 0.8 (CI = 0.5-1.3). These findings need further investigation.

Artificial sweeteners

The question of artificial sweeteners has been addressed in five case-control studies. In four of them,[19,35,36,52] the results were negative and did not indicate any association between RCC risk and consumption of saccharine or other artificial sweeteners. In the analyses by McLaughlin *et al*,[19] adjustments were made for age, smoking, and weight. The most recent study, by Asal *et al*,[49] showed a significantly increased risk in men (odds ratio [OR] = 2.1, CI = 1.3-3.5) after adjustments for age, smoking, and weight; the association in women was not significant (OR = 1.3).

Body weight

The most consistent findings in case-control studies of renal cell cancer have been those concerning overweight and obesity[12,15,19,20,36,38,40,41,49,51-54,57-59] (Table 4). Only one hospital-based study[38] failed to show a positive association between BMI and RCC. Irrespective of the measure used, *i.e.*, relative body weight (RBW) or BMI (weight [kg] divided by height squared [m^2], or by height raised to a power of 1.5 [in women]), increasing body weight was associated with an increasing risk of RCC. Most studies were consistent, with a linear relationship between body weight and risk of RCC. The collective evidence from the case-control studies presented in Table 4 and especially the results from the large multicenter study based on 1,732 cases[12] seem to indicate that body weight might have stronger impact on RCC in women than in men.

In this multicenter study, rate of weight change (estimates as kg of weight change *per annum*) appeared to be an independent risk factor among women but not among men. Weight changes (fluctuations) which were associated positively with RCC risk in univariate analyses were not significant in the multivariate model including simultaneously BMI level, rate of weight change, and number of changes.[12] The Swedish center (one of five centers included in the multicenter analyses of relative weight and RCC) analyzed data on BMI and weight fluctuations in detail.[60]

In contrast to the overall multicenter analyses, this substudy indicated that women who have decreased their weight ≥ 5 kg two or more times during their lifetime are at increased risk of RCC, independently of BMI (OR = 3.9, CI = 1.2-12.5; adjusted for age, education, smoking, BMI, amphetamine use). In men, the number of weight-loss periods (criterion for weight loss in men was ≥ 10 kg) was not associated with an increased risk of RCC. However, few male cases and controls reported such weight losses, and the statistical power was thus low. Lack of agreement between the Swedish substudy and the multicenter results for weight changes might indicate a random effect observed in the substudy. Therefore, the hypothesis about increased RCC risk associated with weight changes/fluctuations should be investigated further.

Hormonal influences are one plausible mechanism by which BMI and weight fluctuations might be involved in renal carcinogenesis. Estrogen and progesterone receptors have been demonstrated in normal and malignant renal cells.[61] In male Syrian hamsters, potent estrogens given in high doses induce renal tumors, with a cumulative incidence approaching 100 percent.[62-64] Sex steroids may affect renal cell proliferation and growth and thereby carcinogenesis, by direct endocrine receptor-mediated effects,[61] by regulation of receptor concentrations,[65] or through paracrine growth factors (*e.g.*, epidermal growth factor).[66]

Another possibility is that obesity and weight fluctuations are associated with a metabolic syndrome in a subset of persons with abdominal or upper body obesity. As abdominal fat tissue is mobilized more easily,[67] voluntary weight reduction may be expected to be more successful in persons with upper body obesity than in those with obesity in the lower part of the body. The metabolic syndrome entails a multitude of features, *e.g.*, hypertension, decreased insulin sensivity, increased levels of biologically active insulin-like growth factor, and, in women, anovulation and excessive androgen production.[67] Further renal damage may occur as a result of hypertension and metabolic complications of obesity, with or without association with a metabolic syndrome. Such damage may predispose the kidney to other carcinogens. There is some logical consistency between apparent risk reported for total energy intake and risk associated with BMI.

Cohort studies

Vitamin A

In a prospective cohort of about 16,000 men,[68] serum samples were collected and stored. During follow-up of one to four years, eight men developed kidney cancer. They did not have a significantly lower, mean-standardized retinol concentration in the serum than 172 controls in whom no cancer in any form developed (218 *cf* 229 IU/dl).[68] In a community cohort of 3,012 individuals from Evans County, Georgia (USA),[69] followed up for 12 to 14 years, kidney cancer developed in two persons; their mean serum retinol was 11.4 μg/dl lower than in the control group. Both these studies are based on numbers too small to allow any conclusion to be drawn.

Table 3. Foods and renal cell cancer

Study (ref.) Year	Location Population	Number of cases	Relative risks for high- *cf* low-intake categories				
			Meat	Dairy	Fats	Vegetables	Fruits
Case-control studies							
Armstrong, *et al*[35] 1976	UK Men and women	106	NA[a] meat NA poultry	NA milk NA cheese	— —	— —	— —
McLaughlin, *et al*[17] 1984	Minnesota, USA Men and women	495	1.5 meat	1.8 dairy	—	0.8 total vegetables 0.8 cruciferous	1.5 fruits
Yu, *et al*[36] 1986	Los Angeles, CA, USA Men and women	160	NA beef	NA milk	—	NA total	NA total
McCredie, *et al*[37] 1988	Australia Men and women	360	NA meat NA poultry	1.5 milk NA cheese	NA —	— —	— —
Maclure and Willett[20] 1990	Boston, MA, USA Men and women	203	3.4 beef 1.5 hamburger 1.3 chicken 1.3 processed meat 1.1 wurst 1.0 hotdog 0.9 bacon 0.7 pork, ham	1.7 whole milk 0.3 skimmed milk 0.7 yogurt 0.9 cheese	1.3 margarine 1.1 butter	0.5 spinach 0.6 cabbage 0.8 carrots 0.8 cauliflower 0.9 broccoli 0.9 string beans 1.0 brussel sprouts	0.5 banana 1.2 peach 1.3 plum
Talamini, *et al*[38] 1990	Northern Italy Men and women	240	1.1 meat 1.3 salami	1.4 milk 1.4 cheese	1.7 margarine 1.9 oils 1.3 butter	0.6 carrots	0.9 total
Negri, *et al*[39] 1991	Northern Italy Men and women	147	—	—	—	0.4 green vegetables	0.6 total
McLaughlin, *et al*[40] 1992	Shanghai, China Men and women	91 men 66 women	4.0 meat (men) 1.3 meat (women) 0.4 fish (men) 1.6 fish (women)	— — — —	— — — —	0.3 total (men) 1.6 total (women) NA allium (all) NA cruciferous (all)	0.2 total (men) 0.7 total (women) — —
Kreiger, *et al*[41] 1993	Ontario, Canada Men and women	312 men 201 women	1.4 meat (men) 1.6 meat (women) 1.2 poultry (men) 2.3 poultry (women) 0.7 fish (men) 1.0 fish (women)	1.0 dairy fat (men) 1.4 dairy fat (women) — — — —	— — — — — —	— — — — — —	— — — — — —
Wolk, *et al*[13] 1996	Multicenter study: Australia, Denmark USA Men and women	1,185	0.9[b] red meat 0.9[b] preserved meat 1.2[b] poultry 0.9[b] fish 1.2[b] protein-rich animal food	1.3[b] milk/yogurt 0.9[b] cheese	1.1[b] margarine, butter	0.8[b] total 0.8[b] cruciferous 0.8[b] allium 0.7[b] orange/dark-green vegetables	0.9[b] total 0.9[b] apples 0.9[b] citrus
Prospective studies							
Fraser, *et al*[42] 1990	California, USA Seventh-day Adventists	14	1.6 beef 0.5 poultry	— —	— —	0.3 green salad	0.2 total

[a]NA = not associated with risk of renal cell carcinoma.
[b] Energy-adjusted risk estimates.

Table 4. Body weight and renal cell cancer

Study (ref.) Year	Location Population	Number of cases	Variable studied	Time period	Relative risks (95% confidence interval) for high *cf* low weight	
					Men	Women
Wynder, *et al*[15] 1974	USA	129 men 73 women	RBW[a]	Recent weight	RBW > 125 NA	RBW > 125 29% cases *cf* 10% controls ($P = 0.05$)
McLaughlin, *et al*[19] 1984	Minnesota, USA	313 men 182 women	BMI[b]	Recent weight	> 28 *cf* < 24 1.5 (1.0-2.4)	> 26 *cf* < 22 2.1 (1.2-3.9)
Goodman, *et al*[52] 1986	USA	173 men 71 women	BMI[b]	Recent weight	> 28 *cf* < 24 2.7 (1.5-5.9)	> 28 *cf* < 24 2.4 (1.2-6.9)
Yu, *et al*[36] 1986	Los Angeles, CA, USA	107 men 51 women	BMI[b]	—	Q4 *cf* Q1[d]	Q4 *cf* Q1[d]
				1 year ago	1.8 (0.8-4.0)	2.7 (0.8-9.3)
				10 years ago	2.5 (1.0-5.9)	3.3 (1.0-11.5)
				Age 20	2.2 (1.0-4.9)	3.1 (0.9-10.5)
Asal, *et al*[49] 1988	Oklahoma, USA	209 men 105 women	BMI[b]	—	> 140 *cf* < 120	> 140 *cf* < 120
				Age 20	2.5 (1.4-4.6)	2.0 (0.9-4.2)
				Highest weight	2.8 (1.6-5.0)	1.8 (0.8-4.0)
				Recent weight	3.3 (1.8-6.1)	1.2 (0.6-2.6)
Kadamani, *et al*[57] 1989	Oklahoma, USA	21 men 40 women	RBW[a]	Recent weight	> 140 *cf* < 120 3.8	> 140 *cf* < 120 3.0($P < 0.05$)
Maclure and Willett[20] 1990	Boston, MA, USA	135 men 68 women	BMI[b]	Recent weight	> 28 *cf* < 28 1.7 (1.1-2.8)	> 28 *cf* < 28 1.7 (0.9-3.2)
Talamini, *et al*[38] 1990	Northern Italy	150 men 90 women	BMI[b]	Recent weight	both genders	> 27 *cf* < 24 0.7 (0.5-1.1)
Partanen, *et al*[51] 1991	Finland	338 men and women	Overweight Obesity	Recent weight	Overweight *cf* normal: both genders	1.2 (0.9-1.7)
McCredie and Stewart[58] 1992	Australia	310 men 179 women	BMI[c]	Usual weight	> 25 *cf* < 23 1.6 (1.1-2.5)	> 31 *cf* < 27 1.3 (0.8-2.1)
McLaughlin, *et al*[40] 1992	Shanghai, China	82 men 59 women	BMI[c]	Age 40	> 22 *cf* < 19 3.6 (1.1-12.6)	> 29 *cf* < 24 3.6 (0.9-14.7)
				Age 50	> 23 *cf* < 20 1.7 (0.5-5.7)	> 29 *cf* < 24 3.3 (0.7-15.1)
Benhamou, *et al*[53] 1993	France	134 men 57 women	BMI[b]	Age 20	≥ 24 *cf* ≤ 18 1.1 (0.5-2.4)	≥ 24 *cf* ≤ 18 4.6 (1.3-16.4)
				Prior to diagnosis	≥ 27 *cf* ≤ 20 2.4 (1.0-5.9)	≥ 27 *cf* ≤ 20 3.5 (1.0-11.8)
Finkle, *et al*[59] 1993	USA Kaiser Program	161 women	BMI[c]	Recent weight	—	> 75 *cf* < 25 2.6 (1.4-4.8)
Kreiger, *et al*[41] 1993	Ontario, Canada	282 men 181 women	BMI[b]	5 years ago	> 27 *cf* < 23 1.3 (0.8-2.2)	> 25 *cf* < 21 2.5 (1.4-4.6)
				Age 25	> 30 *cf* < 26 1.9 (1.2-3.1)	> 28 *cf* < 23 1.0 (0.5-1.8)
	USA			Two periods combined	2.2 (1.5-3.4)	2.2 (1.4-3.5)
Hiatt, *et al*[54] 1994	Kaiser Program	163 men 88 women	BMI[b]	Recent weight	> 28 *cf* < 25 0.9 (0.5-1.6)	> 28 *cf* < 22 1.2 (0.5-2.9)
Mellemgaard, *et al*[12] 1995	Multicenter study: Australia, Denmark, Sweden, USA	1,050 men 682 women	BMI[c]	Usual weight	> 27 *cf* < 23 1.6 (1.3-2.1)	> 33 *cf* < 27 2.0 (1.5-2.7)
				Highest weight	> 30 *cf* < 25 1.4 (0.9-1.8)	> 37 *cf* < 29 2.5 (1.8- 3.5)
					Q_4 *cf* Q_1[d]	Q_4 *cf* Q_1[d]
				Age 20	1.4 (1.0-1.9)	1.5 (1.1-2.1)
				Age 30	1.8 (1.3-2.3)	2.2 (1.16-3.1)
				Age 40	1.6 (1.2-2.0)	2.1 (1.5-2.8)
				Age 50	1.4 (1.1-1.9)	2.3 (1.6-3.3)
				Age 60	1.4 (1.0-1.9)	1.9 (1.3-2.8)

[a] RBW = relative body weight (%), *i.e.*, percent in comparison with an average in the population.
[b] BMI = body mass index (kg/m^2).
[c] BMI = body mass index (kg/m^2 for men; kg/m$^{1.5}$ for women).
[d] Cut-points for quartiles not specified in the article.
NA = not associated with risk.

Foods

In a prospective cohort study of 34,198 Seventh-day Adventists from California (USA), 14 subjects developed RCC during a six-year period (Table 3). The investigators found a negative association with fruits (RR = 0.2 for ≥ 3 fruits/wk) and vegetables (RR = 0.3 for green salads ≥ 3/wk). Consumption of beef or fish more than once per week increased the risk to 1.6, while poultry decreased the risk to 0.5.[42] None of the risk estimates was statistically significant.

Coffee

Coffee (≥ 7 cups *cf* ≤ 2 cups/day) was found to have a negative association with RCC (RR = 0.3, *P* trend = 0.01) in a prospective cohort[70] of 13,664 Norwegian men and 2,891 women; during 11.5 years of follow-up, 35 renal cell cancers were detected. However, this finding is not supported by the findings in a larger Norwegian cohort[71] comprising 21,735 men and 21,238 women. Among these, 30 men and 13 women developed kidney cancer during 10 years of follow-up. RRs for drinking ≥ 7 *cf* ≤ 2 cups of coffee per day were 0.7 in men and 1.2 in women; the trends were not significant. In the analyses of both Norwegian cohorts, adjustments were made for age and smoking.

Tea

In a cohort of 14,085 men from London,[72] 26 deaths due to kidney cancer occurred during 19 years of follow-up. A weak positive association was found between tea drinking and kidney cancer (*P* trend = 0.04); ≥ 10 cups of tea per day was associated with an 80 percent increase in risk.[72]

Contamination of drinking water

In a cohort of 31,000 subjects from Washington County (USA),[73] 31 kidney cancers occurred (18 men, 13 women) during 12 years of follow-up. No association was observed between kidney cancer and drinking of chlorinated surface water at home compared with drinking of unchlorinated ground water (men: RR = 0.8, CI = 0.3-2.7; women: RR = 1.0, CI = 0.3-6.0). Although the postulated relationship between organic chemical by-products of water chlorination and risk of kidney cancer was not confirmed, the CIs were wide.[73] In an area of endemic chronic arsenicism in Taiwan,[74] 64 deaths from kidney cancer were noted in a cohort of 898,806 person-years. A significant dose-response relationship was found between the ingested amount of inorganic arsenic and mortality from kidney cancer in both men and women; for increasing water-arsenic concentrations (170, 470, and 800 μg/l), the corresponding mortality rate ratios were 4.9, 11.9, and 19.6 in men and 4.0, 13.9, and 37.0 in women, with *P*-values for linear trend < 0.001 in men and women.[74,75] These high mortality rate ratios make confounding by some other risk factors unlikely; thus, the study suggests a causal relationship. Smith *et al*[75] estimated that more than 350,000 people in the US may be supplied with water containing more than 50 μg arsenic per liter (the US Environmental Protection Agency standard) and more than 2.5 million people may be supplied with water with arsenic concentrations above 25 μg/l.

Alcohol

No evidence of an increased risk associated with alcohol drinking was found in a population-based Swedish cohort[76] of 8,340 men and 1,013 women with a discharge diagnosis of alcoholism followed up for an average of 7.7 years. This finding is in accordance with results from other cohort studies.[77-80]

Body weight

The results of prospective studies of body weight and risk of kidney cancer are in conformity with those of case-control studies. In a nested case-control study,[81] it was found that within a cohort of 47,261 men (students from Harvard and Pennsylvania University) followed up for 16 to 50 years, 77 subjects died of kidney cancer. Those who weighed more than 180 lbs in college had a 2.5-fold (CI = 0.9-6.8) higher risk than those weighing under 140 lbs.[81] The risk expressed per 10 lbs additional body weight was RR = 1.2 (CI = 1.0-1.3).[82] In a long-term, population-based prospective cohort[83] of 750,000 men and women in the USA followed-up for 13 years, the risk of death from renal cancer was twice as high in women with a relative body weight of over 140 percent of average weight as in those with a relative weight of 90 to 110 percent. In a Danish cohort[84] of 43,965 persons with obesity as a discharge diagnosis, 79 kidney cancers (21 men, 58 women) occurred during one to 10 years of follow-up. Compared with the national incidence rates, the RR in obese women was 2.0 (CI = 1.5-2.6) and in men 1.2 (CI = 0.7-1.8).[84] In a similar Swedish cohort (Wolk *et al*, unpublished), 17,547 obese subjects followed up for an average of 11.4 years, 75 kidney cancers developed (49 women, 26 men). The standardized incidence ratio for kidney cancer was 2.4 (CI = 1.8-3.2) in women and 2.3 (CI = 1.5-3.4) in men; specifically for RCC (66 cases), it was 2.4 (CI = 1.9-3.1). The aggregated results from these four prospective studies provide strong evidence that high body weight is an important risk factor for kidney cancer both in men and women.

Animal/mechanistic studies

The interpretability of the results of epidemiologic studies is limited by the difficulties in accurately assessing past and current human nutrient consumption and of

disentangling the possible impact of many dietary factors, such as energy, protein, fat, and animal products, which often vary in concert. Analysis of their interactive effects in animal models – where multiple variables can be controlled simultaneously and precisely – may contribute to a better understanding of epidemiologic studies.

Protein, fat, energy intake

In the experiments in rats given diets with three different protein contents and three different contents of fat, the effects of protein and fat on the initiation and promotion of azoxymethane (AOM)-induced carcinogenesis in the kidney were studied.[85] During the *initiation* phase, the low-protein diet was associated with an increased risk of renal adenocarcinoma ($P < 0.001$). McLean and Magee[86] also reported that severe protein deficiency during dimethylnitrosamine (DMN) administration increased the risk of renal tumor development in rats. Subsequent studies showed that DMN metabolism, by liver slices, was reduced by 50 percent in rats on a protein-free diet.[87] The reduction of DMN metabolism by the liver may have allowed a larger fraction of the administered dose to reach the systemic circulation with critical targets in the kidney. Dietary protein has profound effects on the metabolism and biological action of many xenobiotics.[88,89]

In a study by Clinton *et al*,[85] rats initially fed a low-protein diet (eight percent) and switched to 16 percent protein diets following carcinogen (AOM) administration showed a compensatory increase in growth after the change in diet. Hypothetically, the nutritional and hormonal changes during this period of compensatory growth may have increased local proliferative stimuli in renal tissue to enhance the accumulation and expression of genetic lesions, contributing to an acceleration of the malignant transformation. In the *promotion* phase of the same study,[85] the renal effects of dietary protein were less pronounced. High-protein diets (32 percent) fed to AOM-treated rats were associated with an increased frequency of inflammatory changes and renal atrophy, but not with occurrence of carcinoma. Variations in dietary fat had no effects on renal pathology, either during the initiation or the promotion phase in the study. *Ad libitum* energy intake was not associated with renal carcinogenesis. In contrast, in the same study, a significant positive association with energy intake was observed for intestinal carcinogenesis (14 kcal/day difference in mean *ad libitum* intake corresponded to a 146 percent increase in the odds of developing an intestinal adenocarcinoma).

Vitamin C, α-tocopherol, and other antioxidants

Long-term chronic administration of estradiol (E_2) or diethylstilbestrol to male Syrian hamsters induces kidney tumors.[90] The studies reviewed by Liehr[91] clearly demonstrated that vitamin C inhibits the induction of renal tumors by estrogen by about 50 percent. Moreover, there is evidence that vitamin C inhibits both the covalent modification of cellular macromolecules, *i.e.*, direct covalent binding of estrogen quinones, and the damage by free radicals formed by redox cycling between quinones and their respective hydroquinones. A reduction of estrogen quinones by vitamin C, and hence a decrease in quinone concentrations, is a possible explanation for the decrease in both types of damage to cellular macromolecules. A reduction in estrogen quinones by vitamin C will result in decreased DNA and protein-adduct formation. Free radical damage to cellular macromolecules also may be diminished by the free radical scavenging action of vitamin C. This protection of cells from covalent damage may result in a decrease in tumor initiation. The possibility of an influence of vitamin C on renal tumor promotion and progression has not yet been investigated.[91]

Effects of the dietary antioxidants α-tocopherol, t-butylhydroquinone, propyl gallate, and butylated hydroxytoluene – used widely throughout the world – were examined using a multi-organ carcinogenesis model in male rats. Histopathologic examination showed that α-tocopherol reduced the incidence and multiplicity of kidney atypical renal tubules, and propyl gallate was effective in reducing this latter multiplicity. Butylated hydroxytoluene decreased the incidence and multiplicity of renal cell tumors.[92]

Quercetine, a major constituent of bioflavonoids in plant foods, has antioxidant properties.[93] The influence of quercetine on kidney tumor induction by estradiol (E_2) in male Syrian hamsters was investigated by Zhu and Liehr[94] in an attempt to understand estrogen-induced carcinogenesis and its prevention by dietary modification. The administration of a diet containing quercetine to hamsters does not induce tumors. However, co-treatment of hamsters with E_2 and quercetine potentiated E_2-induced renal tumorigenesis. Increased formation of 4-hydroxyestradiol together with inhibited inactivation of this catechol estrogen by catechol-*O*-methyltransferase, may result in elevated levels of this estrogen metabolite, specifically in the hamster kidney, where it may undergo metabolic redox cycling and generate mutagenic free radicals. Thus, the potentiaton of estradiol-induced tumorigenesis by quercitin in hamster kidneys supports a role of 4-hydroxyestradiol in estrogen-induced carcinogenesis in this species.

Other exposures

Results from a study in rats suggest that high dietary calcium intake in the presence of lead may increase the incidence of renal tumors.[95] Potassium bromate ($KBrO_3$) is an oxidizing agent used as a food additive, mainly in bread-making. Although adverse effects have not been

evident in animals fed bread-based diets made from flour supplemented with $KBrO_3$, the agent is carcinogenic in rats and hephrotoxic in both man and experimental animals when given orally. Potassium bromate is a complete carcinogen, possessing both initiating and promoting activities for rat renal tumorigenesis. Its potential, however, seems to be weak in mice and hamsters.[96]

Summary and conclusions

The cumulative evidence from analytical epidemiologic studies–both of case-control and cohort design – is most consistent for the positive association of body weight with risk of RCC. The dose-response observed in these studies supports a causal relationship. However, there are still many aspects of overweight and obesity – *e.g.*, weight development during lifetime, weight cycling, body fat distribution, potential mechanisms of action – that should be further investigated.

The evidence accumulated from ecologic and case-control studies suggests that diet has an important role in the development of RCC. However, methodologic problems in most previous case-control studies (*e.g.*, small numbers of subjects; use of hospital controls; not analyzed at nutrient level, thus without possibility of recognizing whether total energy intake is a risk factor/confounder) markedly limit the possibility of inferences concerning diet and RCC. One of the most intriguing findings, the apparent positive association of total energy intake with RCC, needs further investigation in prospective cohort studies to eliminate the risk of biased estimates. Energy intake is the key problem, since if a high-calorie intake is a real risk factor for RCC it will entail methodologic consequences in most of the analyses, both at the nutrient and at the food level.

The statistically significant positive associations between a low intake of vitamin E and magnesium and risk of RCC found in one large, multicenter, population-based case-control study need further confirmation. A possible interaction of antioxidants – vitamin C, β-carotene, and those included in specific vegetables (allium, cruciferous, orange/dark-green) and fruits – with smoking status also needs more detailed assessment. Moreover, confusing results concerning alcohol that suggest differences between men and women in response to these factors require more investigation. The potential risk associated with consumption of fried meats should be clarified in studies using a more quantitative approach to exposure to heterocyclic amines.

In summary, several dietary factors should be considered as potentially involved in the development of renal cell cancer at different stages of tumorigenesis. However, they need more cumulative confirmation before recommendations for public health can be made.

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