The impact of nutrition in urogenital cancers

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Abstract

Prostate, bladder and kidney cancers remain the most common cancers of the urinary tract. Despite improved primary prevention, detection and treatment, the incidence of age-related cancers of the urinary tract is likely to rise as a result of global population ageing. An association of diet with prostate, bladder and kidney carcinogenesis is plausible since the majority of metabolites, including carcinogens, are excreted through the urinary tract. Moreover, large regional differences in incidence rates of urologic tumours exist throughout the world. These rates change when people relocate to different geographic areas, which is suggestive of a strong environmental influence. As a result of these observations, numerous studies have been conducted to assess the effects of diet and nutritional status in kidney, bladder and prostate carcinogenesis. Here, we review the literature assessing the effect of diet and nutritional status on urological cancer risk, which has attracted the most interest.

Key words: diet, prostate cancer, bladder cancer, kidney cancer.

Introduction

Kidney, bladder and prostate cancers remain the most common cancers of the urinary tract. In recent years, there have been substantial changes in urologic cancer related mortality in Europe as well as in North America [1, 2]. This has been a result of therapeutic improvements for prostatic cancer, decreased exposure to tobacco smoking and occupational carcinogens for bladder and possibly kidney cancers [3–8].

Despite improved primary prevention, early detection and treatment, the incidence of age-related cancers of the urinary tract is likely to rise as a result of global population ageing. As both modifiable and non-modifiable risk factors are believed to be involved in carcinogenesis, and the multistage process of initiation, promotion and progression of cancer requires many years, it therefore provides an opportunity to employ preventive measures.

Diet and nutritional factors are believed to act as pro- and antitumor risk modifiers across the entire complicated process of urogenital tumourigenesis [9]. Consequently, malnutrition, which is a pathologic state of varying severity with clinical features caused by deficiency, excess, or imbalance of essential nutrients, may also play a role [10]. So far, however, no specific diet has been shown to prevent or eradicate urinary tract cancers. This can likely be explained by the complexity of

the disease, where both genotypic and phenotypic alterations occur as a result of generalised carcinogen exposure and clonal proliferation of mutated cells. On the other hand, there is often a lack of high quality long-term randomized controlled studies that could observe remote effects of diet modification on cancer development and progression. Dietary studies are commonly limited in their conclusions because of heterogeneity of the study population, variations in lifestyles and the complexity of diet, with different components of the food exerting potential chemopreventive effects. Nevertheless, large regional differences in incidence rates of urologic tumours exist throughout the world. Moreover, these rates change when men and women relocate to different geographic areas, which is suggestive of a strong environmental influence. As a result of these observations, many cell culture, animal and human studies have been conducted to assess the effects of diet and nutritional status in kidney, bladder and prostate carcinogeneses.

Here, we review the literature assessing the effect of diet and nutritional status on urological cancer risk, which has attracted the most interest.

Obesity

The hypothesis of obesity and fatty diet involvement in prostate and renal carcinogenesis was made after having analysed differences in the overall prevalence of these two cancers in people of various ethnic origins and, also, men who migrated to the USA from countries of low baseline incidence of prostate and renal cancers [11–14]. Obesity is the strongest environmental risk factor in the aetiology of prostate cancer. Multiple studies have also shown its positive correlation with more aggressive tumours, as well as a higher likelihood of tumour recurrence following surgery or radiation therapy [15–19]. The study, which analysed the Cancer Prevention Study derived data on 10 258 men who underwent prostate biopsy, revealed that obesity (defined as body mass index (BMI) $\geq$ 30 kg/m^2) was associated with an 18% decreased risk of developing a low-grade cancer (Gleason < 7) and a 29% increased risk of developing high-grade adenocarcinoma. Patients who were obese and had a Gleason sum of 8 to 10 were at a 78% increased risk of malignant transformation [20]. Similarly, the Cancer Prevention Study II results confirmed the inverse association between BMI and risk of low-grade cancer, as well as a positive correlation between raised BMI and risk of high-grade, metastatic or fatal cancer [21]. This study also showed that men who lost > 5 kg of weight during 10 years of follow-up reduced their risk of diagnosis with non-metastatic high-grade prostate cancer. This was until Calle *et al.* published their breakthrough results which showed that prostate cancer and renal cell carcinoma (RCC) related mortality was proportionally greater in subjects with higher BMI. The same relationship was noted in patients who suffered from bladder cancer [22].

In contrast, the association between BMI and the risk of developing urothelial bladder cancer (UBC) is poorly understood and still remains controversial. In the study conducted by Koebnick *et al.*, a cohort of 47 1760 people was prospectively followed from 1995 to 2003. A diagnosis of bladder cancer was documented in 1719 cases where, compared with normal weight, obesity carried a 28% increased risk of developing UBC [23]. Multivariate analysis showed that in higher BMI subgroups a further increase in the relative risk of bladder cancer was not as marked. For BMI 18.5–24.9, 25.0–29.9, 30.0–34.9 and $\geq$ 35 kg/m^2 relative risk of bladder cancer was respectively 1.0, 1.15, 1.22 and 1.28 (95% confidence interval (CI): 1.02–1.61; p = 0.028). This contrasts, however, with the study results reported by Holick, together with a Harvard University group, who prospectively analysed data from two cohorts of the Health Professionals Follow-Up Study and the Nurses' Health Study. This study, which included 121 700 women and 51 529 men, did not show any relationship between BMI and risk of bladder cancer [24]. Of added interest is the evidence suggesting that TP53 mutation frequency (which correlates well with UBC initiation and progression) was lower in obese and overweight patients as compared to normal weight patients (25%, 44.8% and 68.4% respectively ($p < 0.05$)) [25]. Hence, considering all available evidence, one cannot be certain if the association between obesity and an increased risk of urothelial carcinoma of the bladder is true.

In contrast, the relationship between BMI and the risk of renal cell cancer, with its clear cell variant in particular, is well known. Earlier studies reported a stronger relation between obesity and RCC in women [26]. A recent review, however, found a positive relation between BMI and RCC, which was equally strong for both sexes [14]. In a quantitative summary analysis, Bergström *et al.* estimated that the relative risk for renal cell cancer was 1.07 (95% CI: 1.05–1.09) per unit of increase in BMI, irrespective of gender. This corresponds with a 7% increased risk of RCC with each 3 kg weight gain [27]. Over the past decade there have been several research projects focusing on the incidence of RCC and the age of onset of obesity. The majority of them reported inconclusive results, except for one prospective study from 2008. The authors analysed a cohort of 32 0618 men and women and not only proved an apparent link between BMI and RCC, but also that weight gain in early (age 18–35) and mid- (age 35–50)

adulthood is strongly associated with RCC risk. This correlation, however, was not observed when weight gain occurred after 50 years of age [28]. The mechanisms involved in increased risk of RCC in overweight and obese patients are most likely related to excess production of insulin-like growth factor (IGF-1), steroid hormones and some specific type proteins [29]. Lipid peroxidation also seems to play an important role [30].

Dietary fat and lipids

A possible link between fatty diet and prostate cancer attracted researchers' attention following a report of a study from 31 countries, which revealed a close correlation between the average per capita fat intake and increased prostate cancer mortality in Western Europe and the USA, as opposed to countries with proportionally low fat consumption [31, 32]. Interestingly, introducing a westernized diet to Japanese men, who normally eat low fat foods, led to increased prostate cancer incidence [33]. A positive association of prostate cancer risk and total fat intake seems to depend on the fat type and its compounds. Whittemore *et al.* analysed the relation between diet, physical activity and body size in white, black and Asian populations. They found that the ingested amount of saturated fats in the diet was the only prostate cancer risk factor present [34]. Similar results come from the study by Giovannucci *et al.*, who reported that men who eat large amounts of animal fat in their diet, particularly α-linolenic acid from red meat, are not only at a greater risk of developing prostate cancer in general but also tend to develop more advanced tumour [35]. It seems that the relationship between the amount of ingested animal and saturated fat correlates well with the risk of prostate cancer. A clear cause and effect relationship, however, has not yet been shown. One of the proposed mechanisms underlying the role of dietary fat in the initiation and progression of prostate cancer explains it by an alteration in androgen levels, damage caused by lipid-derived free radicals as well as proinflammatory cytokines (leukotrienes and prostaglandins), which may exhibit pro-carcinogenic and cancer growth promoting properties [36–38]. Moreover, a low-fat diet seems to positively correlate with low IGF-1 serum levels and also with slower growth of human prostate cancer cells [39].

The evidence, so far, confirming an association between the amount and type of dietary fat and the risk of bladder cancer, is rather scarce and equivocal [40]. This is mainly because of a paucity of epidemiological data, as well as being due to the different types of lipids being reported on, in relation to this topic [41, 42]. Both Swedish and Spanish studies have shown a direct link between dietary fat intake and the risk of urothelial carcinoma of the bladder [41, 43]. The estimated cancer risk was between 1.4 and 1.7. In the Spanish study UBC was predominantly associated with saturated fats. This association, however, could not be found with regard to the mono- and polyunsaturated fats. Contrasting results were obtained from the cohort analysis of Japanese men living in Hawaii, which did not confirm the link between dietary fat content or the total calorific intake and bladder cancer [44]. Nonetheless, a meta-analysis of 36 epidemiologic studies, which investigated the impact of six dietary variables – retinol, β-carotene, fruits, vegetables, meat, and fat – on the risk of developing bladder cancer, did confirm the link between ingested fat and bladder cancer (relative risk (RR) = 1.37; 95% CI: 1.16–1.62), but failed to show its association with a high dietary meat intake (RR = 1.08; 95% CI: 0.82–1.42) [45].

The protective role of plant oils rich in unsaturated fatty acids seems therefore compelling from the bladder cancer chemoprevention perspective. In their study Radosavljevic *et al.* found a protective role for sunflower oil against the development of bladder cancer, in people consuming large amounts of animal fats [42]. Similarly, olive oil was reported to harbour the same protective properties in a study from 2011 [46].

The association between RCC and dietary fat content has also been looked at for the past few decades. The evidence in this field, however, is generally limited, mainly focusing on meat consumption, and is, overall, inconclusive [47]. In a large multicentre study which involved 18 countries, Wynder *et al.* found a positive correlation between RCC related mortality and *per capita* animal fat and protein consumption [48]. However, the latest systematic review of 12 published case-control studies, 3 cohort studies and 1 analysis of 13 pooled international cohort studies revealed no relation between red meat consumption and RCC [49].

For the past few decades a lot of research has been dedicated towards recognising the beneficial properties of omega-3 and carcinogenic properties of omega-6 polyunsaturated fatty acids. A study by Ritch *et al.*, which investigated 148 Jamaican men (Jamaica has the world's highest incidence of prostate cancer, and Jamaican food is rich in omega-6 fatty acids) found positive correlations between omega-6 fatty acids and Gleason score as well as the omega-3/omega-6 fatty acid ratio and tumour volume [50]. These results are suggestive of stimulatory effects of omega-6 fatty acids, and inhibitory effects of omega-3 fatty acids in prostate carcinogenesis.

An interesting report was published by a British group in which they described the protective properties of fish oils in renal cell cancer pathogenesis.

The authors demonstrated that the docosahexaenoic acid (DHA) derived from fish oil can increase levels of tissue inhibitors of metalloproteinase-1 (TIMP-1) in the renal cancer clear cell line and it also reduces cancer invasion through the basement membrane [51].

Cholesterol and statins

Preclinical studies suggest that statins may play a role in cancer biology and may therefore be used in chemoprevention. Studies *in vitro* proved that lovastatin as well as simvastatin can stop both normal and neoplastic cell growth in mice, hamsters and humans by holding the cell cycle in G1 phase and enhancing apoptosis [52, 53]. These drugs, moreover, have anti-inflammatory, anti-angiogenic and antiproliferative properties. They also prevent migration, adhesion and cell invasion [54]. The most recent meta-analysis, which critically reviewed 27 high quality studies and pooled a total of 56 847 prostate cancer patients, demonstrated a 7% decrease in the overall cancer risk in men taking statins as compared to men not taking them. Furthermore, the statin treatment group had a lower risk of more advanced malignancy [55].

One interesting study in rats investigated the chemopreventive efficacy of atorvastatin against bladder cancer [56]. In four study groups animals received: 1. placebo, 2. statin, 3. carcinogen (N-butyl-N-(4-hydroxybutyl)nitrosamine) or 4. carcinogen and statin for 8 weeks. Bladder cancer risk was estimated 12 weeks later and a statistically significant cancer risk reduction was found in the group receiving carcinogen together with atorvastatin, as compared to rats receiving the carcinogen alone (12.5% and 68% respectively). This effect was explained as being mainly due to the antiproliferative, antioxidant and anti-inflammatory properties of statins. In humans, however, clear-cut evidence to support the protective properties of statins against bladder cancer is lacking [57]. The latest meta-analysis in this field reported that statins have some minor protective properties in UBC pathogenesis [58].

A similar effect of statins was also found in relation to renal cancer [59]. Not all studies, however, confirm this observation. An observational-clinical study from the USA provided evidence consistent with the hypothesis that statin use does not have a substantial effect on cancer risk [60]. In addition, the most recent meta-analysis studying the effect of statins in renal cell cancer did not find any statistically significant correlation [58].

The cumulative evidence from analytical epidemiologic studies supports the hypothesis that cholesterol lowering with statins is beneficial for both prostate cancer prevention and for clinically important advanced adenocarcinoma. However, the role of prostate-specific antigen (PSA) screening and underlying biological mechanisms for the observed association needs to be more thoroughly investigated. Despite preclinical data attributing statins with chemopreventive properties in bladder cancer, it is not quite certain whether its anticarcinogenic properties can be definitely recognised and likely requires further investigation. Further research is needed to address the role of cholesterol-lowering medications in renal cancer.

Diabetes

Diets high in glycaemic index or glycaemic load have been hypothesised to increase the risks of certain cancers by increasing blood glucose or insulin concentrations. Epidemiologic data suggest that individuals with type 2 diabetes are at an increased risk of developing several types of cancer including pancreas, liver, breast, colorectal, and female reproductive organs [61].

Similarly, a series of recent studies and meta-analyses confirmed that the risk for kidney and bladder malignancies is elevated in diabetic patients [62–64].

The increased incidence and mortality for kidney cancer have been attributed to hyperinsulinaemia, obesity and hypertension, as well as the frequent kidney diseases occurring in diabetic patients [65, 66]. A modest increase in the risk of bladder cancer in patients with diabetes mellitus is most likely related to hyperinsulinaemia and the increased frequency of urinary tract infections.

Interestingly, men with diabetes have been found to be less likely to develop prostate cancer [67]. A 2006 meta-analysis of 19 studies involving a total population of one million including 20 373 prostate cancer cases showed a 16% decreased risk of developing prostate cancer. The latest pooled analysis of 45 studies indicated that patients with type 2 diabetes were associated with an estimated reduction of 14% in the risk of developing prostate cancer, as compared with those without diabetes [68].

This association has been attributed to the change of insulin and testosterone levels in diabetic patients. Initially, many type 2 diabetic men are hyperinsulinaemic, but as the disease progresses, the levels of insulin may decline [67]. As growth of both normal and cancerous prostate cells is positively associated with raised levels of insulin, a decreased level of this hormone may have a growth inhibitory effect on these cells [69]. Several other factors, including altered leptin concentrations, the use of medications such as statins and metformin, and changes in diet and lifestyle in order to control diabetes, have also been implicated in biological mechanisms behind

the decreased risk of prostate cancer in patients with diabetes mellitus [70, 71].

Although diabetic patients have a reduced risk of prostate cancer, once an insulin-resistant, overweight man has been diagnosed with prostate cancer, his likelihood of dying from the disease is four times higher than a non-diabetic individual with BMI < 25 kg/m^2 [72].

With the present evidence, one cannot accurately define the general and the specific organ cancer risks in any individual diabetic patient. Future studies are needed to elucidate potential pathophysiological links between diabetes and urinary tract cancers.

Nutritional deficiency

The prevalence of nutritional deficiency in oncology patients is higher compared to the background of a healthy population. This is due to the cancer-specific characteristics, as well as treatment processes, and it is suspected to be associated with approximately 20–50% of deaths in cancer patients [73].

Both prospective and retrospective studies, in patients diagnosed with non-urologic malignancy, demonstrated that patient's pre- as well as postoperative nutritional status correlate well with the risk of postoperative complications and mortality [74–77]. There are also reports suggesting that some elements of the nutrition, such as hypoalbuminaemia, weight loss, anorexia, and malaise, can independently affect survival in renal cancer patients [78, 79]. One retrospective study analysed 369 patients diagnosed with renal cancer, who underwent radical or partial nephrectomy, and it showed that preoperative malnourishment was associated with a 41.5% 3-year mortality rate compared with a 19.6% mortality rate in patients with normal preoperative weight [80]. Similarly, several reports suggest that hypoalbuminaemia, preoperative loss of weight and fall in BMI are powerful predictors of 90-day perioperative mortality rate, overall survival in patients undergoing radical cystectomy, as well as the risk of perioperative complications [81–84]. The latest and the largest retrospective study analysed how preoperative nutritional status can influence survival rate in 538 surgically treated patients who were diagnosed with bladder cancer [83]. The results of this study indicated an inverse association of preoperative nutritional deficiency, assessed clinically and biochemically, and perioperative mortality in patients undergoing radical cystectomy for bladder cancer. The 90-day mortality rate in the malnourished patient group was greater than in the control group of normal weight patients (16.5% vs. 5.1% respectively). This difference was even more significant when the study period was extended to 3 years (55.5% vs. 32.4% respectively). Both studies, however, had a few major limitations related namely to their retrospective study design. As the authors applied the clinical definition of nutritional deficiency based solely on symptoms, one could never be sure whether they were caused by the paraneoplastic syndrome or malnourishment independent of the cancer. This posed a significant challenge to answering the question of whether preoperative nutrition deficiency, which is unrelated to cancer, can further predict postoperative survival, or postoperative survival is simply a derivative of the preoperative cancer burden. In addition, there was no postoperative nutritional status assessment in both studies. It is likely, therefore, that postoperative survival in patients diagnosed with renal and bladder cancers has more to do with the postoperative than the preoperative nutritional status. Finally, a patient's general condition, which can also serve as a marker of future survival, has never previously been evaluated in those cancer patients.

So far there are no prospective data providing better evidence of whether nutritional status could be related to the risk of postoperative complications and mortality in renal as well as bladder cancer patients.

Discussion

The evidence from epidemiologic studies linking diet and nutritional status with prostate, bladder and kidney cancers is still limited and inconsistent. Although the amount of the research is overwhelming, most of the published studies are not of the highest quality and have a short follow-up. This is due to the difficulties in obtaining homogeneity of the study population and the number and quality of foods or nutrients that would allow for randomised controlled studies to be performed. However, despite limitations and inconsistencies which make it difficult to reach explicit conclusions in most of the cases investigating the correlation between diet and urinary tract tumours, the cumulative evidence is compelling for a strong association of obesity with the risk of prostate and kidney cancers. However, several aspects of being overweight or obese, including weight development during lifetime, weight cycling, body fat distribution and its potential mechanisms of action, require further investigation.

Findings from a study in the transgenic mouse model suggest that the ability of calorific restriction to inhibit or delay prostate cancer incidence and progression is mediated in part by changes in energy balance, body mass, and/or body composition rather than calorie intake per se. This implies that the risk of tumourigenesis depends on excess caloric retention, rather than consumption [85].

However, it is not known whether these results can be expected in humans.

Interestingly, cardiovascular disease, which is a leading cause of prostate cancer mortality, is also related to BMI [86–91]. Although not enough evidence exists to warrant recommending particular dietary changes, in order to reduce the risk of urinary tract tumours, data have shown that a diet consisting mainly of vegetables, fruits and fish, combined with adequate calorific intake and exercise, is effective in reducing the risk of obesity and diabetes as well as death from cardiovascular disease. Therefore, any clinical counselling or public health message on nutrition and prevention of the aforementioned cancers should stress the importance of dietary modifications that reduce dietary fat intake along with increased regular physical activity. The role of other dietary components on the process of urinary tract tumour carcinogenesis remains open until strong evidence is obtained.

In summary, obesity is the most significant diet-related risk factor for prostate and renal cancers. However, as the complexity of the disease cannot be explained by a single element, it is likely that no specific diet will completely prevent the development of a neoplasm or alter the growth of an existing tumour. Thus, primary prevention should aim to reduce an individual's exposure to all known modifiable risk factors involved in urinary tract carcinogenesis, including both dietary and non-dietary ones. Implementation of lifestyle changes for the obese or smokers, through weight control and smoking cessation programmes, needs to be encouraged and supported. Further prospective trials, focused on at-risk populations and malnutrition, are needed.

Conflict of interest

The authors declare no conflict of interest.

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