Lifestyle and non-muscle-invasive bladder cancer:

prognosis, quality of life, and patients' awareness

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Table of contents

1

General introduction

Bladder cancer epidemiology

Urinary bladder cancer (UBC) is a common malignancy, which ranks ninth in worldwide cancer incidence with approximately 430,000 new cases and 165,000 deaths in 2012 (1). In the Netherlands, roughly 5,300 men and 1,650 women were newly diagnosed in 2017 (2). This difference in UBC incidence between men and women is probably a reflection of historical gender differences in smoking behavior and occupational exposures. Even though the highest incidence rates of UBC are found in Western countries, both incidence and mortality rates among men have been slowly declining in the United States and large parts of Europe since the 1990s (3). Interestingly, incidence rates in women have been increasing in many European countries, as well as in other parts of the world (3). These trends may reflect changes in smoking behavior and protective measures to occupational exposures (3).

Established risk factors

The most important risk factor for UBC is tobacco smoking, and 43% of all cases in men and 26% of all cases in women in Europe are attributable to smoking (4). Compared to never smokers, current smokers have an over three-fold increased risk of UBC (95% confidence interval (CI): 2.53-3.75) (4). Smoking cessation can lower UBC risk, and a slight decrease in risk to less than three-fold that of never smokers can already be observed after 5 years of cessation (4). However, even 25 years after smoking cessation, UBC risk remains 1.5 times higher than the risk of never smokers (4). Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons have played an important role in UBC etiology for decades, with an estimated population attributable fraction of 20% (5). Nowadays, the population attributable fraction has dropped to 10% due to more hygienic working environments and work-safety guidelines in industries using these substances (6).

There is a growing understanding of the involvement of genetics in UBC development. Having a first-degree relative with UBC, independent of age at diagnosis, has been associated with a two-fold increase in risk (7). Genome-wide association studies identified multiple independent loci associated with UBC risk (8-11). Also, genetic factors can affect individual susceptibility to other risk factors, and thereby increase the risk of UBC (12). For example, ever smokers with a slow acetylation genotype for N-acetyltransferase 2 (*NAT2*) have consistently been shown to have a higher UBC risk (13).

Other risk factors include arsenic in drinking water, schistosomiasis infection, exposure to radiation in the pelvic area, cyclophosphamide treatment, and chronic urinary tract infections (12, 14). A long history of chronic infections of the bladder are more associated with squamous cell carcinoma of the bladder, a histological subtype of UBC, than with urothelial carcinoma (12).

Lifestyle factors and UBC risk

Evidence on the association of lifestyle factors, other than smoking, with UBC risk was summarized by the World Cancer Research Fund / International American Institute for Cancer Research in 2015 (15-17). They concluded that there is limited suggestive evidence that a greater consumption of fruit, vegetables, and tea decreases the risk of UBC (14). No conclusions could be drawn for other dietary factors, physical activity or BMI (14). However, other recent meta-analyses of prospective cohort studies partly including different studies did find small increased UBC risks with a higher BMI (overweight vs. normal weight; pooled relative risk (RR)=1.07, 95% CI 1.01-1.14, I^2=37.6%, p=0.03; obesity vs. normal weight: pooled RR=1.10, 95% CI 1.06-1.14, I^2=15.5%, p=0.24) (18), and decreased risks with higher levels of physical activity (high vs. low level; pooled RR=0.89, 95% CI 0.80-1.00, I^2=64%) (19) and vitamin E (high vs. low intake; pooled RR=0.80, 95% CI 0.69-0.91, I^2=21.1%) (20).

Since diet consists of many macro- and micronutrients that are correlated and can potentially interact with each other in a complex way, it may be better to evaluate dietary patterns rather than single nutrients when estimating diet-disease associations (21). However, to our knowledge, only one study investigated dietary intake patterns in relation to UBC risk (22). This study found that a pattern characterized by consumption of high vs. low amounts of coffee, tea, and added sugar (odds ratio (OR)=3.27, 95% CI 1.96-5.45), as well as a pattern high vs. low in red meat, fried eggs, potatoes, and red wine (OR=2.35, 95% CI 1.42-3.89) were associated with a higher risk of UBC.

There are several hypotheses about mechanisms by which lifestyle habits can influence UBC risk. Potentially harmful substances from food, such as N-nitroso-compounds, polycyclic aromatic hydrocarbons and heterocyclic aromatic amines in red meat, are excreted through the urinary tract. They come into close contact with urothelial cells and may be involved in carcinogenesis by directly acting on the urothelium and causing DNA damage (23-29). For example, a study in normal human urothelial mucosa and bladder tumor tissue showed that the levels of urothelial DNA adducts, a marker for carcinogen exposure, increased after exposure to the carcinogens 4-aminobiphenyl and acrolein (30). A larger fluid volume intake is thought to be protective as it dilutes carcinogens in the urine, and decreases contact time with the urothelium through an increased micturition frequency (26). However, the investigation of fluid volume intake in relation to UBC risk is complicated as it provides no information about the composition of the urine and micturition frequency (26).

Multiple nutrients with a potential protective effect, such as vitamin A and E, phenols, flavonoids and phytochemicals, are also excreted in the urine and can be involved in numerous carcinogenic pathways as well (29). Examples are the reduction of oxidative stress and DNA damage, the inhibition of cell proliferation, and enhancement of the immune response (27-29).

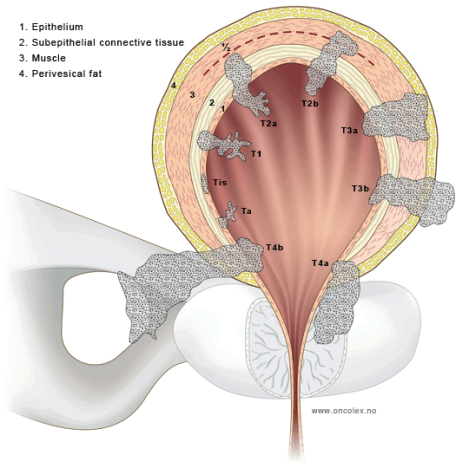
Further, body fatness, often measured by body mass index (BMI), and physical activity are independently linked to several biochemical and immunological changes involved in carcinogenesis (31). For example, a higher amount of body fat is related to an elevated secretion of pro-inflammatory cytokines which induces chronic inflammation. Inflammation in turn leads to increased cell proliferation and worsening of insulin sensitivity, both of which are related to increased cancer risk (31). Physical activity on the other hand improves insulin sensitivity, enhances both innate and acquired immunity, and can decrease oxidative stress (31).

Clinical presentation, prognosis and treatment

Urothelial carcinoma accounts for 90-95% of all bladder tumours in western countries (32). Other less frequent histological subtypes are squamous cell carcinoma (2-5%), adenocarcinoma (1-2%), and numerous very rare subtypes (32, 33). However, in recent years more and more histological variants are being described (34).

Approximately 75% of bladder cancer patients present with non-muscle-invasive bladder cancer (NMIBC), where the tumour is confined to the mucosa (stages Ta and carcinoma in situ (CIS)) or submucosa (stage T1) of the bladder wall (Figure 1) (6). The remainder is diagnosed with muscle-invasive or metastatic bladder cancer (MIBC), where the tumour is invading the muscle layer of the bladder, perivesical tissue, or surrounding organs (6). Women are more likely to present with more advanced tumours, at least partly because of a longer diagnostic delay (35).

Figure 1 Illustration showing T staging of bladder cancer.



Source: http://oncolex.org/bladder-cancer/background/staging

NMIBC and MIBC have been traditionally viewed as separate disease entities, since clinical behaviour is very different. NMIBC is especially characterized by a high but relatively benign recurrence risk, whereas cancer-specific mortality is the most relevant outcome for MIBC patients (6). This thesis will be focused on NMIBC.

Also within NMIBC, there is a large heterogeneity with regard to prognosis. NMIBC patients can be divided into risk groups based on stage, grade, prior recurrence rate, and number of tumours (36). Low-risk tumours are defined as primary, solitary, low-grade/grade 1, stage Ta tumours smaller than three centimeters and without concomitant carcinoma in situ. High-risk tumours are either high-grade/grade 3, stage T1, carcinoma in situ, or multiple and recurrent Ta grade 1 or 2 tumours larger than three centimeters. Tumours that cannot be classified in one of the two categories are classified as intermediate risk (6). One- and five year risks of tumour recurrence are 14% and 28% for NMIBC patients with low-risk tumours and 33% and 52% for patients with high-risk tumours, respectively (36). Often, multiple recurrences per patients are observed in patients with low-risk as well as in patients with high-risk tumours (36). Even though recurrence rates decreased in the last decades due to improvement in treatments, they are still high, indicating the need to identify additional prognostic factors that may support treatment. The five-year disease-specific survival is generally high, ranging between 89 and 99% (36). However, 21% of the high-risk tumours may invade the muscle, which dramatically worsens the prognosis and decreases five-year disease-specific survival to 35% (37).

NMIBC is treated with a transurethral resection of the tumour, preferably followed by an intravesical instillation of chemotherapy within 24 hours (6). For patients with a low-risk tumour, this combination is considered as a complete treatment, but other patients should be further treated with adjuvant chemotherapy (generally mitomycin C or epirubicin) or immunotherapy (bacillus Calmette-Guerin; BCG) (6). In a sub-group of high-risk patients and in patients with BCG failure, radical cystectomy should be considered (6).

Due to the high risk of recurrence, patients need regular long-term follow-ups with minimally invasive cystoscopies and treatment, making bladder cancer one of the most expensive tumours per patient per year (38).

Lifestyle and UBC prognosis

Research on lifestyle and cancer to date has mainly focused on primary prevention of cancer. Due to earlier diagnosis, more effective treatments and an ageing population, survival rates and the number of survivors in the Western world are rapidly increasing (39). Although evidence for an association of different lifestyle factors with cancer prognosis is increasing, the role of lifestyle in UBC prognosis has hardly been investigated (40). Also, prospective studies investigating lifestyle before and after diagnosis, and the impact of lifestyle modifications after diagnosis are currently lacking. Especially for NMIBC patients,

it may be beneficial to alter their lifestyle to influence disease prognosis, since they have a high risk of recurrence, but high survival rates. Apart from a potential effect on NMIBC prognosis, improvements in lifestyle can have a beneficial effect on lifestyle-related comorbidities such as type II diabetes mellitus and cardiovascular disease (41).

Most studies on lifestyle and NMIBC prognosis conducted to date were focused on smoking. A meta-analysis of historical cohort studies suggests that both former and current smokers are at an over 20% higher risk of disease recurrence than non-smokers (42). Evidence for an association of smoking with risk of progression is still weak, but results do suggest an increased risk of disease-specific mortality in smokers (42-44). Smoking cessation may limit the detrimental effects of smoking, but there is no conclusive evidence yet whether smoking cessation after diagnosis can favorably alter the course of disease (43, 45, 46). However, almost all research that has been performed on smoking and UBC prognosis to date is based on historical cohort studies. These studies often suffer from several methodological disadvantages, such as selection bias due to differential loss to follow-up, and poor quality of the data when data is collected from medical records. Also, no evidence for a dose-response association across cumulative smoking exposure is available yet (47). However, since studies generally suggest an increased risk of recurrence and an impaired response to immunotherapy for active smokers, the European Association of Urology guidelines on NMIBC currently recommend smoking cessation counseling (48).

Other lifestyle factors, such as fluid intake, and fruit and vegetable consumption, could also be associated with UBC prognosis through mechanisms comparable to those involved in etiology. Further, lifestyle factors that are associated with systemic inflammation, e.g. BMI and physical activity, could thereby possibly influence UBC prognosis as well (49, 50). However, research on lifestyle and UBC prognosis is still limited.

Health-related quality of life

With the increasing numbers of cancer survivors, patient-reported health-related quality of life (HRQoL) is increasingly being appreciated as an indication of long-term effects of cancer and cancer treatment (39). In NMIBC patients, the frequent and invasive follow-up visits and treatments, which are often accompanied by side-effects, could potentially have a large impact on HRQoL (51, 52). Several studies compared different follow-up regimes and treatment options in terms of HRQoL, showing that patients often have emotional concerns and complaints related to urinary symptoms that are partially dependent on the type of treatment (53-55). In comparison to a normative population, patients with NMIBC were shown to have a worse mental and/or physical health (55-57). However, most of the studies conducted to date had a retrospective or cross-sectional design, may be subject to recall bias, and did not study development of HRQoL over time. Therefore, no firm conclusions about changes in HRQoL after diagnosis and effects of treatment on HRQoL can be drawn.

Lifestyle and UBC health-related quality of life

Several health behaviors have been linked to better HRQoL in survivors of numerous cancers. Exercise, smoking cessation, maintaining a healthy weight, and eating a healthy diet have all been associated with a better quality of life (58-67). A systematic review of studies investigating the association between diet, physical activity, and smoking status with HRQoL in UBC survivors showed that there is suggestive evidence for a positive association of higher physical activity levels with certain HRQoL domains such as general health, functional well-being, and emotional well-being (68). However, differences were often small and not clinically relevant. Interestingly, a recent study not included in the review found an over 2 times increased chance of a higher HRQoL for patients reporting high compared to low physical activity levels (69). For diet, smoking status, and BMI the evidence is insufficient to draw conclusions (68, 70).

Behaviour change after diagnosis

A sustained change of lifestyle behaviours is difficult to attain (71-73). A cancer diagnosis may provide a so-called 'teachable moment', an event which may lead to a high motivation of the patient to change his or her behaviour (74, 75). Therefore, it might be an important window of opportunity to have a meaningful impact on lifestyle and thereby prognosis and quality of life. Also, by changing lifestyle habits patients can become actively involved in the management of their own disease.

An important first step in behaviour change is awareness of risk factors for disease and awareness of one's own behaviour with regard to that risk factor. This is related to an individual's perceived susceptibility to a risk and the perceived severity of that risk (71). Previous research suggests that awareness of smoking as UBC risk factor among patients was generally low, but estimates were highly divergent (10-85%) (76-79). Less is known about NMIBC patients' awareness of other risk factors and what they perceive as being the cause of their own disease (77). Also, it is important to know whether patients are open towards receiving lifestyle advice and whether they already receive advice from their physician. The European Association of Urology guidelines on NMIBC recommend smoking cessation counseling (48), but to what extent this guideline is followed and whether urologists give other lifestyle advice is unknown.

Aim and outline of thesis

The aim of this thesis is to investigate the association of smoking, fluid intake, and dietary patterns with risk of recurrence and HRQoL in NMIBC patients, and to investigate patients' awareness of, adherence to and interest in lifestyle recommendations for cancer prevention. We focused on smoking and fluid intake, since most research with regard to lifestyle and NMIBC prognosis was available for smoking, and the hypotheses regarding both smoking and fluid intake were well-founded in literature. Further, patients seem to be most often advised on these factors when receiving lifestyle advice from their physician.

First, an overview is given of the body of existing evidence on the associations of BMI, diet, and dietary supplements with bladder cancer recurrence, progression, and mortality in the form of a systematic review and meta-analysis (**Chapter 2**).

In **Chapter 3**, we address the association of smoking status, smoking cessation, cumulative smoking exposure, and fluid intake with risk of NMIBC recurrence in the UroLife study, a prospective cohort study on the association between dietary and lifestyle factors and NMIBC prognosis and HRQoL.

Evaluation of the association of different empirically derived dietary patterns with risk of recurrence and progression in NMIBC was described in **Chapter 4**, using data from a large ongoing cohort study performed at M.D. Anderson Cancer Center and Baylor College of Medicine.

Chapter 5 describes the health-related quality of life of NMIBC patients participating in the UroLife study, and whether this is associated with smoking behavior and fluid intake. What factors bladder cancer patients thought contributed to the development of their own disease is described in **Chapter 6** with data from the Nijmegen Bladder Cancer Study. In **Chapter 7**, we investigated whether NMIBC patients are aware of certain (bladder) cancer risk factors and whether they adhere to several lifestyle recommendations for cancer prevention within the UroLife study. Also, we evaluated whether they received lifestyle advice, and their attitudes towards receiving lifestyle advice from their physician.

This thesis ends with a general discussion of the studies described in this thesis in the context of relevant existing literature including recommendations for future research to deepen our understanding of the role of lifestyle in the prognosis and quality of life of NMIBC patients (**chapter 8**).

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2

Review: Body mass index, diet-related factors, and bladder cancer prognosis: a systematic review and meta-analysis

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Abstract

Background: Urologists are frequently confronted with questions of urinary bladder cancer (UBC) patients about what they can do to improve their prognosis. Unfortunately, it is largely unknown which lifestyle factors can influence prognosis.

Objective: To systematically review the available evidence on the association between body mass index (BMI), diet, dietary supplements, and physical activity and UBC prognosis.

Methods: We searched PubMed and Embase up to May 2017. We included thirty-one articles reporting on observational and randomized controlled trials investigating BMI, diet and dietary supplements in relation to recurrence, progression, cancer-specific or all-cause mortality in UBC patients.

Results: In non-muscle invasive bladder cancer (NMIBC) patients, both overweight (3 studies, pooled hazard ratio (HR) 1.29, 95% CI 1.05-1.58, I^2=0%) as well as obesity (3 studies, pooled HR 1.82, 95% CI 1.12-2.95, I^2=79%) were associated with increased risk of recurrence when compared to normal weight. No association of BMI with risk of progression was found. Results for BMI and prognosis in muscle-invasive or in all stages series were inconsistent. Observational studies on diet and randomized controlled trials with dietary supplements showed inconsistent results. No studies on physical activity and UBC prognosis have been published to date.

Conclusions: Evidence for an association of lifestyle factors with UBC prognosis is limited, with some evidence for an association of BMI with risk of recurrence in NMIBC. Well-designed, prospective studies are needed to develop evidence-based guidelines on this topic.

Keywords**:** Body mass index; Diet; Dietary Supplements; Prognosis; Urinary bladder cancer

Introduction

Urologists are frequently confronted with questions by urinary bladder cancer (UBC) patients how they can influence the course of their disease, for example by changing habits concerning smoking, diet, and physical activity. As lifestyle factors have been linked to cancer-specific prognosis of many common malignancies (1), it is important to gain more knowledge about the association of lifestyle factors with urinary bladder cancer (UBC) prognosis as well.

The impact of tobacco smoking on prognosis has recently been reviewed (2, 3). Smoking status was found to be associated with increased risk of disease recurrence in both non-muscle-invasive bladder cancer (NMIBC) (3) and all stages series (2). Evidence for an association of smoking with risk of progression, cancer-specific mortality and all-cause mortality was weak in the review of Crivelli et al. (3), but the more recent meta-analysis of Hou et al. (2) found an increased risk of cancer-specific mortality. Interestingly, some studies showed that former smokers had a lower risk of recurrence or progression than current smokers (3). There is no conclusive evidence yet whether smoking cessation after UBC diagnosis will favorably influence clinical outcomes. However, the European Association of Urology guidelines on NMIBC recommend smoking cessation counseling. This is based on studies suggesting increased risk of recurrence and progression and impaired response to immunotherapy for active smokers (4).

Besides smoking, a high body mass index (BMI) and certain dietary factors have also been hypothesized to be associated with UBC prognosis. Excess body fat is associated with increased circulating concentrations of insulin and insulin-like growth factor-1, as well as systemic inflammation, all of which may be related to worse UBC outcomes (5). Also, certain examinations and surgical procedures might be more complicated in obese patients (6). Dietary factors such as vegetables and fruits are hypothesized to influence UBC prognosis, as favorable components from these foods come into close contact with urothelial cells when excreted via urine (7, 8). A high fluid intake may reduce exposure to carcinogens by diluting the urine and reducing the contact time through increased micturition frequency (9). On the other hand, potential carcinogens in the urine can come into contact with deeper layers of the bladder when the bladder wall is extended because of high fluid intake or low micturition frequency (10).

Thus far, except for smoking, no systematic review of studies on the association between lifestyle factors and prognosis of patients with UBC has been performed. This information is important since it may provide a means to patients to get some control over their disease. The aim of this systematic review is to summarize the available evidence regarding the association of BMI, diet, dietary supplements and physical activity with UBC prognosis and to identify necessary next steps in research.

Methods

Search strategy

A systematic search of the literature up to May 2017 in the PubMed and Embase databases was conducted by using a combination of MeSH and Emtree terms and related key words in title and abstract. The complete search strategy is attached as supplementary material (**Appendix A**). No limits were applied on publication date or type of study during this search. Reference lists of included articles were checked to identify potentially relevant studies that were missed in the initial search.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria (**Figure 1**)(11) for evaluating records identified during the literature search. To warrant integrity, the retrieved references were checked independently by two authors (E.W. and A.V.), and disagreements were discussed and resolved.

Study eligibility

Studies were considered relevant to this review if they reported on observational or intervention studies in UBC survivors with respect to BMI, dietary factors or supplements, or physical activity before, at the time of or after diagnosis in relation to recurrence, progression, cancer-specific mortality (CSM), or all-cause mortality (ACM) (**Appendix II**). Only articles written in the English language were considered for inclusion. When multiple articles reported on the same study, only the most recently published article was taken into consideration unless there were differences in the endpoints or subgroups reported. Animal studies, and investigation of BMI, diet or physical activity with intermediate endpoints of disease or with tumor characteristics only without addressing recurrence, progression, or mortality were excluded.

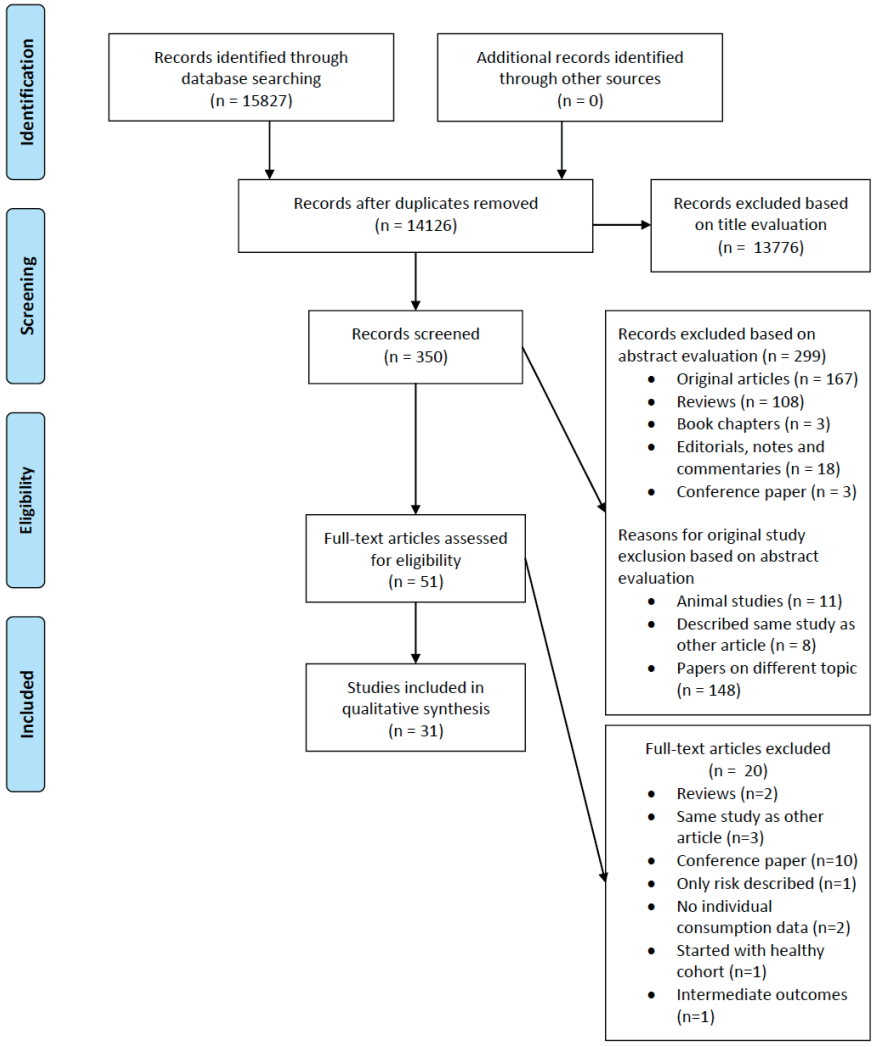
Data extraction

Information extracted from the selected studies included, wherever available, the first author, year of publication, country, sample size and sample characteristics, years of diagnosis, follow-up time, outcome, variable of interest, risk estimates with 95% confidence intervals (CI) or p-values, and factors that were adjusted for in the analysis. When necessary, authors were contacted for additional data.

Statistical analysis

Meta-analysis was performed using Review Manager 5.3 (12). The inverse variance technique was used for meta-analysis of hazard ratios. Due to the clinical heterogeneity inherent in our data, random-effects models were used for all meta-analyses. Statistical heterogeneity was assessed with I^2 values. When no meta-analysis could be performed, we narratively described the study results separately for BMI, dietary factors, dietary supplements and physical activity.

Figure 1 PRISMA flow diagram for the study selection process.



Results

The initial search retrieved 14,126 articles of which 31 were considered relevant for this review (5, 6, 9, 13-40). These articles reported on BMI (n=13), dietary factors (n=4) or dietary supplements (n=14) in UBC survivors. Studies on physical activity were not available. Meta-analysis could be performed for BMI in relation to risk of recurrence and progression in NMIBC patients and in all stages series. The results of these meta-analyses and retrieved studies are discussed in detail below.

Body mass index

Twelve historical cohort studies (5, 6, 16, 18, 19, 22, 23, 25, 29, 33, 39, 40) and one prospective cohort study (38) investigated the association of BMI with the prognostic endpoints of interest (**Table 1**). Nine studies assessed BMI at time of diagnosis or at time of surgery (6, 16, 18, 19, 22, 23, 25, 38, 39) and four studies did not report on the timing of BMI assessment (5, 29, 33, 39).

Three studies including 892 T1 high grade (5), 338 Ta, T1, Tis (38), and 403 Ta, T1 NMIBC patients (39) reported or provided sufficient data to be subjected to meta-analysis. Both overweight (pooled hazard ratio (HR) 1.29, 95% CI 1.05-1.58, p=0.02, I^2=0%; Fig. 2A) as well as obesity (pooled HR 1.82, 95% CI 1.12-2.95, p=0.02, I^2=79%; Fig. 2B) were statistically significantly associated with increased risk of recurrence when compared to normal weight. Based on two studies (5, 39), neither overweight (pooled HR 1.03, 95% CI 0.63-1.70, p=0.91, I^2=0%; Fig. 2C) nor obesity (pooled HR 1.90, 95% CI 0.93-3.88, p=0.08, I^2=51%; Fig. 2D) were statistically significantly associated with risk of progression.

Six studies were performed in NMIBC and muscle-invasive bladder cancer (MIBC) patients combined, which results are more difficult to interpret because of the difference in relevant disease outcomes (i.e., risk of recurrence and CSM, respectively). Four studies investigated BMI in relation to recurrence. Three studies reported sufficient data to be subjected to meta-analysis (18, 19, 23). Neither overweight (pooled HR 0.87, 95% CI 0.67-1.14, p=0.31, I^2=60%; Fig. 3A), nor obesity (pooled HR 1.12, 95% CI 0.54-2.31, p=0.76, I^2=95%; Fig. 3B) were statistically significantly associated with risk of recurrence. One study did not find an association for continuous BMI (16). Four studies investigated CSM, three of them reporting sufficient data to be included in a meta-analysis (18, 19, 23). Neither overweight (pooled HR 0.82, 95% CI 0.65-1.02, p=0.08, I^2=45%; Fig. 3C), nor obesity (pooled HR 0.98, 95% CI 0.46-2.10, p=0.97, I^2=94%; Fig. 3D) were statistically significantly associated with CSM. One study did not find an association for continuous BMI (16). Four studies investigated ACM (6, 16, 18, 33). One study reported an association of overweight and obesity compared to normal weight with higher risk of ACM (HR 1.40, 95% CI 1.23-1.57 and HR 1.81, CI 95% CI 1.60-2.05, respectively)(18), while three studies did not find an association (6, 16, 33). Progression was not investigated in any of these studies.

Four historical cohort studies investigated clinical outcomes exclusively in MIBC patients. Three studies investigated ACM (22, 29, 40), two of them reporting a lower ACM for higher BMI (26.3-29.1 compared to <23.6: HR 0.80, 95% CI 0.69-0.93 and ≥31.2 compared to <31.2: HR 0.46, 95% CI 0.26-0.83, respectively)(29, 40) and the other not showing an association for ACM and CSM (22). One study found no differences in risk of progression or ACM when comparing overweight or obesity with underweight (25).

Dietary factors

Four small cohort studies evaluated the association of dietary factors with UBC outcomes (**Table 2**). These studies examined the effects of vitamin A intake (27), intake of different (alcoholic) drinks (37), fluid intake (9), and fruit and vegetable intake (36).

In a study of 102 NMIBC patients, patients with a prediagnosis dietary intake of vitamin A below the median (not specified) were found to have a 1.8 times higher recurrence rate per 1000 person-months (p =0.02), but no statistically significantly increased risk of recurrence (RR 1.34, 95% CI 0.5-3.34) compared to patients having a dietary intake of vitamin A above the median (27).

Three studies were performed in NMIBC and MIBC patients combined (9, 36, 37). A Japanese study in 258 patients found an inverse association for ever versus never prediagnostic consumption of alcoholic beverages with 5-year ACM (HR 0.46, 95% CI 0.26-0.79)(37). No associations for non-alcoholic beverages and artificial sweeteners were found. Daily post-diagnostic total fluid intake measured using repeated fluid intake questionnaires was not associated with risk of recurrence in a US study in 267 patients (9). A US study in 239 patients investigated self-reported prediagnostic intake of fruits and vegetables in relation to CSM and ACM (36). Patients consuming ≥1compared to those consuming <1 serving per month of raw broccoli had a lower CSM (HR 0.43, 95% CI 0.25-0.74) and ACM (HR 0.57, 95% CI 0.39-0.83, data not shown). Consumption of 1-3 servings of raw cruciferous vegetables per month compared to <1 serving per month was inversely associated with ACM (HR 0.67, 95% CI 0.46-0.97), but not with CSM. No association was found for consumption of more than three servings. Consumption of total fruit, total vegetables or individual cooked cruciferous vegetables was not associated with CSM or ACM.

Dietary supplements

Fourteen dietary supplementation studies in UBC patients were identified (**Table 3**). In these randomized controlled trials, the effects of the retinoids etretinate (13, 32, 35) and fenretinide (20, 34), vitamin B6 (pyridoxine)(17, 31), vitamin E (tocopherol)(26), multivitamins (24, 30), a Lactobacillus casei preparation (14, 28, 41), and selenium (21) were investigated. Thirteen of the 14 studies were performed in NMIBC patients (13, 14, 17, 20, 21, 26, 28, 30-32, 34, 35, 41) and one trial was conducted in NMIBC and MIBC patients combined (24).

Three studies evaluating the effect of the aromatic retinoid etretinate had conflicting results (13, 32, 35). One small study (13) in 32 patients found a lower recurrence rate in the etretinate group compared to the placebo group, while a study of 96 patients (32) and a trial of 79 patients (35) found no differences in recurrence. Nevertheless, in the last study the mean interval to the second recurrence was longer in the etretinate group (20.3 versus 12.7 months, p=0.006), resulting in less transurethral resections of the bladder per patient-year (p <0.01). This may suggest that etretinate needs to be taken for a prolonged period before an effect becomes evident. Fenretinide did not affect recurrence in 99 Italian (20) and 137 US (34) patients.

Table 1 Observational cohort studies on body mass index and prognosis of bladder cancer.

Source (Study location)	Sample (size and key characteristics)	Years of diagnosis	Median follow-up
NMIBC			
Kluth, 2013, US, Germany, France, Italy, Canada (5)	892 NMIBC (T1 high grade) 341 recurrence (38%) 104 progression (12%) 184 deaths (21%) 59 UBC deaths (7%) TURB w/wo IVT (70% IVT)	1996-2007	Median 42.8 mo (IQR 14.8-70.8)
Wyszynski, 2014, US (38)	338 NMIBC (Ta, T1 Tis) In total sample (n=726): 373 recurrence (51%) In total sample: TURB (75%), TURB with immunotherapy (16%), immunotherapy (9%)	1994-2001	Median 6 y (range 0.25-15)
Xu, 2015, China (39)	403 NMIBC (Ta, T1) 177 recurrence (44%) 30 progression (7.4%) TURB w/wo intravesical chemotherapy	2006-2014	Median 53 mo (range 6-102)
NMIBC and MIBC			
Maurer, 2009, Germany (6)	390 NMIBC and MIBC (% NMIBC N/S) Radical cystectomy	1986-2004	N/S
Chromecki, 2012, US, Austria, Germany, Canada, Czech Republic (18)	4118 NMIBC and MIBC (32% NMIBC) 1365 recurrence (33%) 1121 UBC deaths (27%) Radical cystectomy	1979-2008	Median alive at last follow-up 44 mo
Bachir, 2014, Canada (16)	847 NMIBC and MIBC (% NMIBC N/S) Radical cystecomy	1998-2008	Median 23.4 mo

	Outcome	BMI	HR (95% CI)	Covariates adjustment
	Recurrence	Continuous 25-30 vs. <25[1] ≥30 vs. <25[1] ≥30 vs. <30	**1.07 (1.04-1.09)** 1.05 (0.73-1.51) **2.72 (2.00-3.69)** **2.66 (2.12-3.32)**	Gender, concomitant carcinoma in situ, tumor size, number of tumors, intravesical therapy
	Progression	Continuous 25-30 vs. <25[1] ≥30 vs. <25[1] ≥30 vs. <30	**1.08 (1.04-1.12)** 0.90 (0.49-1.64) 1.43 (0.86-2.38) **1.49 (1.00-2.21)**	
	ACM	Continuous ≥30 vs. <30	**1.29 (1.20-1.37)** **3.15 (1.74-5.67)**	
	CSM	Continuous ≥30 vs. <30	**1.06 (1.04-1.09)** **1.42 (1.06-1.92)**	
	Recurrence	24.9-29.9 vs. ≤24.9 ≥30 vs. ≤24.9 >24.9 vs. ≤24.9 Current smokers: >24.9 vs. ≤24.9	1.39 (0.96-2.01) 1.22 (0.80-1.87) 1.33 (0.94-1.89) **2.24 (1.15-4.34)**	Age, sex, stage, grade, tumor size, multiplicity, treatment, smoking
	Recurrence	≥24-<28 vs. <24 ≥28 vs. <24	**1.44 (1.03-2.00)** **1.71 (1.12-2.60)**	Prior recurrence, grade, tumor size, tumor in trigone, concomitant CIS
	Progression	≥24-<28 vs. <24 ≥28 vs. <24	1.36 (0.57-3.23) **3.04 (1.24-7.42)**	
	5 year survival rate	25-29.9 vs. <25 ≥30 vs. <25	No difference[2] No difference[2]	Univariable
	Recurrence	25.0-29.9 vs. <25 >30 vs. <25	0.91 (0.76-1.06) **1.67 (1.46-1.91)**	Age, sex, pT stage, tumour grade, lymphvascular invasion, lymph node metastasis, soft tissue surgical margin, concomitant carcinoma in situ, adjuvant chemotherapy
	CSM	25.0-29.9 vs. <25 >30 vs. <25	**0.80 (0.68-0.95)** **1.43 (1.24-1.66)**	
	ACM	25.0-29.9 vs. <25 >30 vs. <25	**1.40 (1.23-1.57)** **1.81 (1.60-2.05)**	
	OS CSM Recurrence	Continuous Continuous Continuous	0.98 (0.96-1.01) 0.99 (0.96-1.02) 0.98 (0.96-1.00)	Age, grade, pathological stage, lymph nodal metastasis, surgical margin status, adjuvant chemotherapy

Table 1 Continued.

Source (Study location)	Sample (size and key characteristics)	Years of diagnosis	Median follow-up
NMIBC and MIBC			
Kwon, 2014, Korea (23)	714 NMIBC and MIBC (% NMIBC N/S) Radical cystectomy	1990-2012	Median 64.1 mo (range 1-231.4)
Psutka, 2015, US (33)	262 NMIBC and MIBC (29% NMIBC)	2000-2008	Median 6.3 y (IQR 5.7-9.5)
Dabi, 2016, France (19)	701 NMIBC and MIBC (33% NMIBC) 163 recurrence (23%) 127 UBC deaths (18%) Radical cystectomy and pelvic lymphadenectomy	1995-2011	Median 45 mo (IQR 23-75)
MIBC			
Hafron, 2005, US (22)	288 MIBC 203 deaths (71%) Radical or partial cystectomy	1990-1993	Median 39 mo (range 1-168)
Leiter, 2016, US, Germany, Greece, Taiwan (25)	537 MIBC 417 deaths (77%) Chemotherapy	1998-2011	
Xu, 2016, US, Canada (40)	360 MIBC (0.6% NMIBC and 0.6% unknown)	N/S	N/S
Necchi, 2017, US, Canada, Europe, Israel (29)	1020 urothelial cancer (81.2% bladder cancer) 664 deaths (65%)[3] Chemotherapy	2006-2011	Median 31.6 mo (95% CI 29.4-35.0)

HR (95% CI) printed in bold means result statistically significant at the p<0.05 level; [1] Data needed for this comparison was received from the authors; [2] p value not reported; [3] Percentage of deaths among primary bladder cancer patients is not reported.

Abbreviations: ACM: all-cause mortality; BMI: body mass index; CIS: carcinoma in situ; CSM: cancer-specific mortality; ECOG-PS: Eastern Cooperation Oncology Group Performance Status; IQR: interquartile range; IVT: intravesical therapy ; MIBC: muscle invasive bladder cancer; mo: months; NMIBC: non-muscle-invasive bladder cancer; NS: not specified; TURB: transurethral resection of the bladder; y: years.

	Outcome	BMI	HR (95% CI)	Covariates adjustment
	Recurrence	23-25 vs. <23 ≥25 vs. <23	**0.66 (0.48-0.90)** **0.52 (0.37-0.73)**	Age, sex, performance status, serum albumin level, clinical stage, pathological T stage, lymph node metastastis, grade, lymphovascular invasion, soft tissue surgical margin
	CSM	23-25 vs. <23 ≥25 vs. <23	**0.67 (0.48-0.94)** **0.41 (0.27-0.62)**	
	ACM	≥30 vs. <30	0.79 (0.50-1.26)	Age, smoking status, ASA and ECOG score, pTN stage
	Recurrence	25.1-30 vs. 18-25 >30 vs. 18-25	1.14 (0.78-1.66) **1.58 (1.06-2.34)**	Age, stage, grade, lymphovascular invasion, concomitant CIS, lymph node metastasis
	CSM	25.1-30 vs. 18-25 >30 vs. 18-25	1.13 (0.74-1.74) **1.58 (1.01-2.48)**	
	ACM	≥30 vs. ≤29.9	0.87 (0.71-1.06)	Age, sex, pathological stage, lymph node status, soft tissue margin status, urothelial margin, smoking
	CSM	≥30 vs. ≤29.9	No difference	
	Progression	18.5-24.99 vs. <18.5 25-29.99 vs. <18.5 ≥30 vs. <18.5	1.14 (0.70-1.85) 1.31 (0.80-2.13) 1.23 (0.72-2.11)	ECOG-PS ≥ 1, visceral metastasis
	ACM	18.5-24.99 vs. <18.5 25-29.99 vs. <18.5 ≥30 vs. <18.5	0.97 (0.59-1.59) 1.19 (0.73-1.95) 1.08 (0.63-1.87)	
	ACM	≥31.2 vs <31.2 ≥27 vs. 27	**0.46 (0.26-0.83)** 0.77 (0.51-1.17)	Univariable
	ACM	26.3-29.1 vs. <23.6	**0.80 (0.69-0.93)**	White blood cell count, ECOG-PS, lung/liver/bone metastases, ethnicity, prior perioperative chemotherapy, age

Table 2 Observational studies on dietary factors and prognosis of bladder cancer.

Source (Study location)	Sample (size and key characteristics)	Years of diagnosis	Median follow-up
NMIBC			
Michalek, 1987, US (27)	102 NMIBC 34 recurrences (33%) Treatment unknown	1960-1965	N/A
NMIBC and MIBC			
Wakai, 1993, Japan (37)	258 NMIBC and MIBC (%NMIBC N/S) 81 deaths (31%) Treatment unknown	1976-1978	Median 29.8 mo
Donat, 2003, US (9)	267 primary and recurrent NMIBC and MIBC (90% NMIBC) 123 recurrences (46%) TURB (unknown %), partial cystectomy (7.5%) and/or IVT (65.5%)	N/S	Median 2.6 y (range 0.96-3.77)
Tang, 2010, US (36)	239 NMIBC and MIBC (% NMIBC N/S) 179 deaths (75%) 101 UBC deaths (56%) TURB (64.4%), cystectomy (27.6%), unknown (7.9%) w/wo IVT	1980-1998	Median 77 mo (range 1-301)

HR (95% CI) printed in bold means result statistically significant at the p<0.05 level; [1] Ever vs. never consumed, hazard ratios are for male patients only; [2] Servings per month, highest tertile vs. lowest tertile; [3] Servings per month, ≥1 vs. <1 .

Abbreviations: ACM, all-cause mortality; CSM: cancer-specific mortality; IVT: intravesical therapy ; MIBC: muscle invasive bladder cancer; mo: months; NA: not assessed; NMIBC: non-muscle-invasive bladder cancer; NS: not specified; TURB: transurethral resection of the bladder; y: years.

	Outcome	Dietary Factor	HR (95% CI)	Covariates adjustment
	Recurrence	Lower 50% vs. upper 50% of vitamin A consumption	OR 1.34 (0.50-3.34)	Univariable
	Recurrence rate (number of recurrences per 1,000 person-months)	Lower 50% vs. upper 50% of vitamin A consumption	**Rate 1.8 (p=0.02)**	Age, sex, smoking status
	5-year ACM	Alcoholic beverages[1] Artificial sweetener[1] Coffee[1] Black tea[1] Green tea[1] Matcha[1] Cola[1]	**0.46 (0.26-0.79)** 1.05 (0.62-1.79 0.88 (0.49-1.59) 0.77 (0.44-1.33) 0.62 (0.22-1.74) 1.36 (0.75-2.44) 1.11 (0.61-2.01)	Age at first consultation, stage, histological type and grade, distant metastasis
	Recurrence	Average daily fluid intake postdiagnosis, continuous	RR 1.05 (0.92-1.19)	Age, gender, years since initial diagnosis, months since last tumor, recurrence within 3 months before study, recurrence risk group, persistent positive cytology, smoking status
	CSM	Fruits[2] Vegetables[2] Cruciferous vegetables cooked[2] Cruciferous vegetables raw[2] Broccoli raw[3] Broccoli cooked[3] Cabbage raw[3] Cabbage cooked[3] Cauliflower raw[3] Cauliflower cooked[3] Brussels sprout[3] Kale, turnip, collard, mustard greens[3]	1.09 (0.66-1.81) 1.06 (0.63-1.78) 0.89 (0.53-1.48) 0.73 (0.44-1.21) **0.43 (0.25-0.74)** 0.68 (0.45-1.01) 1.11 (0.74-1.66) 1.15 (0.75-1.77) 1.08 (0.66-1.77) 0.95 (0.63-1.42) 1.37 (0.86-2.18) 1.07 (0.63-1.79)	Age at diagnosis, tumor stage, radiation therapy, pack-years of smoking, total meat intake

Table 3 Intervention studies on dietary supplements and prognosis of bladder cancer.

Source (Study location)	Study population	Years of diagnosis	Follow-up	No. of subjects per treatment group
Etretinate				
Alfthan, 1983, Finland (13)	Recurrent NMIBC diagnosed mean 5 (range 1.5-26) y ago TURB or electrocoagulation (unknown %)	N/A	17.6 mo (10-26)[1]	15 etretinate – 25 mg/day 15 placebo
Pedersen, 1984, Denmark (32)	NMIBC with at least 2 recurrences within previous 18 mo	N/A	Up to 8 months	47 etretinate – 50 mg/day 49 placebo
Studer, 1995, Switzerland (35)	Primary and recurrent NMIBC TURB	N/A	Control 30 mo Treatment 33 mo,	37 etretinate – 25 mg/day 42 placebo
Fenretinide				
Decensi, 2000, Italy (20)	Primary and recurrent NMIBC TURB w IVT or diathermy	1993-1994	Up to 36 mo	49 fenretinide – 200 mg/day 50 controls
Sabichi, 2008, US (34)	Primary and recurrent NMIBC (with minimum preceding 12- month disease- free interval) TURB w/wo IVT (27.7% IVT)	1998-2003	N/A	70 fenretinide – 200 mg/day 67 placebo
Pyridoxine				
Byar, 1977 (17)	Primary and recurrent NMIBC TURB	1971-1976	31 mo	33 pyridoxine – 25 mg/day 38 intravesical thiotepa[3] 50 placebo
Newling, 1995, England (31)	NMIBC with estimated survival >3 y TURB or fulguration	1979-1981	Mean 3.4 y	147 pyridoxine – 20 mg/day 144 placebo
Vitamin E				
Mazdak, 2012, Iran (26)	NMIBC TURB	2006-2010	Control 12.1 mo Treatment 16.2 mo	21 vitamin E – 400 IU/day 25 placebo

	Treatment duration	Drop-out (n)	Outcome and timing of measurement	Effect	Covariates adjustment
	Range 10-26 mo	2	Recurrence rate Timing N/S	**60% vs. 87% (p<0.02)**	N/A
	8 mo	12 etretinate 7 placebo	Recurrence at 8 mo	No difference[2]	N/A
	Median etretinate 33.0 mo Median placebo 30.0 mo	15 etretinate 15 placebo	Mean time to first recurrence	13.6 mo vs.13.5 mo	N/A
	24 mo, 3 day drug free period at the end of each mo	12 fenretinide 12 controls	No. of recurrence at end of follow-up	27 vs. 21 in control group (p=0.36)	Baseline values (N/S)
	12 mo, 3 day drug free period every 28 days	70 (N/S which group)	Recurrence at 1 y	31.5% vs. 32.3% (p=0.88)	N/A
	Mean 30 mo	1 pyridoxine 2 placebo	Mean time to first recurrence Pyridoxine vs. placebo Thiotepa vs. placebo Thiotepa vs. pyridoxine Recurrence rate per 100 patient months Pyridoxine vs. placebo Thiotepa vs. placebo Thiotepa vs. pyridoxine Mean time to progression Pyridoxine vs. placebo Thiotepa vs. placebo Thiotepa vs. pyridoxine	 No difference[2] No difference[2] No difference[2] No difference [2,4] p 0.016 p 0.015 No difference[2] No difference[2] No difference[2]	N/A
	Duration N/S	6 pyridoxine 6 placebo	Mean time to first recurrence Recurrence rate per year Progression at end of follow-up Survival at end of follow-up	No difference (p=0.30) No difference (p=0.992) No difference[2] No difference (p=0.53)	Recurrence rate before entry, numbers of tumors at entry, tryptophan metabolite levels
	Duration N/S	N/S	Recurrence at the end of follow-up	**RR 0.53 (0.11-0.94)** **OR 0.42 (p=0.04)**	N/A

Table 3 Continued.

Source (Study location)	Study population	Years of diagnosis	Follow-up	No. of subjects per treatment group
Multiple vitamins				
Lamm, 1994, US (24)	NMIBC and MIBC (control 87% NMIBC; treatment 88.6% NMIBC) TURB w IVT	1985-1992	Control 40 mo (6-80) Treatment 49 (6-81)	30 RDA of multiple vitamins/day 35 RDA plus megadose[5] of vitamin A, B6, C, E and zinc/day
Nepple, 2010, US (30)	NMIBC 113 recurrences RDA (33.6%) 118 recurrences megadose vitamins (35.3%) Biopsy or TURB (98.5%) and IVT	1999-2003	Median 24 mo	336 RDA of multiple vitamins 334 megadose vitamins[6]
Lactobacillus casei preparation				
Aso, 1992, Japan (41)	Primary and recurrent NMIBC TURB	1988-1989	Control 428 days Treatment 427 days	29 Lactobacillus casei preparation - 3 g/day 29 placebo
Aso, 1995, Japan (14)	Primary and recurrent NMIBC TURB	1990-1991	N/S	68 Lactobacillus casei preparation - 3 g/day 70 placebo
Naito, 2008, Japan (28)	Primary and recurrent NMIBC 26 recurrences Lactobacillus casei preparation (26%) 42 recurrences control (41%) 4 progression (1.9%) 5 deaths (2.4%) 2 BC deaths (1%) TURB and IVT	1999-2002	Median 43.6 mo (range 0.2 to 75.0) vs. 26.9 (range 0.6 to 79.9)	100 Lactobacillus casei preparation - 3 g/day 102 control
Selenium				
Goossens, 2016, Belgium (21)	Primary and recurrent NMIBC 43 recurrences selenium (28%) 45 recurrences placebo (32%) 15 progression selenium (10%) 14 progression (10%) placebo TURB	2009-2013	Median 17.9 mo (range 0.1 to 36) vs. 17.8 (range 0.4 to 36)	151 selenium – 200 µg/day 141 placebo

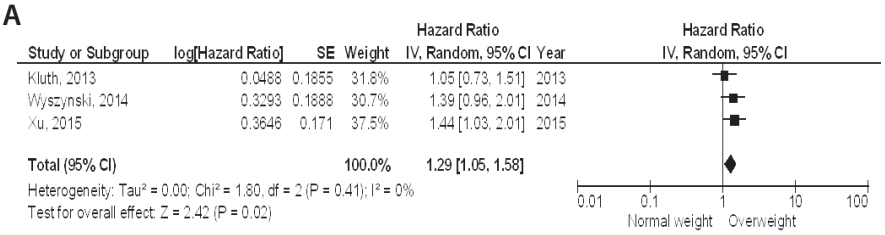
HR (95% CI) printed in bold means result statistically significant at the p<0.05 level; [1] Excluding one patient in the placebo group who died after 6 months; [2] p value not reported; [3] Thiothepa is a cytotoxic, alkylating agent used as chemotherapy; [4] When patients followed up less than 10 months are excluded p 0.03; [5] Daily dose of patients in megadose group: 40,000 IU vitamin A, 100 mg vitamin B6, 2,000 mg vitamin C, 400 IU vitamin E and 90 mg zinc; [6] Daily dose of patients in megadose group: 36,000 IU vitamin A, 100 mg vitamin B6, 2,000 mg vitamin C, 1,600 IU vitamin D3, 1.6 mg folate, 400 IU vitamin E and

	Treatment duration	Drop-out (n)	Outcome and timing of measurement	Effect	Covariates adjustment
	Duration N/S	N/S	Recurrence at 1y Overall recurrence rate Survival rate	**37% vs. 9% (p=0.008)** **80% vs. 40% (p=0.001)** 76% vs. 74% (p=N/S)	N/A
	Median 24 mo	N/S	Time to first recurrence	HR 1.07 (0.83-1.39)	N/A
	12 mo	2 drop-out Lactobacillus casei preparation	50% recurrence-free interval	Treatment 350 d; placebo 195 d **HR 2.41 (p=0.028)**	Age, grade, primary or recurrent tumor, multiplicity, tumor size
	12 mo	4 drop-out Lactobacillus casei preparation 4 drop-out placebo	50% recurrence free period all patients 50% recurrence free period group A and B[7]	No difference (p=0.325) Treatment 688 d; placebo 543 d **HR 2.58 (p=0.013)**	Univariable Clinical and patient characteristics (N/S)
	12 mo	N/S	Recurrence free survival rate at 3 y Progression free survival rate (timing N/S) Overall survival rate (timing N/S)	**HR 0.57 (0.35-0.93)** No difference[2] No difference[2]	Multiplicity, tumor size, stage
	36 mo	41 drop-out selenium 35 drop-out placebo	Recurrence Progression free interval	HR 0.88 (0.58-1.35) HR 0.89 (0.42-1.86)	Age, gender, smoking status, staging, baseline serum selenium level, hospital

30.4 mg zinc; [7] Only 78 patients with primary multiple tumors or recurrent single tumors were evaluated (39 Lactobacillus casei preparation; 39 placebo).
Abbreviations: d: days; IU: International Unit; IVT: intravesical therapy ; MIBC: muscle invasive bladder cancer; mo: months; NMIBC: non-muscle-invasive bladder cancer; NA: not assessed; NS: not specified; RDA: recommended daily allowance; TURB: transurethral resection of the bladder; y: years.

Figure 2 BMI and NMIBC prognosis: (**A**) Overweight vs. normal weight and risk of recurrence; (**B**) Obesity vs. normal weight and risk of recurrence; (**C**) Overweight vs. normal weight and risk of progressoin; (**D**) Obesity vs. normal weight and risk of progression.

A



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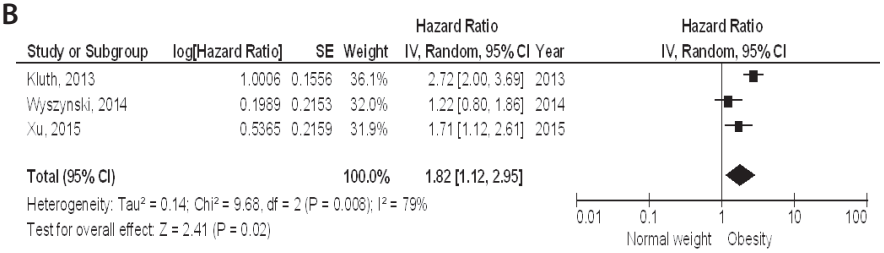

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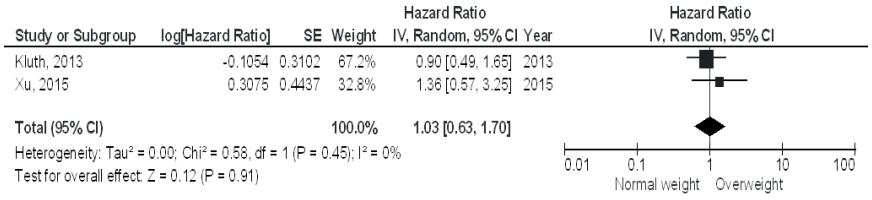

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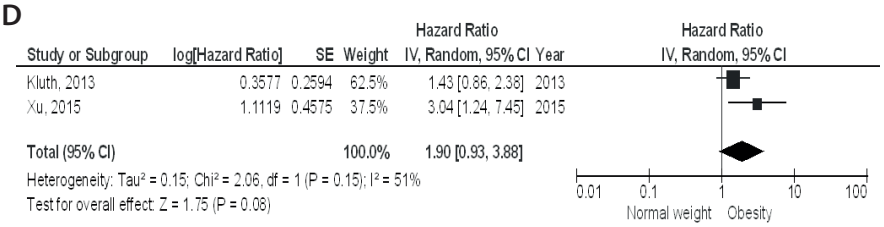
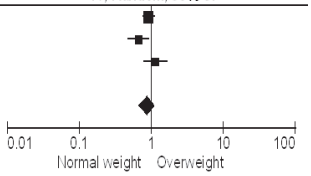


Figure 3 BMI and prognosis in all stages series: (**A**) Overweight vs. normal weight and risk of recurrence; (**B**) Obesity vs. normal weight and risk of recurrence; (**C**) Overweight vs. normal weight and risk of CSM; (**D**) Obesity vs. normal weight and risk of CSM.

A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Chromecki, 2012	-0.0943	0.0919	43.9%	0.91 [0.76, 1.09]	2012
Kwon, 2014	-0.4155	0.1625	30.5%	0.66 [0.48, 0.91]	2014
Dabi, 2016	0.131	0.1936	25.6%	1.14 [0.78, 1.67]	2016
Total (95% CI)			**100.0%**	**0.87 [0.67, 1.14]**	

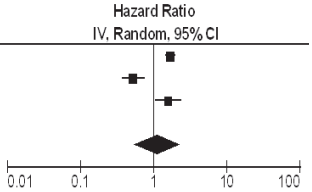
Heterogeneity: Tau² = 0.03; Chi² = 5.05, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 1.01 (P = 0.31)



B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Chromecki, 2012	0.5128	0.0686	35.0%	1.67 [1.46, 1.91]	2012
Kwon, 2014	-0.6539	0.1736	32.9%	0.52 [0.37, 0.73]	2014
Dabi, 2016	0.4574	0.2037	32.0%	1.58 [1.06, 2.36]	2016
Total (95% CI)			**100.0%**	**1.12 [0.54, 2.31]**	

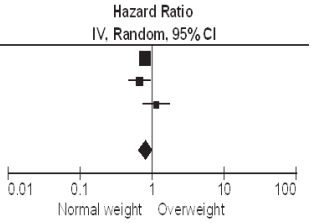
Heterogeneity: Tau² = 0.39; Chi² = 39.30, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.30 (P = 0.76)



C

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Chromecki, 2012	-0.2231	0.0829	52.0%	0.80 [0.68, 0.94]	2012
Kwon, 2014	-0.4005	0.1702	27.8%	0.67 [0.48, 0.94]	2014
Dabi, 2016	0.1222	0.216	20.2%	1.13 [0.74, 1.73]	2016
Total (95% CI)			**100.0%**	**0.82 [0.65, 1.02]**	

Heterogeneity: Tau² = 0.02; Chi² = 3.63, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 1.76 (P = 0.08)



D

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Chromecki, 2012	0.3577	0.0727	35.5%	1.43 [1.24, 1.65]	2012
Kwon, 2014	-0.8916	0.2131	32.5%	0.41 [0.27, 0.62]	2014
Dabi, 2016	0.4574	0.2283	32.0%	1.58 [1.01, 2.47]	2016
Total (95% CI)			**100.0%**	**0.98 [0.46, 2.10]**	

Heterogeneity: Tau² = 0.42; Chi² = 31.72, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.04 (P = 0.97)

Supplementation with pyridoxine was found not to affect recurrence or progression in 121 stage I patients (17). However, when patients with recurrences during the first ten months or followed up less than ten months were excluded, recurrence rate was significantly lower for pyridoxine compared to placebo. Again, this suggests that a longer duration of supplementation is required. A study in 291 patients (31) did not find an effect of pyridoxine on risk of recurrence, progression, or ACM.

A small trial in NMIBC patients in Iran (n=46) reported that daily intake of 400 IU vitamin E after diagnosis resulted in a lower risk of recurrence (RR=0.53, 95 CI% 0.11-0.94) compared to a control group (26).

Two trials tested if supplementation with a megadose of multivitamins had an effect on recurrence (24, 30). In 65 NMIBC and MIBC patients, a reduced risk of recurrence was found in the experimental group that received a supplement with the recommended daily allowance (RDA) plus a megadose of vitamin A, B6, C, E and zinc compared to RDA alone (24). In contrast, a large multicenter trial in 670 BCG naïve patients found no difference in recurrence-free survival (30).

Three studies conducted in Japan investigated the effect of 3 gram/day of the orally administered probiotic Lactobacillus casei preparation on prognosis (14, 28, 41). A study of 202 patients receiving standard treatment of intravesical instillations with epi-adryamicin randomized to a daily administration of Lactobacillus casei preparation for one year versus a control condition (no Lactobacillus casei preparation), reported that the recurrence rate was lower in the Lactobacillus casei group compared to the control group (HR 0.57, 95% CI 0.35-0.93)(28). No effect on progression or ACM was found. A study in 138 patients receiving either a Lactobacillus casei preparation or placebo did not find a difference in recurrence-free interval when all patients were included in a univariable analysis (14). However, when analysis was restricted to78 patients with primary multiple tumors or recurrent single tumors, Lactobacillus casei preparation was associated with a longer recurrence-free interval as compared to placebo (688 days versus 543 days; HR 2.58; p=0.013). In a study of 58 patients, the recurrence-free survival interval of the group who received the Lactobacillus casei preparation was prolonged to 1.8 times the interval of the control group (350 days versus 195 days; HR 2.41, p=0.028)(41).

A study in 292 NMIBC patients conducted in Belgium showed that selenium supplementation did not lower the risk of recurrence compared to placebo (21).

Discussion

This review was conducted to provide a complete overview of available evidence regarding the impact of lifestyle factors on the prognosis of patients with UBC. A total of 31 studies on BMI, diet or dietary supplements were included while studies on physical activity were not available. Overweight and obesity compared to normal weight were

associated with increased risk of recurrence but not progression in NMIBC. Results of studies on BMI in relation to prognosis in NMIBC and MIBC patients combined or restricted to MIBC patients were inconsistent and sometimes even opposite. Observational cohort studies on diet and dietary supplementation studies found some inverse associations with risk of recurrence, CSM, or ACM, but only for single foods and specific supplements.

The biologic mechanisms underlying the association of lifestyle factors with cancer prognosis in general, and UBC prognosis in particular, are not well understood (1). Our results that show an increased recurrence risk in overweight or obese NMIBC patients may be explained by systemic and local changes induced by obesity, such as altered levels of insulin, insulin-like growth factor-1, leptin, adiponectin, steroid hormones, and cytokines (42, 43). In NMIBC patients, markers of systemic inflammatory response have indeed been associated with increased risk of recurrence and progression (44). Also, potential difficulties in performing a high quality (complete) transurethral resection of the bladder may play a role, particularly for obese patients (5, 39). For NMIBC patients it therefore seems advisable to attain or maintain a healthy body weight. However, it should be kept in mind that available evidence is limited to three studies of which only one was adjusted for smoking (38). For MIBC patients, results were inconsistent and no recommendations can be made.

Dietary factors are also likely to be relevant in UBC carcinogenesis and prognosis. Several harmful as well as beneficial substances from food are excreted via the urine and may directly act on urothelial cells. Bioactive food compounds can be involved in numerous pathways, such as inhibition of inflammation (45), inhibition of cell proliferation, invasion, angiogenesis, and metastasis and induction of apoptosis (46), and suppression of self-renewal of cancer stem cells (45, 47). However, based on the current available evidence, no recommendations on diet and UBC prognosis can be made.

Limitations of the studies included

Studies on BMI and dietary factors conducted to date mostly included a heterogeneous study population with different stages and grades of UBC and undergoing different treatments. Risk of recurrence, progression and CSM differs by UBC stage and grade (48). This should be taken into account when evaluating the association of BMI and dietary factors with these disease endpoints. However, none of the studies included in our review performed subgroup analyses by tumor stage and grade, possibly masking true associations. Also, disease progression was investigated in a minority of the studies and several observational studies only investigated the association with CSM or ACM, which are not preferable endpoints for NMIBC. Since risk of death from NMIBC is relatively low, mortality mainly reflects the general health condition of the participants instead of the consequences of bladder cancer. Thus, a possible association of BMI and dietary factors with disease outcomes in these heterogeneous UBC populations may have been missed.

In several studies, BMI and diet were not the primary factor of interest, and only one or a few single dietary factors were studied in relation to UBC prognosis. Since dietary

components interact with each other in a complex way, it is preferable to take the entire dietary pattern into account instead of single dietary factors. Furthermore, depending on dose, dietary supplements can prevent or promote growth of tumor cells or existing (pre) cancerous lesions. For example, the ATBC study reported an increased instead of expected decreased incidence of lung, prostate and stomach cancer in Finnish male smokers receiving supplements with supraphysiological doses of β-carotene versus placebo (49). In addition, recent mouse experiments showed that antioxidants may protect melanoma and lung cancer cells and promote growth and the ability to metastasize (50, 51). UBC survivors could be using dietary supplements more frequently than population controls, as is observed for prostate cancer survivors (52). Given the lack of evidence for a beneficial effect on prognosis in UBC, and reasoning that the same biology may apply for UBC as for other neoplasms, urologists may consider to advise UBC survivors against using dietary supplements. This advice is in line with the WCRF/AICR cancer prevention recommendation not to use dietary supplements to protect against cancer (53).

The observational studies on BMI were generally based on historical cohorts with information retrospectively collected from medical records of consecutive patient series. This may have led to selection bias and incomplete retrieval of information. Also, almost none of the included studies compared the same BMI categories, and some studies (29, 40) did not use official BMI categories as defined by the World Health Organization to compare patients, possibly explaining the inconsistent results. Furthermore, only one of the studies included other measures to assess obesity or body composition, such as waist-to-hip ratio or densitometry (33). The observational studies on dietary factors were mostly based on follow-up of existing case-control studies, were small, did not report the type of questionnaire used, and defined only two broad comparison groups (e.g. ever vs. never, > vs. < median, ≥1 vs. <1 servings per month)(27, 36, 37). None of the studies investigated post-diagnostic BMI and only one study investigated post-diagnostic diet but was restricted to overall fluid intake (9). Post-diagnostic changes in BMI or diet in relation to prognosis were not addressed, while the most relevant question for patients is whether making lifestyle changes affects their prognosis. Most supplementation studies also had a limited sample size and in some of these studies only a few patients experienced the outcome(s) of interest, highly limiting the statistical power. Some studies did not report whether study participants and investigators were blinded (13, 14, 17, 24, 26, 32, 41) and one study was not blinded (28). In addition, for both observational and supplementation studies heterogeneity was present in type of exposure, timing of exposure assessment and outcomes of interest which makes it difficult to compare studies and to draw conclusions. Incomplete reporting of patient characteristics and methods aggravated this problem. Also, smoking was only taken into account in some studies. Thus, there is a potential risk of bias in individual studies.

Ongoing challenges and steps to be taken

Taking into account the shortcomings of the studies published to date, there is an urgent need for well-designed, prospective cohort studies on the association of dietary and other lifestyle factors with UBC prognosis. There are several considerations for the design of such studies. First of all, patients newly diagnosed with UBC should be recruited rapidly so that data collection can start shortly after diagnosis. Ideally, questionnaires should cover the entire diet, and assessment of pre-diagnostic dietary and lifestyle habits should be followed by repeated post-diagnosis assessments to capture changes in lifestyle. In this way, the most relevant question for the patient can be addressed, i.e. whether lifestyle changes are related to UBC prognosis. Furthermore, blood samples should be collected to investigate biomarkers of dietary and lifestyle habits. A representative, population-based sample of UBC patients should be included to assure generalizability, but NMIBC and MIBC patients should be investigated separately and, if possible, by molecular subtype as relevant disease outcomes and prognosis are clearly different for these subgroups (54). Sample size should be large enough to study associations with sufficient power, and to study progression which is a less frequent outcome. Smoking and perhaps antidiabetic medication use should be taken into account as the association between lifestyle and UBC prognosis may be confounded by these factors, or may be different according to subgroups of these factors. Furthermore, physical activity may be a relevant lifestyle factor for further investigation as well, since it has been suggested to improve immune system functioning and to reduce systemic inflammation, thereby positively influencing the course of disease (55, 56).

Also, studying body composition may be more relevant than BMI, as BMI cannot distinguish between fat mass and skeletal muscle mass, and only low muscle mass but not fat mass has been associated with increased risk of ACM in MIBC patients (33, 57).

Conclusions

This review suggests that BMI and certain dietary factors and supplements may influence bladder cancer prognosis, but no strong conclusions can be drawn. Well-designed prospective studies are neededto provide UBC patients with evidence-based lifestyle guidelines to improve their prognosis. These studies should include patients shortly after diagnosis, need repeated lifestyle measurements and examine appropriate endpoints (recurrence and progression in NMIBC, CSM and ACM in MIBC). Until new evidence becomes available, UBC patients are advised to follow the World Cancer Research Fund/American Institute for Cancer Research recommendations for cancer prevention which are focused on maintaining a healthy weight, being physically active and eating a healthy diet.

Acknowledgements

Author contributions

EW conceived the study concept and design, completed the literature search, performed the study selection, prepared tables and figures, drafted the manuscript, and contributed to the interpretation of the findings; AV conceived the study concept and design, completed the literature search, performed the study selection, prepared tables and figures, drafted the manuscript, and contributed to the interpretation of the findings, and was involved in supervision of the research; EK and LAK drafted the manuscript, contributed to the interpretation of the findings, and were involved in the supervision of the research; and all authors: were involved in acquisition of the data, critically reviewed the manuscript for important intellectual content, and approved the final version.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to the study.

Ethical approval

As a review paper, this article does not require ethical approval and does not contain any Studies with human participants or animals performed by any of the authors.

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Appendix A

PubMed search

BMI, physical activity, nutrition and bladder cancer recurrence, progression and survival

A

"Urinary bladder neoplasms"[MeSH Terms] OR (("malignant"[tiab] OR "malignancy"[tiab] OR "malignancies"[tiab] OR "neoplasm"[tiab] OR "neoplasms"[tiab] OR "carcinoma"[tiab] OR "carcinomas"[tiab] OR "cancer"[tiab] OR "cancers"[tiab] OR "tumor"[tiab] OR "tumors"[tiab] OR "tumour"[tiab] OR "tumours"[tiab]) AND ("bladder"[tiab] OR "urothelial"[tiab]))

B

"Recurrence"[MeSH Terms] OR "Neoplasm Recurrence, Local" OR "Disease Progression"-[MeSH Terms] OR "Disease-Free Survival"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "Mortality"[Subheading] OR "Survival Analysis"[MeSH Terms] OR "recur"[tiab] OR "recurrence"-[tiab] OR "recurrences"[tiab] OR "relaps"[tiab] OR "relapse"[tiab] OR "relapses"[tiab] OR "survivor"[tiab] OR "survivors"[tiab] OR "progression"[tiab] OR "survival"[tiab] OR "mortality"-[tiab] OR "death"[tiab]

C

"Body Weights and Measures"[MeSH Terms] OR "Body Composition"[Mesh Terms] OR "Adipose Tissue" [Mesh Terms] OR "weight"[tiab] OR "body weight"[tiab] OR "body mass index"[tiab] OR "bmi"[tiab] OR "quetelet index"[tiab] OR "waist circumference"[tiab] OR "hip circumference"[tiab] OR "waist hip ratio"[tiab] OR "waist to hip ratio"[tiab] OR "body fat distribution"[tiab] OR "body fat"[tiab] OR "overweight"[tiab] OR "obesity"[tiab] OR "weight gain"[tiab] OR "weight change"[tiab] OR "body composition"[tiab] OR "adipose tissue" [tiab]

D

"Exercise"[MeSH Terms] OR "Sports"[MeSH] OR "physical activity"[tiab] OR "motor activity"[tiab] OR "exercise"[tiab] OR "sports"[tiab] OR "running"[tiab] OR "jogging"[tiab] OR "swimming"[tiab] OR "walking"[tiab]

E

"Diet"[MeSH Terms] OR "diet therapy"[MeSH Terms] OR "food and beverages"[MeSH Terms] OR "nutritional sciences"[MeSH Terms] OR "antioxidants"[MeSH Terms] OR "micronutrients"-[MeSH Terms] OR "antineoplastic agents"[MeSH terms] OR "diet"[tiab] OR "diets"[tiab] OR "dietary"[all fields] OR "intake"[tiab] OR "nutrition"[tiab] OR "food"[tiab] OR "antioxidant"-[tiab] OR "antioxidants"[tiab] OR "micronutrient"[tiab] OR "micronutrients"[tiab] OR "vitamin"[tiab] OR "vitamins"[tiab] OR "supplement"[tiab] OR "supplements"[tiab]

EMBASE search

BMI, physical activity, nutrition and bladder cancer recurrence, progression and survival

A

exp bladder tumor/ OR ((malignant OR neoplasm OR neoplasms OR carcinoma OR carcinomas OR cancer OR cancers OR tumor OR tumors OR tumour OR tumours) AND (bladder OR urothelial)).ti,ab

B

exp recurrent disease/ OR exp disease progression/ OR exp disease-free survival/ OR exp mortality/ OR exp cause of death/ OR exp survival/ OR exp survival rate/ OR (recur OR recurrence OR recurrences OR relapse OR Disease-Free Survival OR Disease-Free Survivals OR Event Free Survival OR Event Free Survivals OR survivor OR survivors OR Progression-Free Survival OR Progression-Free Survivals OR survival OR survival rate OR remission).ti,ab

C

exp body height/ OR exp body weight/ OR exp body mass/ OR exp waist circumference/ OR exp waist hip ratio/ OR exp adipose tissue/ OR exp obesity/ OR exp body composition/ OR (weight OR body weight OR body mass index OR bmi OR quetelet index OR waist circumference OR hip circumference OR waist hip ratio OR waist to hip ratio OR body fat OR overweight OR obesity OR weight gain OR weight change OR body composition OR adipose tissue).ti,ab

D

exp motor activity/ OR exp exercise/ OR exp sport/ OR (physical activity OR motor activity OR exercise OR sports OR running OR jogging OR swimming OR walking).ti,ab

E

exp diet/ OR exp diet therapy/ OR exp food/ OR exp nutritional science/ OR exp antioxidant/ OR exp trace element/ OR exp antineoplastic agent/ OR (diet OR diets OR dietary OR dietary intake OR intake OR nutrition OR food OR antioxidant OR antioxidants OR micronutrient OR micronutrients OR vitamin OR vitamins OR supplement* OR dietary supplement OR food supplement).ti,ab

3

Smoking and fluid intake in relation to risk of recurrence in non-muscle invasive bladder cancer: a prospective cohort study

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Abstract

Introduction: Smoking has been associated with a higher risk of recurrence in non-muscle-invasive bladder cancer (NMIBC), but evidence is inconsistent. Fluid intake is hypothesized to have an effect on bladder cancer risk, but its role in NMIBC prognosis has only scarcely been investigated.

Methods: We studied the association of self-reported smoking status at diagnosis, cumulative smoking exposure, time since smoking cessation, and post-diagnostic fluid intake with risk of first recurrence in the prospective cohort study UroLife, including 550 NMIBC patients diagnosed between 2014 and 2016. Patients completed a questionnaire on smoking at 6 and 12 weeks after diagnosis and a 4-day diary on fluid intake at 12 weeks after diagnosis. Detailed data on tumour characteristics, treatment, and clinical outcomes were collected. Hazard ratio's (HR) and 95% confidence intervals (CI) were calculated with multivariable Cox proportional hazards regression analysis, adjusted for age, gender, stage, grade, and treatment.

Results: During a median follow-up of was 19 months, 103 patients (19%) developed at least one recurrence. No statistically significant associations with risk of recurrence were found for either smoking or fluid intake. Former (HR 1.41; 95% CI 0.79-2.51), but not current (HR 0.87; 95% CI 0.44-1.73) smokers had a non-statistically significant increased risk of recurrence compared to never smokers. Among ever smokers, the highest versus lowest amount of pack-years was associated with a non-statistically significant increased risk of recurrence (HR 1.32; 95% CI 0.75-2.33; p-trend=0.14).

Conclusion: In our study, smoking and fluid intake were not markedly associated with risk of recurrence in NMIBC patients. However, future analyses with a larger sample size and longer follow-up time are needed before definitive conclusions can be drawn.

Introduction

Non-muscle-invasive bladder cancer (NMIBC) is a common malignancy which is characterized by a high risk of disease recurrence (1). Therefore, patients require frequent check-ups with cystoscopies and usually undergo multiple treatments (2), which makes bladder cancer one of the most expensive tumours per patient per year (3). Despite improvements in treatment such as single postoperative instillations of chemotherapy and enhanced cystoscopy, recurrence rates are still high, indicating the need to identify additional prognostic factors that may support treatment.

Several lifestyle factors have been associated with prognosis in other cancer types (4, 5), but evidence for NMIBC is scarce and equivocal. Smoking is the most important risk factor for both NMIBC and muscle-invasive bladder cancer and evidence of an association with risk or recurrence is increasing (6-8). A meta-analysis of thirteen cohort and two case-control studies showed that former and current smokers may be at a more than 20% (95% confidence interval 1.05-1.45; I^2=56%) higher recurrence risk than never smokers (7). Smoking cessation may limit the detrimental effects of smoking, thereby favorably altering the course of disease (6, 9, 10). However, evidence from prospective studies is lacking.

Fluid intake has also been hypothesized to be associated with urinary bladder cancer (UBC) risk (11, 12). The urogenous contact hypothesis suggests that increased fluid consumption results in lower concentrations of carcinogens in the urine and a higher micturition frequency, reducing urothelial exposure to carcinogens such as those from cigarettes (11, 12). However, different types of beverages may exert different effects due to their nutrient composition, complicating the investigation of the role of fluid intake (12). Studies on fluid intake and UBC risk yield inconsistent results (13), and the association of fluid intake with UBC recurrence has only scarcely been investigated (14).

Therefore, we aimed to investigate the association of smoking and fluid intake with the risk of recurrence risk in a prospective cohort of newly diagnosed NMIBC patients.

Methods

Study design and patient population

We used data from a population-based, prospective cohort study, which was initiated to investigate the association of dietary and lifestyle habits with prognosis and HRQoL in NMIBC patients, named the UroLife study (Urothelial cancer: Lifestyle, prognosis and health-related quality of Life). Permission was asked from all urologists of the 22 participating hospitals to identify their eligible patients in the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organization (IKNL). Dutch speaking men and women between 18 and 80 years old with a primary NMIBC tumour (stage Ta, T1, Tis) diagnosed between April 1, 2014 and April 25, 2017 were identified

approximately 4 weeks after diagnosis and invited on behalf of their urologist to participate in this study. Only patients with a histologically confirmed NMIBC tumour that was surgically removed with a transurethral resection were invited. Patients were excluded if they had a previous cancer diagnosis in the last five years, positive lymph nodes, or distant metastases. For the current study, we included patients diagnosed up to March 18, 2016 for whom clinical data were collected in September 2017. Written informed consent was obtained from all participants. The UroLife study received ethical approval from the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494).

Lifestyle data collection – smoking and fluid intake

Patients completed self-reported web-based or paper-and-pencil questionnaires at six weeks (T1), twelve weeks (T2), and fifteen months (T3) after diagnosis. Web-based questionnaires were collected via the data collection tool of the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry (15). T1 referred to the situation before diagnosis up to 6 weeks after diagnosis, and T2 and T3 to the situation after diagnosis. The questionnaires included questions about socio-demographic characteristics (T1 only), smoking, alcohol consumption, body mass index (BMI), and other lifestyle and medical factors. At T2 and T3, patients filled out a paper-and-pencil four-day fluid and micturition diary as well. Only the T1 and T2 questionnaires and the T2 diary were used in the current study.

Smoking status was assessed by asking whether patients smoked at the time of filling out the questionnaire or if they had smoked in the past. Patients were categorized into never, former and current smokers at diagnosis. Patients who were current or former smokers were asked to indicate at what age they started smoking, the age or date they quit (when applicable), the average number of cigarettes smoked per day, and the duration of cigarette smoking. To evaluate the impact of smoking cessation, patients were categorized using both the T1 and T2 questionnaires into never smokers, former smokers who quit ≥10 years before diagnosis, former smokers who quit <10 years and ≥1 year before diagnosis, former smokers who quit between 1 year before and <3 months after diagnosis, and current smokers. For patients with missing data for T2, smoking status was only based on data for T1. Pack-years at diagnosis were calculated to describe cumulative smoking exposure, by multiplying duration of cigarette smoking in years with the average number of cigarettes smoked per day divided by 20. Fluid intake was measured with a four-day fluid and micturition diary. Patients filled out how much they drank on that day either in mL or in household measures, and average fluid intake in mL per day was calculated.

Lifestyle data collection – potential confounders

Educational level was categorized into low (primary, secondary, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), or high (university of vocational education, university). Status of

smoking pipe and/or cigar was assessed by asking whether patients smoked at the time of filling out questionnaire T1 or had smoked in the past. Patients were categorized into never, former and current pipe/cigar smokers at diagnosis. BMI (kg/m^2) was calculated based on self-reported weight and height, and patients were classified as normal weight (<25 kg/m^2), overweight (25-30 kg/m^2), and obese (>30 kg/m^2) (16). Alcohol consumption was assessed by questions about the number of week days and weekend days patients usually consumed alcoholic drinks, and the average number of drinks per week day or weekend day. The average number of alcoholic drinks per day was calculated. Average frequency of micturition was obtained from the four-day fluid and micturition diary in which patients filled out how many times per day they urinated.

Clinical data collection

Detailed clinical data were collected by well-trained data managers from IKNL from medical records in August 2017. These included TNM classification, grade, concomitant carcinoma in situ (CIS; yes/no), tumour multiplicity (solitary/multiple), immediate postoperative instillation of chemotherapy (yes/no), treatment (TURBT only, TURBT with intravesical chemotherapy, TURBT with intravesical immunotherapy), recurrence (yes/no), vital status, and duration of follow-up. Follow-up started at the date of TURBT for the primary tumour, or at the date of re-TURBT for patients who underwent a re-TURBT. A recurrence was defined as the clinical or pathological confirmation of a new bladder tumour or a tumour in the prostatic urethra of any grade, with at least one tumour-negative cystoscopy in between two tumour-positive cystoscopies, or at least three months between the primary tumour and the recurrence. Patients who received both adjuvant chemotherapy and immunotherapy were categorized according to which therapy they received most often. Patients were divided into low-, intermediate- and high-risk tumour categories based on the EAU guidelines (2), without taking into account the tumour size (not available) and the recurrent nature of the tumour (only primary tumours included).

Statistical analysis

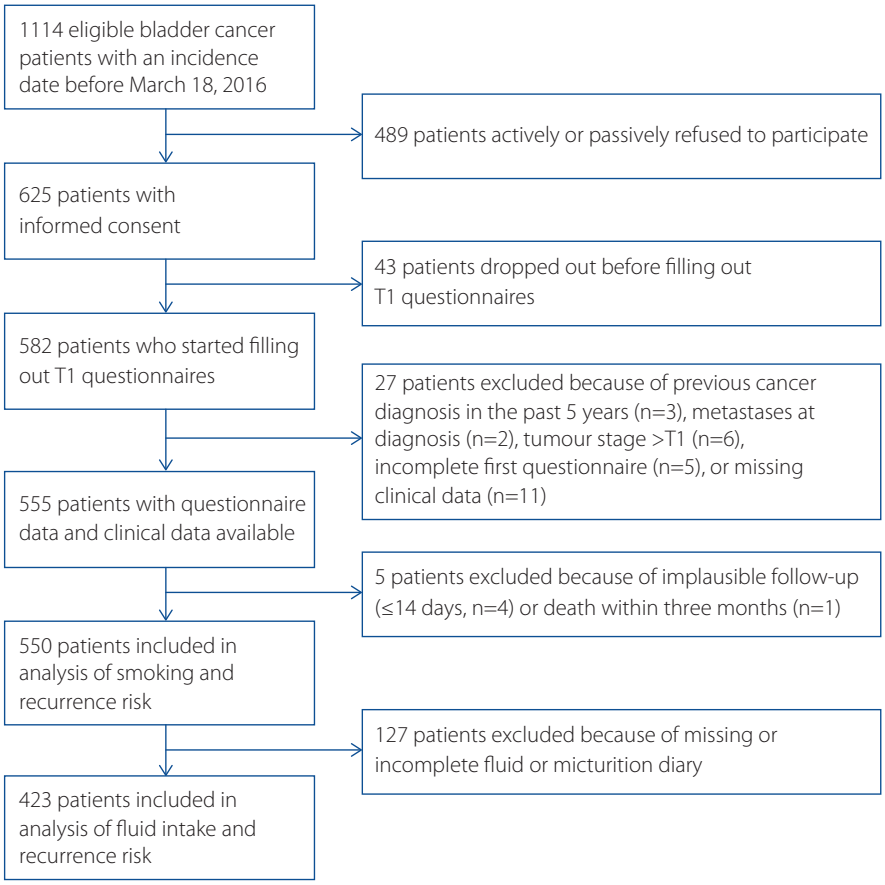
Descriptive statistics were calculated to summarize baseline characteristics in means with standard deviations or medians with interquartile ranges for continuous variables, and percentages for categorical variables, both for the total study population as well as by smoking status and by fluid intake in quartiles. Recurrence free survival (RFS) was defined as the time period between the date of TURBT or, if applicable, date of re-TURBT when a re-TURBT was performed, and the date of first recurrence, last check-up with clinical information, or death, whichever came first. Univariable and multivariable Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of smoking status at diagnosis, cumulative smoking exposure in pack-years (quartiles and continuous), smoking cessation, and fluid intake (quartiles and

continuous per 100 mL/day) with RFS. The proportional hazards assumption was tested by modeling time-dependent covariates and using Schoenfeld residuals (17). The assumption was fulfilled for all exposures of interest and potential covariates. All multivariable analyses were adjusted for age, gender, tumour grade and stage, and treatment modality. Other potential confounders did not change the risk estimates by 10% or more when tested in the model and were therefore not included in the final model, i.e. level of education, concomitant CIS, tumour multiplicity, immediate postoperative instillation of chemotherapy, BMI, alcohol consumption (in quartiles), fluid intake (in smoking analyses only), cigarette smoking status at diagnosis and micturition frequency (both in fluid intake analyses only). Tests for linear trends across quartiles of cumulative smoking exposure and fluid intake were conducted by adding the quartiles as ordinal variables to the model. Further, a sensitivity analysis was performed using date of initial TURBT as start of the follow-up for all patients as this is a more standard procedure. Stratified analyses were conducted for patients with a low- or intermediate-risk tumour versus patients with a high-risk tumour, and for fluid intake stratified by smoking status. Statistical significance was defined as a two-sided p-value of below 0.05. All statistical analyses were performed using IBM SPSS Statistics, version 22.

Results

Of all 1,114 eligible and invited NMIBC patients diagnosed up to March 18, 2016, 582 agreed to participate (response rate 52%) (Figure 1). Thereafter, 32 patients were excluded because they had a previous cancer diagnosis in the past five years (n=3), clinical data were not yet collected (n=11), they had metastases at diagnosis (n=2), a tumour stage >T1 (n=6), did not complete their first questionnaire (n=5), had a follow-up of ≤14 days (n=4), or died within three months after diagnosis (n=1). In total, 550 (95%) patients were included in the analyses on smoking, and 427 (73%) who completed the four-day diary were included in the analyses on fluid intake. Descriptive characteristics for the total study population and by smoking status at diagnosis are shown in Table 1, and descriptive characteristics by quartile of fluid intake are shown in Supplementary Table 1. Median age at diagnosis was 67 years, 79% of patients were men, and 74% had a Ta tumour. Median follow-up time was 19 months (range 0 - 37), 25 patients died (5%), and 103 patients (19%) developed at least one recurrence (78% pathologically confirmed; 22% coagulation). In 19 patients (3%), this concerned progression to a higher stage or grade. Most patients were former (58%) or current (26%) smokers. Median average fluid intake was 1840 mL (IQR 1500 – 2215). Descriptive characteristics differed slightly by smoking status. Current smokers were somewhat younger at diagnosis and less likely to have grade 3 tumours, while former smokers were more often obese compared to never smokers. Both current and former smokers were lower educated, had a higher alcohol consumption, and were more likely to

Figure 1 Flowchart of patients included in smoking, fluid intake and recurrence analyses.



have been diagnosed with multiple tumours and to have received a postoperative installation of chemotherapy compared to never smokers.

Univariable analysis did not show statistically significant associations with RFS for smoking status at diagnosis, cumulative smoking exposure, smoking cessation, or fluid intake (Table 2). Also, no associations with RFS were found in the multivariable models adjusted for age, gender, grade, stage, and treatment (Table 2). Risks of recurrence were non-statistically significant increased for former compared to never smokers (HR 1.41; 95% CI 0.79-2.51), but they were not increased for current smokers (HR 0.87; 95% CI 0.44-1.73). Among ever smokers, the highest compared to lowest cumulative smoking exposure was associated with a non-statistically significant increased risk of recurrence (HR 1.32; 95% CI

Table 1 Descriptive characteristics of 550 Dutch non-muscle-invasive bladder cancer patients according to smoking status at diagnosis.

		Smoking status at diagnosis		
	All (n=550)[1]	**Never (n=88)**	**Former (n=319)**	**Current (n=143)**
Age at diagnosis (y), median (IQR)	67 (60-72)	69 (60-74)	68 (61-73)	66 (58-71)
Sex, n (%)				
Female	116 (21%)	22 (25%)	58 (18%)	36 (25%)
Male	434 (79%)	66 (75%)	261 (82%)	107 (75%)
Educational level[2], n (%)				
Low	272 (50%)	36 (41%)	154 (48%)	82 (57%)
Medium	142 (26%)	21 (24%)	88 (28%)	33 (23%)
High	136 (25%)	31 (35%)	77 (24%)	28 (20%)
Body mass index, n (%)				
≤24.9	180 (33%)	33 (38%)	87 (27%)	60 (42%)
25.0-29.9	256 (47%)	42 (48%)	156 (49%)	58 (41%)
≥30.0	110 (20%)	12 (14%)	74 (23%)	24 (17%)
Age at starting smoking, median (IQR)	16 (15-18)[3]	N/A	16 (15-18)	16 (15-17)
Number of cigarettes per day, median (IQR)	15 (10-20)[3]	N/A	15 (10-20)	12 (10-17)
Number of years smoked, median (IQR)	30 (20-42)[3]	N/A	25 (17-35)	45 (35-50)
Cumulative smoking exposure[3,4]				
>0-10.9	114 (25%)	N/A	98 (31%)	16 (11%)
10.9-20.0	115 (25%)	N/A	81 (26%)	34 (24%)
20.0-34.1	113 (24%)	N/A	69 (22%)	44 (31%)
34.1-98.0	114 (25%)	N/A	68 (22%)	46 (33%)
Cumulative smoking exposure[3,5], median (IQR)	20 (10.9-34,1)	N/A	18 (10-30)	27 (17-38)
Average fluid intake in mL/day, median (IQR)	1840 (1500-2215)	1775 (1514-2020)	1884 (1547-2268)	1760 (1422-2158)
Alcohol consumption[6], median (IQR)	10 (6-16)	8 (4-14)	11 (6-17)	11 (6-16)
Micturition frequency, median (IQR)	8 (7-10)	8 (6-10)	8 (7-11)	7 (6-10)

Tumour stage				
Ta	405 (74%)	61 (69%)	236 (74%)	108 (76%)
T1[7]	146 (26%)	27 (31%)	83 (26%)	36 (25%)
Tumour grade[8]				
1	133 (24%)	25 (28%)	75 (24%)	33 (23%)
2	263 (48%)	38 (43%)	142 (45%)	83 (59%)
3	153 (28%)	25 (28%)	102 (32%)	26 (18%)
Concomitant CIS				
Yes	39 (7%)	5 (6%)	23 (7%)	11 (8%)
No	511 (93%)	83 (94%)	296 (93%)	132 (92%)
Tumor focality				
Solitary	373 (68%)	68 (77%)	214 (67%)	93 (65%)
Multiple	99 (18%)	8 (9%)	57 (18%)	34 (24%)
Unknown	76 (14%)	12 (14%)	48 (15%)	16 (11%)
Postoperative instillation of chemotherapy				
Yes	305 (55%)	41 (47%)	180 (56%)	81 (57%)
No	250 (45%)	47 (53%)	139 (44%)	62 (43%)
Therapy				
TURBT only	272 (50%)	45 (51%)	150 (47%)	77 (54%)
TURBT with chemotherapy	142 (26%)	23 (26%)	82 (26%)	37 (26%)
TURBT with immunotherapy	136 (25%)	20 (23%)	87 (27%)	29 (20%)

[1] Where scores do not total 100% this is due to missing values; [2] Low (primary -, secondary -, vocational education), intermediate (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university); [3] Based on former and current smokers only; [4] In pack-years, quartiles; [5] In pack-years, continuous; [6] In glasses per week; [7] T1 including 19 Tis tumours; [8] WHO 1973. Abbreviations: CIS: carcinoma in situ; IQR: interquartile range; m: months; TURBT: transurethral resection of the bladder tumour; y: years.

Table 2 Univariable and multivariable Cox proportional hazards regression models for the association of smoking, fluid intake, socio-demographic, and tumour characteristics with risk of recurrence in 550 non-muscle-invasive bladder cancer patients.

Variable[1]	*n*	*n* events (%)	Crude HR 95% CI	Adj. HR[2] 95% CI
Smoking status at diagnosis				
Never	88	14 (16%)	1.00 (ref)	1.00 (ref)
Former	319	68 (21%)	1.38 (0.78-2.45)	1.41 (0.79-2.51)
Current	143	21 (15%)	0.88 (0.45-1.73)	0.87 (0.44-1.73)
Cumulative smoking exposure[3,4]				
>0-10.9	114	22 (19%)	1.00 (ref)	1.00 (ref)
10.9-20.0	115	13 (11%)	0.56 (0.28-1.11)	0.57 (0.28-1.13)
20.0-34.1	113	24 (21%)	1.09 (0.61-1.95)	1.05 (0.58-1.89)
34.1-98.0	114	28 (25%)	1.34 (0.77-2.35)	1.32 (0.75-2.33)
			p-trend = 0.10	*p*-trend = 0.14
Cumulative smoking exposure[3,5]	456	87 (19%)	1.07 (0.95-1.21)	
Smoking cessation[6]				
Never	77	12 (16%)	1.00 (ref)	1.00 (ref)
Quit ≥10y before diagnosis	217	44 (20%)	1.32 (0.70-2.50)	1.33 (0.70-2.53)
Quit <10y-≥1y before diagnosis	57	14 (25%)	1.56 (0.72-3.38)	1.53 (0.71-3.32)
Quit <1y before-<3m after diagnosis	48	8 (17%)	1.05 (0.43-2.57)	0.97 (0.39-2.40)
Current	76	11 (14%)	0.84 (0.37-1.90)	0.85 (0.37-1.94)
Average fluid intake (mL/day)[4]				
694-1500	106	18 (17%)	1.00 (ref)	1.00 (ref)
1501-1840	106	15 (14%)	0.77 (0.39-1.53)	0.82 (0.41-1.64)
1841-2215	106	24 (23%)	1.34 (0.73-2.46)	1.35 (0.73-2.50)
2216-4131	105	20 (19%)	1.16 (0.61-2.18)	1.19 (0.63-2.27)
			p-trend = 0.33	*p*-trend = 0.33
Average fluid intake (per 100 mL/day)	423	77 (18%)	1.01 (0.97-1.05)	N/A
Age at diagnosis	550	103 (19%)	0.99 (0.97-1.01)	N/A
Sex				
Female	116	21 (18%)	1.00 (ref)	N/A
Male	434	82 (19%)	1.10 (0.68-1.78)	N/A
Tumour stage				
Ta	405	71 (18%)	1.00 (ref)	N/A
T1[7]	145	32 (22%)	1.20 (0.79-1.82)	N/A

Table 2 Continued.

Variable[1]	*n*	*n* events (%)	Crude HR 95% CI	Adj. HR[2] 95% CI
Tumour grade[8]				
1	133	22 (17%)	1.00 (ref)	N/A
2	263	51 (19%)	1.09 (0.66-1.79)	N/A
3	153	30 (20%)	1.09 (0.63-1.89)	N/A
Concomitant CIS				
No	511	92 (18%)	1.00 (ref)	N/A
Yes	39	11 (28%)	1.73 (0.92-3.23)	N/A
Tumour focality				
Solitary	375	61 (16%)	1.00 (ref)	N/A
Multiple	99	26 (26%)	**1.76 (1.11-2.78)**	N/A
Unknown	76	16 (21%)	1.33 (0.77-2.30)	N/A
Postoperative instillation of chemotherapy				
No	248	50 (20%)	1.00 (ref)	N/A
Yes	302	53 (18%)	0.82 (0.56-1.21)	N/A
Therapy				
TURBT only	272	47 (17%)	1.00 (ref)	N/A
TURBT with chemotherapy	142	36 (25%)	1.45 (0.94-2.23)	N/A
TURBT with immunotherapy	136	20 (15%)	0.79 (0.47-1.33)	N/A

[1] Where scores do not total 100% this is due to missing values; [2] HR adjusted for age, gender, stage, grade and treatment; [3] In pack-years, based on former and current smokers only; [4] In quartiles; [5] Continuous per 10 pack-years; [6] Only available for patients who filled in both T1 and T2 questionnaires; [7] T1 including n=19 Tis tumours; [8] WHO 1973. Abbreviations: CIS: carcinoma in situ; TURBT: transurethral resection of the bladder tumour.

0.75-2.33). When calculated for former and current smokers separately, the association was stronger in former, but absent in current smokers (Supplementary Table 2). A sensitivity analysis using date of initial TURBT as start of follow-up for all patients showed similar results (Supplementary Table 3). Results were not different for patients with high-risk tumours compared to patients with low- and intermediate-risk tumours (Table 3). The association between fluid intake and risk of recurrence did not differ according to smoking status (Supplementary Table 4).

Table 3 Multivariable Cox proportional hazards regression models for the association of smoking and fluid intake with recurrence among 351 low- and intermediate-risk, and 199 high-risk Dutch non-muscle-invasive bladder cancer patients

	Low- and intermediate-risk			High-risk		
Variable[1]	***n***	***n* events**	**Adj. HR[2] 95% CI**	***n***	***n* events**	**Adj. HR[2] 95% CI**
Smoking status at diagnosis						
Never	58	9	1.00 (ref)	30	5	1.00 (ref)
Former	193	40	1.45 (0.70-2.99)	126	28	1.39 (0.53-3.66)
Current	100	14	0.83 (0.36-1.93)	42	7	0.92 (0.29-2.92)
Cumulative smoking exposure[3,4]						
>0-10.9	71	13	1.00 (ref)	43	9	1.00 (ref)
10.9-20.0	74	9	0.61 (0.26-1.43)	41	4	0.43 (0.13-1.43)
20.0-34.1	70	14	1.02 (0.48-2.20)	43	10	0.98 (0.38-2.49)
34.1-98.0	75	17	1.23 (0.59-2.58)	39	11	1.44 (0.59-3.50)
			p-trend = 0.35			*p*-trend = 0.24
Smoking cessation						
Never	50	8	1.00 (ref)	27	4	1.00 (ref)
Quit ≥10y before diagnosis	126	26	1.41 (0.63-3.13)	91	18	1.40 (0.47-4.20)
Quit <10y-≥1y before diagnosis	39	7	1.12 (0.40-3.09)	18	7	3.01 (0.85-10.66)
Quit <1y before-<3m after diagnosis	28	4	0.71 (0.21-2.46)	20	4	1.31 (0.32-5.35)
Current	57	9	0.95 (0.36-2.47)	19	2	0.65 (0.12-3.59)
Average fluid intake in mL/day[4]						
694-1500	73	12	1.00 (ref)	33	6	1.00 (ref)
1501-1840	64	12	1.13 (0.50-2.53)	42	3	0.43 (0.10-1.79)
1841-2215	69	14	1.27 (0.58-2.78)	37	10	1.74 (0.59-5.14)
2216-4131	62	12	1.19 (0.53-2.66)	43	8	1.35 (0.45-4.06)
			p-trend = 0.62			*p*-trend = 0.22

[1] Where scores do not total 100% this is due to missing values; [2] HR adjusted for age, gender, stage, grade and treatment; [3] In pack-years, based on former and current smokers only; [4] In quartiles.

Discussion

This study found no evidence for a marked association of smoking or fluid intake with risk of NMIBC recurrence. Neither smoking status at diagnosis, cumulative smoking exposure, time since smoking cessation, nor fluid intake were statistically significantly associated with risk of recurrence.

A systematic review and a meta-analysis based on 13 historical cohort and two case-control studies found a 23% higher recurrence risk for current smokers at diagnosis and a 22% higher risk for former smokers (7). Risks were statistically significantly increased for only 5 and 3 out of the 15 studies, respectively. Our results did not support the hypothesis that current smokers have a higher recurrence risk than never smokers. Although results were not statistically significant, in our study, former smokers seemed to have a higher recurrence risk than never smokers. High vs. low cumulative smoking exposure also seemed to be associated with higher recurrence risk in former smokers. The absence of an association for current smokers could be explained by the limited statistical power of the current study, and larger prospective studies with longer follow-up time are required.

In our study, the distribution of low- and intermediate-risk versus high-risk tumours did not differ by smoking status, and results were not different according to tumour aggressiveness. Previous studies found that (former) smokers present with more aggressive tumours at diagnosis and therefore have a worse prognosis (18-20). In recent years, three molecular subtypes of NMIBC have been identified, i.e. urobasal, genomically unstable, and squamous-cell-carcinoma-like bladder cancer (21-23). The genomically unstable and squamous-cell-carcinoma-like subtypes are mostly found in patients with T1 tumours and have high risk of progression (22). Also, a study in muscle-invasive bladder cancer patients found that former and current versus never smoking was more strongly associated with the genomically unstable subtype than with urobasal tumours (24). Therefore, future studies should investigate whether molecular subtypes also modify and/or mediate associations of smoking and NMIBC prognosis.

The lack of association for smoking cessation may support the hypothesis of 'field cancerization', which offers an explanation for locally recurrent cancer (25, 26). Genetic alterations in stem cells caused by exposure to carcinogens, such as tobacco, can result in the replacement of fields of normal mucosa with preneoplastic cells eventually leading to disease recurrence when only the primary tumour has been removed (25, 26). However, the duration of follow-up of the current study may be inadequate to find associations of smoking cessation with risk of recurrence that may become apparent only after multiple years.

We did not find an association of average daily fluid intake with risk of recurrence. This was also found in a US study in 267 bladder cancer patients (14). However, the US study included patients on average 7 years after diagnosis, and the association of fluid intake with the risk of first recurrence could not be investigated. Other studies on fluid intake and bladder cancer prognosis are not yet available. Furthermore, it is possible that

the (hypothesized) protective or harmful effects of a higher fluid intake on bladder cancer risk and prognosis are not caused by the absolute amount of fluids consumed, but rather by their composition (27, 28). The types of fluids consumed may influence the concentrations of both carcinogenic and anti-carcinogenic substances in the urine, which is further determined by the nutritional content of the diet, but also by possible carcinogenic byproducts in food, and carcinogens in cigarettes (11, 12). The role of fluid intake is further complicated by the frequency of micturition, which could have an influence on both the concentration and the transit time of the urine. Although adjustment for micturition frequency did not change our results, we could not yet incorporate all these factors in our analysis. Therefore, it is recommended to study fluid intake, micturition, diet and smoking together to unravel their independent and potentially different effects.

Limitations of our study include the limited follow-up time and the low number of events, particularly in certain subgroups, which limited the power to detect statistically significant associations. Therefore, in particular stratified analyses should be considered purely exploratory. Adjuvant treatment with immunotherapy could have an influence on patient's fluid intake and micturition frequency (29). Eleven percent of the patients filled out their fluid- and micturition diary during treatment with immunotherapy, however, additional adjustment for treatment did not influence our results. Strengths of the current study include the population-based nature and the short time between diagnosis and inclusion in the study. This decreased the chance of bias with regard to the correct recall of smoking history. Also, our study population is comparable to the general NMIBC population with regard to stage, age, and gender (30). Further, prospective and extensive data collection made it possible to evaluate the effect of smoking cessation after diagnosis, and reduced the chance of misclassification with regards to time since smoking cessation. However, misclassification due to socially desirable answers cannot be ruled out. Information on fluid intake was collected from four-day diaries, which have the advantage that no recall is needed of the patients, and that amounts can be quantified. However, patients could have changed their habitual fluid intake because of the diary, or could have forgotten to write down every consumption. However, consumption is comparable to that measured by a food frequency questionnaire in a Dutch population (12).

This prospective cohort study with limited sample size and follow-up time did not find evidence of differences in risk of recurrence according to smoking status, cumulative smoking exposure or fluid intake. Further research is needed in larger prospective studies with longer follow-up times, also taking into account molecular subtypes. Bladder cancer patients should still be recommended to quit smoking based on its well-established general health benefits.

Contributors

EK, JAW, LAK, and AV designed the study. EW collected the data. EW and AV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EW and AV wrote the report. All authors contributed to the interpretation of the data, critically reviewed iterations of the manuscript and approved the final draft for submission.

Declaration of interests

The authors declare that they have no conflicts of interest related to the study.

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Supplementary Table 1 Descriptive characteristics of 423 Dutch non-muscle-invasive bladder cancer patients according to quartile of fluid intake 12 weeks after diagnosis.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Total fluid intake	≤1500	1501-1840	1841-2215	≥2216
Age at diagnosis (y), median (IQR)	69 (62-73)	68 (60-73)	67 (59-72)	65 (59-71)
Sex, n (%)				
Female	25 (24%)	25 (24%)	18 (17%)	28 (27%)
Male	81 (76%)	81 (76%)	88 (83%)	77 (73%)
Educational level[2], n (%)				
Low	58 (55%)	44 (42%)	49 (46%)	44 (42%)
Medium	23 (22%)	30 (28%)	34 (32%)	31 (30%)
High	25 (24%)	32 (30%)	23 (22%)	30 (29%)
Body mass index, n (%)				
≤24.9	33 (31%)	32 (%)	37 (%)	34 (%)
25.0-29.9	48 (45%)	55 (%)	46 (%)	50 (%)
≥30.0	24 (%)	19 (%)	23 (%)	21 (%)
Smoking status at diagnosis, n (%)				
Never	16 (15%)	22 (21%)	20 (19%)	10 (10%)
Former	60 (57%)	59 (56%)	62 (59%)	73 (70%)
Current	30 (28%)	25 (24%)	24 (23%)	22 (21%)
Age at starting smoking[3], median (IQR)	16 (15-18)	16 (15-17)	16 (15-18)	16 (14-18)
Number of cigarettes per day[3], median (IQR)	14 (10-20)	12 (10-16)	13 (9-19)	15 (10-20)
Number of years smoked[3], median (IQR)	31(24-46)	35 (20-44)	30 (19-40)	23 (15-38)
Cumulative smoking exposure[3,4]				
>0-10.9	22 (25%)	23 (27%)	20 (24%)	26 (28%)
10.9-20.0	15 (17%)	23 (27%)	29 (34%)	25 (27%)
20.0-34.1	28 (32%)	20 (24%)	18 (21%)	23 (25%)
34.1-98.0	23 (26%)	18 (21%)	18 (21%)	20 (21%)

Cumulative smoking exposure[3,5], median (IQR)	25 (11-36)	20 (10-31)	18 (11-31)	20 (10-31)
Alcohol consumption[6], median (IQR)	7 (5-13)	8 (6-14)	12 (6-17)	14 (7-21)
Micturition frequency, median (IQR)	7 (6-10)	7 (6-9)	8 (7-11)	9 (7-11)
Tumour stage				
Ta	82 (77%)	77 (73%)	79 (75%)	77 (73%)
T1[7]	24 (24%)	29 (27%)	27 (26%)	28 (27%)
Tumour grade[8]				
1	28 (26%)	21 (20%)	29 (27%)	25 (24%)
2	54 (51%)	50 (47%)	50 (47%)	42 (40%)
3	24 (23%)	35 (33%)	27 (26%)	38 (36%)
Concomitant CIS				
Yes				
No				
Tumor focality				
Solitary	74 (70%)	75 (71%)	65 (61%)	70 (67%)
Multiple	18 (17%)	15 (14%)	26 (25%)	18 (17%)
Unknown	14 (13%)	16 (16%)	15 (14%)	17 (16%)
Postoperative instillation of chemotherapy				
Yes	62 (59%)	60 (57%)	59 (56%)	55 (52%)
No	44 (42%)	46 (43%)	47 (44%)	50 (48%)
Therapy				
TURBT only	61 (58%)	49 (46%)	47 (44%)	44 (42%)
TURBT with chemotherapy	25 (24%)	24 (23%)	35 (33%)	30 (29%)
TURBT with immunotherapy	20 (19%)	33 (31%)	24 (23%)	31 (30%)

[1] Where scores do not total 100% this is due to missing values; [2] Low (primary -, secondary -, vocational education), intermediate (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university); [3] Based on former and current smokers only; [4] In pack-years, quartiles; [5] In pack-years, continuous; [6] In glasses per week; [7] T1 including 19 Tis tumours; [8] WHO 1973. Abbreviations: CIS: carcinoma in situ; IQR: interquartile range; m: months; TURBT: transurethral resection of the bladder tumour; y: years.

Supplementary Table 2 Multivariable Cox proportional hazards regression models for the association of cumulative smoking exposure with risk of recurrence for former and current smokers separately compared to never smokers.

Variable[1]	*n*	*n* events	Adj. HR[2] 95% CI
Cumulative smoking exposure former smokers[3,4]			
Never smokers	88	14	1.00 (ref)
>0-14.4	125	23	1.24 (0.64-2.41)
14.4-29.2	104	20	1.22 (0.61-2.43)
29.2-98.0	87	24	2.09 (1.07-4.06)
			p-trend = 0.04
Cumulative smoking exposure current smokers[3,4]			
Never smokers	88	14	1.00 (ref)
>0-14.4	26	5	1.17 (0.39-3.53)
14.4-29.2	49	4	0.43 (0.14-1.34)
29.2-98.0	64	11	0.97 (0.43-2.22)
			p-trend = 0.66

[1] Where scores do not total 100% this is due to missing values; [2] HR adjusted for age, gender, stage, grade and treatment; [3] In pack-years; [4] Ever smokers in tertiles with never smokers as reference category.

Supplementary Table 3 Sensitivity analyses of smoking and fluid intake with start of follow-up at date of initial TURBT.

Variable[1]	*n*	*n* events	Adj. HR[2] 95% CI
Smoking status at diagnosis			
Never	88	14	1.00 (ref)
Former	319	68	1.39 (0.78-2.48)
Current	142	21	0.85 (0.43-1.69)
Cumulative smoking exposure[3,4]			
>0-10.9	114	22	1.00 (ref)
10.9-20.0	115	13	0.57 (0.28-1.12)
20.0-34.1	113	24	1.04 (0.58-1.88)
34.1-98.0	113	28	1.32 (0.75-2.33)
			p-trend = 0.14
Smoking cessation			
Never	77	12	1.00 (ref)
Quit ≥10y before diagnosis	217	44	1.31 (0.69-2.48)
Quit <10y-≥1y before diagnosis	57	14	1.52 (0.70-3.29)
Quit <1y before-<3m after diagnosis	48	8	0.95 (0.38-2.36)
Current	76	11	0.82 (0.36-1.88)
Average fluid intake in mL/day[4]			
694-1500	106	18	1.00 (ref)
1501-1840	106	15	0.83 (0.42-1.66)
1841-2215	106	24	1.35 (0.73-2.51)
2216-4131	105	20	1.20 (0.63-2.28)
			p-trend = 0.33

[1] Where scores do not total 100% this is due to missing values; [2] HR adjusted for age, gender, stage, grade and treatment; [3] In quartiles; [4] In pack-years.

Supplementary Table 4 Multivariable Cox proportional hazards regression models for the association of fluid intake with recurrence among Dutch non-muscle-invasive bladder cancer patients stratified for smoking status at diagnosis.

	Never smokers			Former smokers			Current smokers		
Variable[1]	***n***	***n* events**	**Adj. HR[2] 95% CI**	***n***	***n* events**	**Adj. HR[2] 95% CI**	***n***	***n* events**	**Adj. HR[2] 95% CI**
Average fluid intake in mL/day[3]									
694-1500	16	1	1.00 (ref)	60	11	1.00 (ref)	30	6	1.00 (ref)
1501-1840	22	3	3.61 (0.34-38.32)	59	9	0.76 (0.31-1.85)	25	3	0.79 (0.18-3.51)
1841-2215	20	5	5.89 (0.55-63.70)	62	16	1.38 (0.62-3.08)	24	3	0.66 (0.16-2.75)
2216-4131	10	1	2.69 (0.14-53.72)	73	14	1.09 (0.49-2.43)	22	5	1.65 (0.46-5.88)
			p-trend = 0.32			*p*-trend = 0.56			*p*-trend = 0.59

[1] Where scores do not total 100% this is due to missing values; [2] HR adjusted for age, gender, stage, grade and treatment; [3] In quartiles.

4

Dietary patterns and risk of recurrence and progression in non-muscle-invasive bladder cancer

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Abstract

The association of dietary factors with urinary bladder cancer prognosis has scarcely been investigated, and results of studies conducted to date are inconsistent. We investigated whether empirically derived dietary patterns are associated with risks of recurrence and progression in non-muscle invasive bladder cancer patients. Data from 595 newly diagnosed non-muscle-invasive bladder cancer patients from an ongoing prospective cohort study were used to derive dietary patterns using exploratory factor analysis. Factor scores were calculated and then categorized in sex-specific tertiles. Multivariable adjusted proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals for the associations between tertiles of adherence to the dietary patterns and risks of recurrence and progression. We identified four dietary patterns: "fruits and vegetables", "Western", "low-fat", and "Tex-Mex". Patients in the highest tertile of adherence to the Western pattern experienced a 1.48 times higher risk of recurrence (95% CI 1.06-2.06) compared to patients in the lowest tertile. No statistically significant associations of a Western diet with risk of progression, or of the other dietary patterns with risk of recurrence and progression were found. Overall, we found that adherence to a Western diet was associated with a higher risk of recurrence but further studies are needed to confirm our findings.

Introduction

Urinary bladder cancer (UBC) is a common malignancy with an estimated 77,000 new cases and over 16,000 deaths occurring in 2016 in the United States (1). In patients with non-muscle invasive bladder cancer (NMIBC), approximately 75% of all UBC, frequent recurrences that necessitate an intensive follow-up program pose a large burden on quality of life and health care budget (2, 3). In clinical practice, tumor characteristics are used to predict the risk of recurrence and disease progression but the predictive ability of these characteristics is limited (4).

Diet has been linked to the risk of many malignancies (5), but its role in UBC etiology is still inconclusive. A higher fluid intake is hypothesized to be protective in some studies (6-8), as are certain fruits and vegetables (9, 10). On the other hand, (barbecued) meat, pork, and total fat might be associated with a higher risk of developing UBC (11-14). However, a recent comprehensive meta-analysis on UBC only found probable evidence that arsenic in drinking water increases risk and limited suggestive evidence that greater consumption of fruit and vegetables and tea decreases risk (15).

The association of dietary factors with UBC prognosis is largely unknown. Several observational studies on diet and intervention studies with dietary supplements have been conducted, but they either found no associations (16-21) or had inconsistent results (22-25). Most of them had a limited sample size and other methodological shortcomings. Thus, more investigation in this area is needed.

Since diet consists of many components that are correlated and can potentially interact with each other in a complex way, it may be better to evaluate dietary patterns rather than single factors when estimating diet-disease associations (26). Factor analysis is a suitable method to identify dietary patterns which can then be used to predict cancer risk and prognosis (27-29). It is a method that tries to reduce a large amount of observed, correlated variables (here: food items) to a smaller amount of underlying variables, called factors (dietary patterns), that still explain most of the variation in the dataset. However, hardly any study made use of factor analysis to explore associations between dietary intake patterns and UBC risk (30), and to our knowledge, no studies to date have investigated dietary patterns in relation to UBC prognosis. Therefore, we investigated whether empirically derived dietary patterns were associated with risk of recurrence and progression in a large ongoing prospective study of newly diagnosed NMIBC patients.

Methods

Subjects

This study included patients enrolled at The University of Texas M.D. Anderson Cancer Center and the Scott Department of Urology at Baylor College of Medicine from 1995 onwards. The procedures for subject recruitment and eligibility criteria have been described in detail elsewhere (31). In short, patients had histologically confirmed NMIBC and did not undergo previous treatment with chemotherapy or radiotherapy. There were no restrictions on age and gender. The study was approved by the M.D. Anderson and Baylor College of Medicine Institutional Review Boards. All patients provided written informed consent prior to participation in the study.

Exclusions and eligibility

Inclusion and exclusion criteria for this study have been previously described in detail (32). We additionally excluded participants with outlying total energy intake by removing men (*n*=21) and women (*n*=2) with values outside the range between the 25th percentile minus 1.5 times the interquartile range and the 75th percentile plus 1.5 times the interquartile range. Minority participants (*n*=48) were also excluded from the present study due to their limited number, leaving 595 non-Hispanic white patients for inclusion.

Data collection

Data were collected through a 45-minute structured interview and included demographic characteristics, smoking history, family history, occupational history and exposures, and medical history. A participant who had never smoked or had smoked less than 100 cigarettes in his or her lifetime was defined as a never smoker. A participant who had smoked at least 100 cigarettes in his or her lifetime but had quit more than 12 months before diagnosis was classified as a former smoker. Current smokers were those who were currently smoking or had quit less than 12 months before diagnosis. Body mass index (kg/m^2) was calculated from measured weight and height at diagnosis.

Data on dietary intake in the year prior to diagnosis were collected through another 45-minute interview in which a previously validated modified version of the National Cancer Institute Health Habits and History Questionnaire was administered (33). This semi quantitative food frequency questionnaire (FFQ) consists of questions on frequency and portion size of food and beverage items, including ethnic foods frequently consumed in the Houston area, and contains an open-ended section regarding dietary behaviors such as dining in restaurants and food preparation methods. Total energy intake in calories and amount consumed in grams per day were estimated for each food or beverage item using the US Department of Agriculture National Nutrient Database for Standard Reference (34). Calculations for multi-ingredient food items not included in Standard Reference were bases on the US Department of Agriculture Food and Nutrient Database for Dietary Studies (35).

Study staff obtained tumor characteristics and information on treatment, recurrence and progression through detailed chart review of medical records. In this study, recurrence was defined as a new bladder tumor following a previous negative follow-up cystoscopy. Progression was defined as the transition from NMIBC to muscle-invasive or metastatic tumors (31).

Food grouping and dietary pattern analysis

Among the 181 initial food and beverage items, we excluded 19 that were eaten by less than 5% of our study population (sprouts, soy beans, fava beans, rice milk, soy milk, bottled sweetened water, vegetarian chili, tofu, meat substitutes, soy nuts and soy snacks, low-fat bacon, dairy products made of tofu, bread made with soy flour, bread made with flaxseed, Miso soup, tempeh, soy cheese, textured vegetable protein, and metamucil® or psyllium seeds). Twenty-seven foods were grouped into seven predefined food groups according to current US Department of Agriculture food group guidelines or groups with similar nutritional profile. After these steps, there remained 135 single items or food groups (measured in gram/day) to be included in the factor analysis.

We evaluated the correlation matrix of the foods to determine its factorability through both visual inspection of the matrix and the statistical Kayser-Meyer-Olkin measure of sampling adequacy. In order to obtain an approximately normal distribution, we performed a log-transformation of all of the remaining 135 food items or food groups after we added 1 gram/day to all items to avoid food intake values of zero. We then adjusted all food intakes for energy intake with the residual method (36).

We subsequently conducted exploratory factor analysis with the FACTOR command in STATA 14.0 (StataCorp LP, College Station, Texas) to reduce the number of food items and food groups into a small number of factors that explained the maximum proportion of variance in the data. We used the orthogonal varimax rotation and the Horst method to create uncorrelated and normally distributed factors (37). For the identification of factors that best represented the data, we considered the scree plot, eigenvalues and interpretability of the factors. Foods or food groups with absolute loadings greater than 0.30 on a given factor were considered as contributing to that factor.

Retained factors were interpreted as dietary patterns and named after the items that contributed most to that factor. Dietary pattern factor scores were calculated and then categorized in sex-specific tertiles for analysis with recurrence and progression. The first tertile of each dietary pattern corresponded to the lowest factor score or level of adherence to that dietary pattern.

Statistical analysis

Baseline characteristics of the participants were presented separately by tertile for each of the retained dietary patterns. Proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CI for the associations of tertiles of adherence to the

dietary patterns with recurrence and with progression. All models were adjusted for age (continuous) and sex. A multivariable model was further adjusted for education (≤12 years; 13-15 years; ≥16 years), income (<$25,000/year; $25,000-$50,000; ≥$50,000), body mass index (continuous), smoking status (never, former, current) and intensity (pack-years, continuous), total energy intake (kcal/day, continuous), stage (Ta; T1; Tis), grade (1; 2; 3), presence or absence of concomitant carcinoma in situ, tumor multiplicity (1, 2, ≥3), and treatment (transurethral resection (TUR) only; TUR + induction Bacillus Calmette-Guerin (BCG); TUR + maintenance BCG; other intravesical chemotherapy). Tests for linear trends across tertiles of dietary patterns were conducted by adding the tertiles as an ordinal variable in the model. A sensitivity analysis was performed excluding all patients who experienced an event (e.g. recurrence, progression) within 90 days after diagnosis.

Results

The Kayser-Meyer-Olkin measure was equal to 0.72, suggesting adequate sample size relative to the number of dietary items for conducting factor analysis. Four dietary patterns were derived from the factor analysis: "fruits and vegetables", "Western", "low-fat", and "Tex-Mex" (Table 1). Names of the patterns were based on the foods that had absolute factor loadings of 0.30 or higher on that factor. Together these factors represented 37% of the total variance.

Participants were followed-up for a median of 65.7 months. During this period, 317 patients recurred and 120 patients experienced progression to muscle invasive bladder cancer or metastatic tumors. Detailed baseline characteristics of all 595 NMIBC patients by tertile for the Western dietary pattern are summarized in Table 2. Patients adhering most to a Western dietary pattern were older, had a higher body mass index, and smoked more pack-years. Also, coronary heart disease and hypertension were more frequent in the highest tertile, and patients seemed to be lower educated and in the lower and middle income classes. Characteristics by tertile for the other patterns are included as a supplement (Supplementary Table 1-3).

Age- and sex-adjusted, and multivariable-adjusted results for the association of dietary patterns and NMIBC with recurrence and with progression are shown in Table 3. No statistically significant associations were observed in the minimally-adjusted model. Greater adherence to a Western diet was positively associated with recurrence after multivariable adjustment. Patients in the highest tertile of adherence had a 1.48 times higher risk of recurrence than patients in the lowest tertile (95% CI 1.06-2.06, P for trend 0.03). There seems to be a trend towards higher risk of progression as well with a higher intake of a Western diet (HR1.56, 95% CI 0.91-2.65, P for trend 0.10). No significant associations with risk of recurrence and progression were found for the other dietary patterns.

Table 1 Rotated factor pattern loadings[a] for 135 food items or food groups assessed at recruitment in a cohort study of non-muscle invasive bladder cancer patients, Houston, Texas.

Food item	Fruits and vegetables pattern (Factor 1)[b]	Food item	Western pattern (Factor 2)[b]	Food item	Low-fat pattern (Factor 3)	Food item	Tex-Mex pattern (Factor 4)
Deep yellow vegetables	0.56	Cornbread	0.48	Light salad dressing	0.61	Mexican food	0.59
Berries	0.53	Black eyed peas	0.46	Light mayonnaise	0.48	Salsa	0.55
Cruciferous vegetables	0.48	Fried chicken	0.45	Low fat dairy	0.43	Flour tortilla	0.40
Celery	0.47	Fried fish	0.40	Light cookies	0.43	Salty snacks with dips or toppings	0.39
Melons	0.47	Okra	0.38	Light lunchmeat	0.42	Barbecue	0.38
Dark leafy vegetables	0.46	Gravy	0.38	Salty snacks without dips or toppings	0.39	Avocado	0.37
Peaches	0.46	Canned chili	0.38	Light hotdogs	0.32	Refried beans	0.34
Asparagus	0.46	Green beans	0.36	Chicken	0.30	Pizza	0.33
Strawberries	0.45	French fries and fried potatoes	0.35	Bacon	-0.31	Corn tortilla	0.33
Apples	0.40	Bacon	0.35	Soda	-0.32	Beef	0.30
Lentil, pea and bean soup	0.39	Corn	0.34	Hotdogs	-0.33		
Mushrooms	0.39	Hamburgers	0.33	Eggs	-0.34		
Pineapples	0.38	Beef stew or potpie	0.33	Lunchmeat	-0.39		

Table 1 Continued.

Food item	Fruits and vegetables pattern (Factor 1)[b]	Food item	Western pattern (Factor 2)[b]	Food item	Low-fat pattern (Factor 3)	Food item	Tex-Mex pattern (Factor 4)
Oranges	0.38	Pork and ham	0.32	Mayonnaise	-0.45		
Kiwis	0.38	Potatoes	0.32	Salad dressing	-0.46		
Pears	0.37	Sausages	0.32	Dairy	-0.48		
Tomatoes	0.37	Wine	-0.39				
Garlic	0.37						
Vegetable soup	0.35						
Beets	0.35						

[a] The table shows any food item or food group with a factor loading greater than 0.30

[b] For Factor 1 and 2, only the top 20 factor loadings are displayed

Table 2 Baseline Characteristics of 595 NMIBC Patients by Tertiles of Western Dietary Pattern[a]

	Western Dietary Pattern					
	Tertile 1 (n=199)		Tertile 2 (n=199)		Tertile 3 (n=197)	
	No.	%	No.	%	No.	%
Age[b], years	62.5 (10.4)		63.3 (12.1)		66.0 (9.4)	
Follow up[b], months	79.9 (39.0)		70.7 (38.1)		63.2 (40.5)	
Sex						
Male	159	79.9	158	79.4	158	80.2
Female	40	20.1	41	20.6	39	19.8
Body mass index[b,c], continuous	27.5 (4.2)		27.9 (4.7)		29.1 (6.1)	
Body mass index[d]						
Underweight	1	0.5	1	0.5	2	1.0
Normal weight	54	27.1	53	26.6	43	21.8
Overweight	97	48.7	85	42.7	82	41.6
Obese	45	22.6	59	29.7	70	35.5
Unknown/Missing	2	1.0	1	0.5	0	0.0
Energy[b], kcal	2322.9 (1053.0)		2319.8 (975.8)		2354.0 (847.1)	
Smoking status						
Never smoker	67	33.7	53	26.6	52	26.5
Former smoker	98	49.3	106	53.3	91	46.4
Current smoker	34	17.1	40	20.1	53	27.0
Smoking[b], pack years	32.3 (27.3)		38.4 (27.8)		46.8 (33.9)	
Education						
≤12 years	31	15.6	45	22.6	79	40.1
13-15 years	46	23.1	64	32.2	64	32.5
≥16 years	118	59.3	89	44.7	51	25.9
Unknown/Missing	4	2.0	1	0.5	3	1.5
Income[e]						
<25.000	11	5.5	17	8.5	31	15.7
25.000-50.000	29	14.6	29	14.6	50	25.4
≥50.000	127	63.8	114	57.3	79	40.1
Unknown/Missing	32	16.1	39	19.6	37	18.8
Stage						
Tis	94	47.2	82	41.2	81	41.1
Ta	9	4.5	11	5.5	13	6.6
T1	94	47.2	102	51.3	102	51.8
Unknown/Missing	2	1.0	4	2.0	1	0.5

Table 2 Continued.

	Western Dietary Pattern					
	Tertile 1 (n=199)		Tertile 2 (n=199)		Tertile 3 (n=197)	
	No.	%	No.	%	No.	%
Grade						
1	7	3.5	6	3.0	5	2.5
2	65	32.7	62	31.2	66	33.5
3	120	60.3	118	59.3	121	60.8
Unknown/Missing	7	3.5	13	6.5	5	2.5
Treatment						
TUR	58	29.2	59	29.7	48	24.4
TUR + iBCG[f]	59	29.7	52	26.1	54	27.4
TUR + mBCG[g]	47	23.6	53	26.6	53	26.9
Other	35	17.6	35	17.6	42	21.3
Focality						
One tumor	89	44.7	68	34.2	58	29.4
Two tumors	18	9.1	19	9.6	18	9.1
≥ three tumors	41	20.6	49	24.6	53	26.9
Unknown/Missing	51	25.6	63	31.7	68	34.5
Concomitant CIS[h]						
Present	72	36.2	69	34.7	59	30.0
Not present	116	58.3	114	57.3	119	60.4
Unknown/Missing	11	5.5	16	8.0	19	9.6
Medical history[i]						
Coronary heart Disease	28	14.1	33	16.6	48	24.4
Hypertension	75	37.7	95	47.7	103	52.3
Diabetes Mellitus type II	17	8.5	30	15.1	44	22.3
Other comorbidities[j]	69	11.6	61	10.3	96	16.1

[a] For all patterns, the higher tertiles are indicative of higher intake of that diet; [b] Mean (SD); [c] Weight (kg)/height (m^2); [d] <18.5=underweight, 18.5-24.9=normal weight, 25-29.9=overweight, ≥30=obese; [e] Income per year; [f] induction BCG; [g] maintenance BCG; [h] Carcinoma in situ; [i] number and percentage of patients in whom disease is present; [j] Chronic obstructive pulmonary disease, peptic disease, liver disease, chronic renal failure, renal stones, diseases of the central nervous system, diseases of the endocrine system, benign hyperplasia

Table 3 Adjusted Associations of Dietary Pattern Score (in Tertile) with risk of Recurrence and Progression of 595 NMIBC Patients.

Dietary pattern and tertile score	Recurrence/ Total no. of patients	HR (95% CI)	HR (95% CI)	Progression/ Total no. of patients	HR (95% CI)	HR (95% CI)
		Adjusted for age and sex	Multivariable adjusted[a]		Adjusted for age and sex	Multivariable adjusted[a]
Fruits and vegetables pattern						
Tertile 1 (low)	97/198	1 (referent)	1 (referent)	40/198	1 (referent)	1 (referent)
Tertile 2	97/200	1.03 (0.77-1.39)	1.08 (0.79-1.47)	40/200	1.07 (0.67-1.71)	1.16 (0.70-1.92)
Tertile 3(high)	84/197	0.85 (0.62-1.16)	0.90 (0.64-1.26)	40/197	0.95 (0.58-1.57)	1.05 (0.61-1.82)
P for trend		0.30	0.56		0.85	0.87
Western pattern						
Tertile 1 (low)	90/199	1 (referent)	1 (referent)	37/199	1 (referent)	1 (referent)
Tertile 2	90/199	1.02 (0.75-1.37)	1.03 (0.75-1.42)	40/199	1.22 (0.75-2.00)	1.23 (0.73-2.06)
Tertile 3(high)	98/197	1.25 (0.93-1.68)	**1.48 (1.06-2.06)**	43/197	1.41 (0.87-2.28)	1.56 (0.91-2.65)
P for trend		0.14	**0.03**		0.16	0.10
Low-fat pattern						
Tertile 1 (low)	102/199	1 (referent)	1 (referent)	47/199	1 (referent)	1 (referent)
Tertile 2	87/198	0.89 (0.67-1.19)	0.96 (0.71-1.31)	38/198	0.76 (0.48-1.20)	0.78 (0.47-1.28)
Tertile 3(high)	89/198	0.84 (0.62-1.12)	0.86 (0.63-1.18)	35/198	0.70 (0.44-1.11)	0.74 (0.44-1.23)
P for trend		0.23	0.37		0.12	0.24
Tex-Mex pattern						
Tertile 1 (low)	95/199	1 (referent)	1 (referent)	40/199	1 (referent)	1 (referent)
Tertile 2	98/199	1.04 (0.78-1.39)	1.08 (0.79-1.48)	50/199	1.39 (0.89-2.19)	1.27 (0.79-2.06)
Tertile 3(high)	85/197	0.85 (0.63-1.16)	0.92 (0.66-1.27)	30/197	0.75 (0.44-1.28)	0.70 (0.40-1.24)
P for trend		0.32	0.59		0.36	0.26

[a] Adjusted for age, sex, education, income, body mass index, smoking status and intensity, total energy intake, grade, tumor multiplicity, concomitant carcinoma in situ, and treatment

A sensitivity analysis excluding all patients who experienced recurrence or progression within 90 days after diagnosis did not materially alter these associations (data not shown). The association of dietary patterns with risk of recurrence did not differ by tumor grade. When the analyses were restricted to BCG-treated patients only, similar associations with risk of recurrence and progression were found (Supplementary Table 4).

Discussion

In this study, we observed that adherence to a Western dietary pattern, high in fried food and red and processed meat was associated with a higher risk of NMIBC recurrence. No statistically significant associations were observed for the fruits and vegetables pattern, low-fat pattern, and Tex-Mex pattern.

To our knowledge, we are the first to study the association of dietary patterns with UBC prognosis. As is the case for all single studies, it is not possible to draw conclusions based on our findings only. However, several mechanisms that are known or proposed to play a role in cancer prognosis might explain and support our results. Potentially harmful substances present in the Western diet, such as N-nitroso-compounds, polycyclic aromatic hydrocarbons and heterocyclic aromatic amines in red meat, are excreted in the urine. Therefore they come into close contact with the inner lining of the bladder wall and may directly exert a carcinogenic effect on urothelial cells (38, 39). Our finding that having a Western diet is associated with higher risk of NMIBC recurrence might endorse this theory. A recent meta-analysis on dietary patterns and cancer prognosis also showed an association of a Western diet with risk of recurrence for colorectal cancer but not for breast cancer (40).

Likewise, potentially beneficial substances from fruits and vegetables such as antioxidants, phenols, flavonoids and phytochemicals may be involved in carcinogenesis by acting directly on the bladder epithelium when excreted in the urine (10, 41). Furthermore, they may be involved in numerous other carcinogenic pathways, one of which is the reduction of oxidative stress and DNA damage caused by free radicals (14). Nevertheless, results from factor analysis underpinning these hypotheses are scarce. In this study, we did not find an association of a fruits and vegetables pattern with risk of recurrence. This is in line with a US study in 239 NMIBC and MIBC patients, which found no associations for total fruit and vegetables consumption with cancer-specific mortality, except for an inverse association of more than one compared to less than one serving of raw broccoli per month (24). Also for other cancers, no associations for a healthy/prudent dietary pattern with risk of recurrence were found in a recent meta-analysis of four studies conducted in breast, colorectal or head and neck cancer patients (40).

The Tex-Mex pattern is based on an American regional cuisine which is quite specific for the area where this study was conducted. Except for two studies on renal cancer risk

(42) and lung cancer risk (43), no studies reported about this pattern before. The Tex-Mex pattern contains potentially beneficial components such as legumes, as well as potentially harmful components such as red meat and pizza. The effects of the nutrients in these food items might neutralize each other, possibly explaining why we did not find an association.

Lastly, we found the dietary pattern 'low-fat' in our population. Patients adhering most to the low-fat pattern do not necessarily eat healthy but always choose for the low-fat or diet option. None of the food items contributing most to this pattern are directly linked to cancer, which may explain why we did not find an association. However, a dietary intervention trial focusing on fat reduction in early-stage breast cancer patients reported an improved relapse-free survival in the intervention compared to the control group. This finding supports that fat reduction could possibly lower risk of tumor recurrence (44).

This study had several strengths. Most importantly, we are the first to study the association of dietary patterns with UBC prognosis. Since UBC is a common malignancy with a high burden on quality of life and the health care budget, it is important to investigate other strategies to manage the disease besides treatment. Also, we made use of a validated FFQ that provided detailed information and was able to capture the cultural differences in eating habits in the Houston area. Furthermore, we derived dietary patterns using exploratory factor analysis, which we think is the right method considering the lack of confirmed findings in the field of diet and bladder cancer prognosis. The variation explained by the four patterns we derived is relatively low, but not uncommonly so when comparing our results with that of other studies with three or four dietary patterns (45). Also, the Western and the fruits and vegetables patterns have been consistently identified in literature. There was little overlap between patients in the same tertile for different dietary patterns, indicating that energy intake did not play a role of major importance in the derivation of factors (Supplementary figures 1-4).

Potential limitations include all weaknesses associated with the use of self-reported measurements such as recall bias and the underreporting of energy intake (46). Furthermore, food intake was assessed once and shortly after diagnosis, and referred to the year before diagnosis. Post diagnostic diet and dietary changes after diagnosis were not assessed but may be most relevant with respect to risk of recurrence and progression. Since we decided to include only non-Hispanic whites in our analysis, the associations we found may not be generalizable to patients from other ethnic backgrounds. Even though we had a reasonable sample size of 595 NMIBC patients, statistical power for detecting an association with progression was limited. The stratified analyses had limited power as well, which may explain why we did not find any differences by tumor grade. Lastly, we cannot rule out any residual and unmeasured confounding that may to some extent explain the observed associations.

In summary, the most important finding of this study is that having a more Western dietary pattern was associated with a higher risk of NMIBC recurrence. This finding

supports the hypothesis that a Western diet plays a role in the etiology and prognosis of cancer. Since diet-disease associations are complex and causality cannot be drawn from this observational study, further research is needed to confirm our findings and elucidate the association of diet with both muscle invasive and non-muscle invasive UBC prognosis.

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Online Supporting Material

Supplementary table 1 Baseline Characteristics of 595 Non-Muscle Invasive Bladder Cancer Patients by Tertiles of Fruits and Vegetables Dietary Pattern[a]

	Fruits and Vegetables Pattern					
	Tertile 1 (n=198)		Tertile 2 (n=200)		Tertile 3 (n=197)	
	No.	%	No.	%	No.	%
Age[b], years	60.5 (11.8)		64.3 (10.1)		66.9 (9.4)	
Follow up[b], months	73.3 (40.7)		72.2 (40.5)		68.4 (38.0)	
Sex						
Male	159	80.3	158	79.0	158	80.2
Female	39	19.7	42	21.0	39	19.8
Body mass index[b,c], continuous	28.4 (5.2)		28.3 (5.4)		27.7 (4.8)	
Body mass index[d]						
Underweight	1	0.5	2	1.0	1	0.5
Normal weight	44	22.2	50	25.0	56	28.4
Overweight	90	45.5	86	43.0	88	44.7
Obese	61	30.8	61	30.5	52	26.4
Unknown/Missing	2	1.0	1	0.5	0	0.0
Energy[b], kcal	2248.7 (1075.0)		2386.0 (960.3)		2361.4 (831.8)	
Smoking status						
Never smoker	52	26.3	54	27.0	66	33.7
Former smoker	84	42.4	102	51.0	109	55.6
Current smoker	62	31.3	44	22.0	21	10.7
Smoking[b], pack years	44.3 (32.4)		39.6 (31.0)		33.5 (26.3)	
Education						
≤12 years	75	37.9	53	26.5	27	13.7
13-15 years	54	27.3	63	31.5	57	28.9
≥16 years	66	33.3	81	40.5	111	56.4
Unknown/Missing	3	1.5	3	1.5	2	1.0
Income[e]						
<25.000	24	12.1	21	10.5	14	7.1
25.000-50.000	45	22.7	36	18.0	27	13.7
≥50.000	91	46.0	108	54.0	121	61.4
Unknown/Missing	38	19.2	35	17.5	35	17.8

Supplementary table 1 Continued.

	Fruits and Vegetables Pattern					
	Tertile 1 (n=198)		Tertile 2 (n=200)		Tertile 3 (n=197)	
	No.	%	No.	%	No.	%
Stage						
Tis	89	45.0	90	45.0	78	39.6
Ta	11	5.6	13	6.5	9	4.6
T1	96	48.5	95	47.5	107	54.3
Unknown/Missing	2	1.0	2	1.0	3	1.5
Grade						
1	7	3.5	5	2.5	6	3.0
2	63	31.8	69	34.5	61	31.0
3	118	59.6	121	60.5	120	60.9
Unknown/Missing	10	5.1	5	2.5	10	5.1
Treatment						
TUR	58	29.3	56	28.0	51	25.9
TUR + iBCG[f]	61	30.8	49	24.5	55	27.9
TUR + mBCG[g]	43	21.7	60	30.0	50	25.4
Other	36	18.2	35	17.5	41	20.8
Focality						
One tumor	71	35.9	70	35.0	74	37.6
Two tumors	14	7.1	21	10.5	20	10.2
≥ three tumors	50	25.3	47	23.5	46	23.4
Unknown/Missing	63	31.8	62	31.0	57	28.9
Concomitant CIS[h]						
Present	64	32.3	63	31.5	73	37.1
Not present	122	61.6	121	60.5	106	53.8
Unknown/Missing	12	6.1	16	8.0	18	9.1
Medical history[i]						
Coronary heart Disease	35	17.7	40	20.0	34	17.3
Hypertension	87	43.9	93	46.5	93	47.2
Diabetes Mellitus type II	32	16.2	31	15.5	28	14.1
Other comorbidities[j]	76	12.8	77	12.9	73	12.3

[a] For all patterns, the higher tertiles are indicative of higher intake of that diet; [b] Mean (SD); [c] Weight (kg)/height (m^2); [d] <18.5=underweight, 18.5-24.9=normal weight, 25-29.9=overweight, ≥30=obese; [e] Income per year; [f] induction BCG; [g] maintenance BCG; [h] Carcinoma in situ; [i] number and percentage of patients in whom disease is present; [j] Chronic obstructive pulmonary disease, peptic disease, liver disease, chronic renal failure, renal stones, diseases of the central nervous system, diseases of the endocrine system, benign hyperplasia

Supplementary table 2 Baseline Characteristics of 595 Non-Muscle Invasive Bladder Cancer Patients by Tertiles of Low-Fat Dietary Pattern[a]

	Low-Fat Pattern					
	Tertile 1 (n=199)		Tertile 2 (n=198)		Tertile 3 (n=198)	
	No.	%	No.	%	No.	%
Age[b], years	62.9 (11.5)		65.5 (10.0)		63.3 (10.8)	
Follow up[b], months	71.8 (38.4)		69.0 (40.6)		73.2 (40.2)	
Sex						
Male	159	79.9	157	79.3	159	159
Female	40	20.1	41	20.7	39	19.7
Body mass index[b,c], continuous	28.1 (5.4)		27.8 (4.6)		28.6 (5.3)	
Body mass index[d]						
Underweight	3	1.5	0	0.0	1	0.5
Normal weight	47	23.6	56	28.3	47	23.7
Overweight	93	46.7	90	45.5	81	40.9
Obese	55	27.6	52	26.3	67	33.8
Unknown/Missing	1	0.5	0	0.0	2	1.0
Energy[b], kcal	2471.1 (939.6)		2165.2 (957.3)		2359.5 (966.6)	
Smoking status						
Never smoker	44	22.1	58	29.4	70	35.4
Former smoker	92	46.2	98	49.8	105	53.0
Current smoker	63	31.7	41	20.8	23	11.6
Smoking[b], pack years	43.8 (33.5)		39.9 (30.2)		33.3 (25.4)	
Education						
≤12 years	61	30.7	55	27.8	39	19.7
13-15 years	65	32.7	58	29.3	51	25.8
≥16 years	69	34.7	82	41.4	107	54.0
Unknown/Missing	4	2.0	3	1.5	1	0.5
Income[e]						
<25.000	23	11.6	18	9.1	18	9.1
25.000-50.000	38	19.1	35	17.7	35	17.7
≥50.000	102	51.3	105	53.0	113	57.1
Unknown/Missing	36	18.1	40	20.2	32	16.2
Stage						
Tis	80	40.2	79	39.9	98	49.5
Ta	12	6.0	13	6.6	8	4.0
T1	103	51.8	103	52.0	92	46.5
Unknown/Missing	4	2.0	3	1.5	0	0.0

Supplementary table 2 Continued.

	Low-Fat Pattern					
	Tertile 1 (n=199)		Tertile 2 (n=198)		Tertile 3 (n=198)	
	No.	%	No.	%	No.	%
Grade						
1	4	2.0	5	2.5	9	4.5
2	57	28.6	66	33.3	70	35.4
3	131	65.8	115	58.1	113	57.1
Unknown/Missing	7	3.5	12	6.1	6	3.0
Treatment						
TUR	60	30.2	55	27.8	50	25.3
TUR + iBCG[f]	57	28.6	54	27.3	54	27.3
TUR + mBCG[g]	54	27.1	44	22.2	55	27.8
Other	28	14.1	45	22.7	39	19.7
Focality						
One tumor	75	37.7	77	38.9	63	31.8
Two tumors	19	9.6	17	8.6	19	9.6
≥ three tumors	50	25.1	42	21.2	51	25.8
Unknown/Missing	55	27.6	62	31.3	65	32.8
Concomitant CIS[h]						
Present	63	31.7	65	32.8	72	36.4
Not present	117	58.8	117	59.1	115	58.1
Unknown/Missing	19	9.6	16	8.1	11	5.6
Medical history[i]						
Coronary heart disease	32	16.1	37	18.7	40	20.2
Hypertension	83	41.7	97	49.0	93	47.0
Diabetes Mellitus type II	21	10.6	33	16.7	37	18.7
Other comorbidities[j]	81	13.6	73	12.3	72	12.1

[a] For all patterns, the higher tertiles are indicative of higher intake of that diet; [b] Mean (SD); [c] Weight (kg)/height (m^2); [d] <18.5=underweight, 18.5-24.9=normal weight, 25-29.9=overweight, ≥30=obese; [e] Income per year; [f] induction BCG; [g] maintenance BCG; [h] Carcinoma in situ; [i] number and percentage of patients in whom disease is present; [j] Chronic obstructive pulmonary disease, peptic disease, liver disease, chronic renal failure, renal stones, diseases of the central nervous system, diseases of the endocrine system, benign hyperplasia

Supplementary table 3 Baseline Characteristics of 595 Non-Muscle Invasive Bladder Cancer Patients by Tertiles of Tex-Mex Dietary Pattern[a]

	Tex-Mex Pattern					
	Tertile 1 (n=199)		Tertile 2 (n=199)		Tertile 3 (n=197)	
	No.	%	No.	%	No.	%
Age[b], years	67.9 (9.8)		63.3 (9.7)		60.5 (11.5)	
Follow up[b], months	74.5 (41.4)		75.4 (42.3)		63.9 (34.1)	
Sex						
Male	159	79.9	158	79.4	158	80.2
Female	40	20.1	41	20.6	39	19.8
Body mass index[b,c], continuous	27.7 (4.6)		27.7 (4.8)		29.0 (5.8)	
Body mass index[d]						
Underweight	3	1.5	1	0.5	0	0.0
Normal weight	52	16.1	56	28.1	42	21.3
Overweight	81	40.7	89	44.7	94	47.7
Obese	61	30.7	53	26.6	60	30.5
Unknown/Missing	2	1.0	0	0.0	1	0.5
Energy[b], kcal	2343.1 (983.5)		2244.1 (964.9)		2410.1 (932.1)	
Smoking status						
Never smoker	55	27.6	52	26.3	65	33.0
Former smoker	104	52.3	104	52.5	87	44.2
Current smoker	40	20.1	42	21.2	45	22.8
Smoking[b], pack years	44.0 (33.5)		38.9 (29.1)		34.7 (27.4)	
Education						
≤12 years	73	36.7	49	24.6	33	16.8
13-15 years	56	28.1	62	31.2	56	28.4
≥16 years	66	33.2	85	42.7	107	54.3
Unknown/Missing	4	2.0	3	1.5	1	0.5
Income[e]						
<25.000	32	16.1	18	9.1	9	4.6
25.000-50.000	45	22.6	41	20.6	22	11.2
≥50.000	76	38.2	115	57.8	129	65.5
Unknown/Missing	46	23.1	25	12.6	37	18.8
Stage						
Tis	95	47.7	70	35.2	92	46.7
Ta	10	5.0	18	9.1	5	2.5
T1	92	46.2	110	55.3	96	48.7
Unknown/Missing	2	1.0	1	0.5	4	2.0

Supplementary table 3 Continued.

	Tex-Mex Pattern					
	Tertile 1 (n=199)		Tertile 2 (n=199)		Tertile 3 (n=197)	
	No.	%	No.	%	No.	%
Grade						
1	8	4.0	3	1.5	7	3.6
2	70	35.2	57	28.6	66	33.5
3	114	58.8	127	63.8	118	59.9
Unknown/Missing	7	3.5	12	6.0	6	3.0
Treatment						
TUR	52	26.1	54	27.1	59	30.0
TUR + iBCG[f]	58	29.2	59	29.7	48	24.4
TUR + mBCG[g]	51	25.6	49	24.6	53	26.9
Other	38	19.1	37	18.6	37	18.8
Focality						
One tumor	66	33.2	81	40.7	68	34.5
Two tumors	18	9.1	13	6.5	24	12.2
≥ three tumors	55	27.6	46	23.1	42	21.3
Unknown/Missing	60	30.2	59	29.7	63	32.0
Concomitant CIS[h]						
Present	58	29.2	78	39.2	64	32.5
Not present	124	62.3	109	54.8	116	58.9
Unknown/Missing	17	8.5	12	6.0	17	8.6
Medical history[i]						
Coronary heart disease	56	28.1	28	14.1	25	12.7
Hypertension	100	50.3	84	42.2	89	45.2
Diabetes Mellitus type II	34	17.1	22	11.1	35	17.8
Other comorbidities[j]	91	15.3	61	10.3	74	12.4

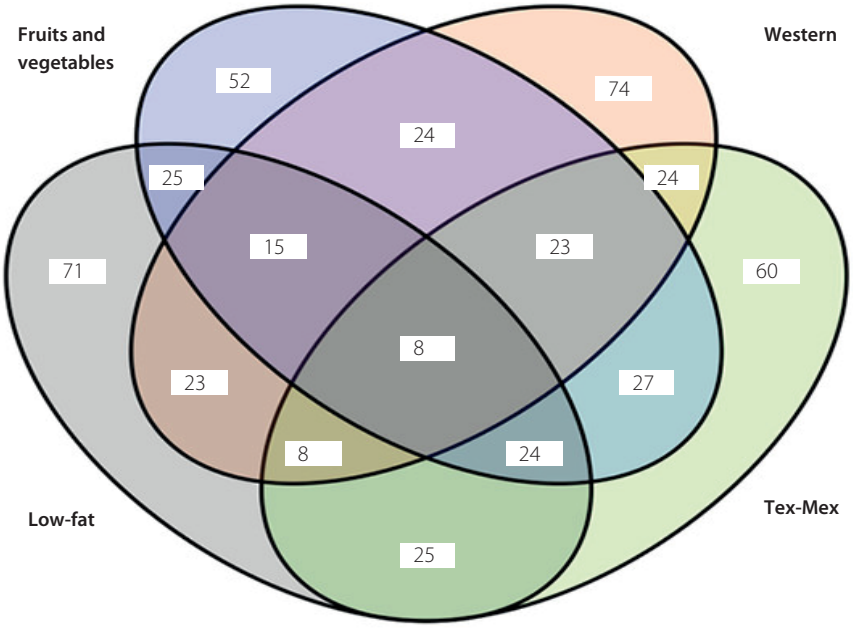
[a] For all patterns, the higher tertiles are indicative of higher intake of that diet; [b] Mean (SD); [c] Weight (kg)/height (m^2); [d] <18.5=underweight, 18.5-24.9=normal weight, 25-29.9=overweight, ≥30=obese; [e] Income per year; [f] induction BCG; [g] maintenance BCG; [h] Carcinoma in situ; [i] number and percentage of patients in whom disease is present; [j] Chronic obstructive pulmonary disease, peptic disease, liver disease, chronic renal failure, renal stones, diseases of the central nervous system, diseases of the endocrine system, benign hyperplasia

Supplementary table 4 Adjusted Associations of Dietary Pattern Score (in Tertile) with risk of Recurrence and Progression of 318 NMIBC Patients treated with BCG.

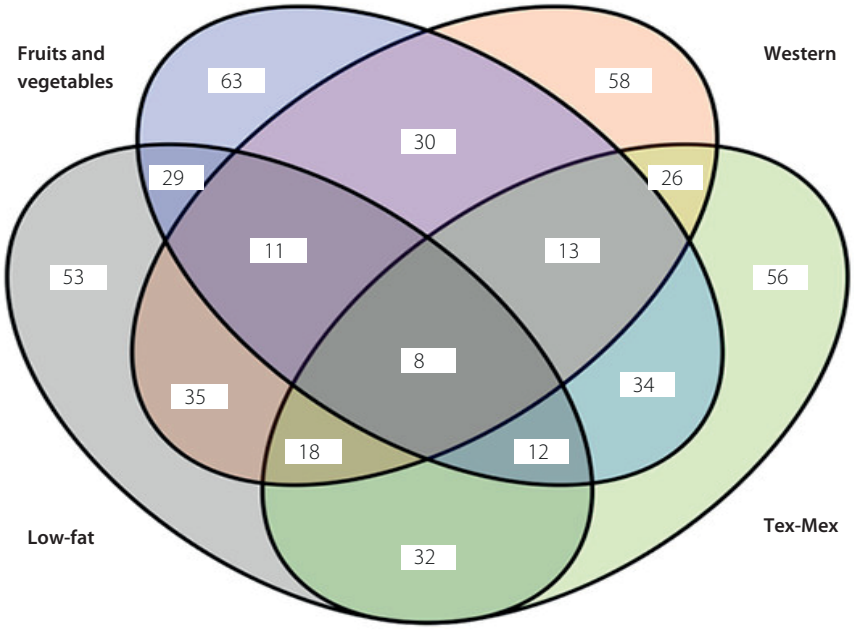
Dietary pattern and tertile score	Recurrence/Total no. of patients	HR (95% CI) [a]	Progression/Total no. of patients	HR (95% CI) [a]
Fruits and vegetables pattern				
Tertile 1 (low)	60/104	1 (referent)	29/104	1 (referent)
Tertile 2	50/109	0.83 (0.55-1.25)	26/109	1.07 (0.58-1.95)
Tertile 3 (high)	48/105	0.70 (0.44-1.11)	28/105	1.23 (0.64-2.37)
P for trend		0.13		0.53
Western pattern				
Tertile 1 (low)	51/106	1 (referent)	26/106	1 (referent)
Tertile 2	49/105	0.95 (0.61-1.47)	23/105	0.90 (0.48-1.67)
Tertile 3 (high)	58/107	**1.76 (1.11-2.79)**	34/107	1.68 (0.88-3.21)
P for trend		**0.02**		0.12
Low-fat pattern				
Tertile 1 (low)	59/111	1 (referent)	32/111	1 (referent)
Tertile 2	49/98	0.88 (0.58-1.34)	24/98	0.79 (0.43-1.46)
Tertile 3 (high)	50/109	0.75 (0.50-1.11)	27/109	0.81 (0.44-1.49)
P for trend		0.16		0.51
Tex-Mex pattern				
Tertile 1 (low)	54/109	1 (referent)	29/109	1 (referent)
Tertile 2	61/108	1.33 (0.87-2.02)	34/108	1.19 (0.67-2.10)
Tertile 3 (high)	43/101	0.78 (0.50-1.23)	20/101	0.60 (0.30-1.20)
P for trend		0.30		0.18

[a] Adjusted for age, sex, education, income, body mass index, smoking status and intensity, total energy intake, grade, tumor multiplicity, concomitant carcinoma in situ, and treatment

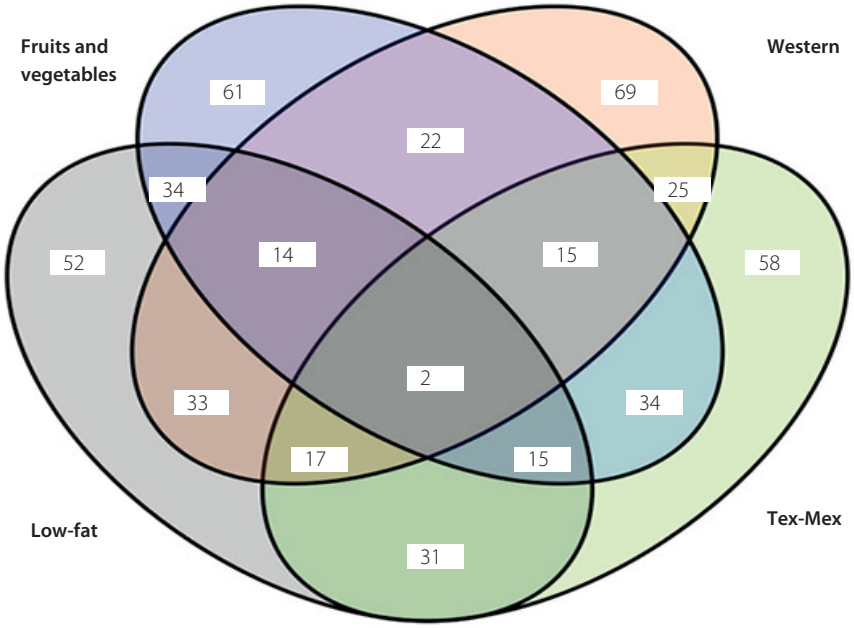
Supplementary figure 1 Overlap in patients who are in the first tertile of different dietary patterns.



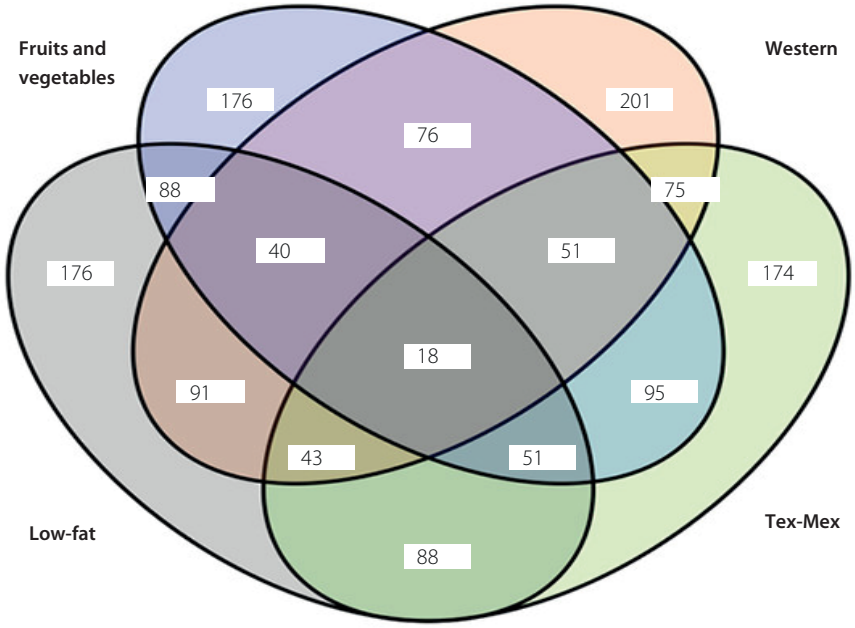
Supplementary figure 2 Overlap in patients who are in the second tertile of different dietary patterns.



Supplementary figure 3 Overlap in patients who are in the third tertile of different dietary patterns.



Supplementary figure 4 Overlap in patients in all tertiles of different dietary patterns simultaneously.



Although food intake was adjusted for energy intake, we evaluated whether energy intake played a role of importance in the derivation of the factors by assessing the proportion of patients that have been classified into the same tertile for different dietary patterns. If energy intake would play a role, you would expect a large amount of overlap. E.g., a patient who is a big eater could be in the third tertile for multiple dietary patterns.

To investigate the amount of overlap in patients per tertile as well as overlap in patients for all tertiles at the same time,we filled out four-circle venn diagrams. All numbers mentioned below can be found in supplementary figures 1 to 4 as well.

Overlap per tertile

For a study of our size (n=595), you would expect an overlap of roughly 200 patients who are in at least two different first (or second or third) tertiles of four dietary patterns, yielding a percentage of 25%. A percentage that is much higher than 25% would be reason for concern. When we look at the tertiles one by one, the number of patients overlapping is very close to what you would expect. This can be seen in supplementary figures 1 to 3.

The percentages we found range between 28.5% and 31.3%, which is in our opinion close enough to 25% to ensure that we used the right methodology.

- Overlap at least two patterns first tertile: 226/793*100=28.5%
- Overlap at least two patterns second tertile: 248/793*100=31.3%
- Overlap at least two patterns third tertile: 242/793*100=30.5%

Overlap for all tertiles

When we look at the overlap between all tertiles of the combinations of two patterns without considering overlap in the other two patterns at the same time, the percentage of overlap ranges between 31% and 36%. This is also close to what you would expect by chance. These results can be seen in supplementary figure 4.

The percentage of overlap in two patterns expected by chance = (1/3*1/3+1/3*1/3+1/3*1/3)= 33.3%, and the following is what we observed:

- Tex-Mex & Western: 187/595*100=31.4%
- Tex-Mex & Low-fat: 200/595*100=33.6%
- Tex-Mex & Fruits and vegetables: 215/595*100=36.1%
- Western & Low-fat: 192/595*100=32.3%
- Western & Fruits and vegetables: 185/595*100=31.1%
- Low-fat & Fruits and vegetables: 197/595*100=33.1%

The percentage of overlap in three patterns expected by chance = (1/3*1/3*1/3+1/3*1/3* 1/3+1/3*1/3*1/3)=11.1%, and the following is what we observed:

- Tex-Mex & Western & Low-fat: 61/595*100=10.3%
- Tex-Mex & Western & Fruits and vegetables: 69/595*100=11.6%
- Tex-Mex & Fruits and vegetables & Low-fat: 73/595*100=12.3%
- Western & Fruits and vegetables & Low-fat: 58/595*100=9.7%

The percentage of overlap in all four patterns expected by chance = (1/3*1/3*1/3*1/3+1/3 *1/3*1/3*1/3+1/3*1/3*1/3*1/3)=3.7%, and the following is what we observed:

- 18/595*100=3.0%

Moreover, in our opinion, there is no clusterization by factors as there is no notable difference in overlap between any of the patterns.

Taken together, we think that the dietary patterns identified through factor analysis are functioning well in separating the patients.

5

Health-related quality of life in non-muscle invasive bladder cancer patients

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Abstract

Background: Non-muscle-invasive bladder cancer (NMIBC) patients have a high risk of recurrence, necessitating a burdensome follow-up program which may impact their health-related quality of life (HRQoL).

Methods: We studied HRQoL among 541 recently diagnosed NMIBC patients recruited for the prospective cohort study UroLife at 6 weeks, 12 weeks, and 15 months after diagnosis, and compared this to an age- and sex-matched normative population. HRQoL was assessed with the EORTC QLQ-C30 and the EORTC QLQ-NMIBC24. Also, we assessed whether HRQoL differed by treatment modality, smoking status, and fluid intake.

Results: NMIBC patients had a statistically significantly worse role, emotional, and social functioning, and reported more fatigue, dyspnoea, insomnia, appetite loss, and diarrhea compared to a normative population. Differences were of small clinical importance, except for diarrhea, which was of medium clinical importance at 12 weeks (mean difference (MD) 9.5; 95% CI 7.2-11.7) and 15 months (MD 9.5; 95% CI 7.2-11.9) after diagnosis. HRQoL of NMIBC patients improved over time in most domains, but more appetite loss and diarrhea was reported at 12 weeks and 15 months after diagnosis as compared to 6 weeks after diagnosis. Forty percent of the patients still reported one or more urinary symptoms, and 24% reported one or more emotional worries at 15 months after diagnosis. Patients treated with intravesical chemotherapy or immunotherapy scored worse on several of the QLQ-NMIBC-24 subscales compared to patients treated with transurethral resection of the bladder tumour only. Smoking and fluid intake did not have a clinically relevant impact on HRQoL.

Conclusion: Caregivers should be alert as specific domains of HRQoL of NMIBC patients are worse than that of the general population, and symptoms and emotional worries may be present for a longer period.

Introduction

About 70% of urinary bladder cancer (UBC) patients are diagnosed with non-muscle-invasive bladder cancer (NMIBC) (1), which has a high survival rate, but tends to recur in more than 40% of the patients within five years (2). In addition, high grade T1 tumors have a 20% 5-year risk of progression, after which prognosis becomes poor (2, 3). To reduce the risk of recurrence and progression, initial surgical treatment with transurethral resection of the bladder tumor (TURBT) is mostly complemented with intravesical chemo- or immunotherapy. Thereafter, NMIBC patients are subjected to frequent follow-up by cystoscopy (4). Intravesical immunotherapy, and to a lesser extent intravesical chemotherapy, are often accompanied by side-effects, such as cystitis, urge, dysuria, and incontinence (5, 6). These side effects in addition to the minimally invasive follow-up method could have a large impact on patients' health-related quality of life (HRQoL).

To date, only a limited number of studies investigated HRQoL in NMIBC patients. Two studies showed that mental and/or physical health of NMIBC patients were worse compared to a normative population (7, 8). Several studies showed that NMIBC patients experienced urinary symptoms and future worries, with problems differing according to treatment (7-14). However, some of the studies had a cross-sectional design and could not evaluate changes in HRQoL over time.

A healthy lifestyle has been linked to better HRQoL in survivors of numerous cancers (15-24). NMIBC patients are often advised by their urologist to quit smoking and to increase their fluid intake because of the hypothesized effect on recurrence, but the effect of smoking and fluid intake on HRQoL has not been investigated in NMIBC patients yet. Non-smoking has been linked to better overall quality of life and physical functioning in survivors of other cancer types (15, 21, 24). In one (25) out of two studies conducted in UBC patients (15, 25), smokers reported increased fear of recurrence and psychological distress compared to non-smokers. No evidence is available about the association of fluid intake with HRQoL. In this study, we investigated HRQoL among newly diagnosed NMIBC patients at 6 weeks, 12 weeks, and 15 months after diagnosis and compared this to an age- and sex-matched normative population. Also, we assessed whether HRQoL differed according to therapy, smoking status, and fluid intake[1]. We hypothesized that patients treated with immunotherapy, current smokers, and patients with a lower fluid intake would report worse HRQoL scores at the different time points.

1 No other lifestyle factors were investigated yet as this manuscript will not be submitted to a journal in this form. In a future version, other lifestyle factors such as body mass index and physical activity will be incorporated.

Methods

Study design and participants

We used data from a population-based, prospective cohort study on the association of dietary and lifestyle habits with prognosis and HRQoL in NMIBC patients, named the UroLife study (Urothelial cancer: Lifestyle, prognosis and health-related quality of Life). Permission was obtained from all urologists of 22 participating hospitals to identify eligible patients in the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organization (IKNL). Patients with newly diagnosed NMIBC (stage Ta, T1, Tis) between April 1, 2014 and April 25, 2017, aged 18 to 80 years old were identified in the NCR and invited to participate approximately four weeks after diagnosis. Patients were excluded if they did not speak Dutch, if the tumor was not histologically confirmed by TURBT, if they had a previous cancer diagnosis in the last five years, positive lymph nodes, or distant metastases. The UroLife study received ethical approval from the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494). Written informed consent was obtained from all participants. For this preliminary analysis, we included patients diagnosed up to March 18, 2016 for whom clinical data were collected in September 2017.

Data collection

Self-reported questionnaire data were collected online or on paper at six weeks (T6wk), twelve weeks (T12wk), and fifteen months (T15mo) after diagnosis and consisted of questions on socio-demographic characteristics (T6wk only), smoking, comorbidities, and HRQoL. Web-based questionnaires were collected via the data collection tool of the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry (26). At T12wk and T15mo, patients filled out a four-day fluid and micturition diary.

HRQoL data collection

HRQoL was assessed using the validated EORTC QLQ-C30 and the EORTC QLQ-NMIBC24 questionnaires (9, 27). The EORTC QLQ-C30 consists of 30 items comprising of a global health status scale, five functioning scales (physical, role, cognitive, emotional, and social functioning), and three symptom scales (fatigue, pain, and nausea and vomiting) and six single items (dyspnoea, insomnia, loss of appetite, constipation, diarrhea, and financial impact). The EORTC QLQ-NMIBC24 consists of 24 items and comprises six scales (urinary symptoms, malaise, future worries, bloating and flatulence, sexual functioning, and male sexual problems) and five single items (intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female sexual problems). All items were scored on a four-point Likert scale ranging from 1 (not at all) to 4 (very much), except global health status, which was answered on a seven-point Likert scale ranging from 1 (very poor) to 7 (excellent). Scores of items were summed and transformed to calculate

subscales ranging from 0 to 100. These procedures have been described in detail elsewhere (28). High scores on functioning scales and global health status, and low scores on symptom scales and items indicate a better QoL. In addition, a summary score of the EORTC QLQ-C30 was calculated by averaging the scores of all subscales and items, except global health status and financial impact (29). Results on the EORTC QLQ-C30 of our population were compared with normative data on all three time points (30). For this, we made use of data of the PROFILES registry. Normative population data was obtained from CentERpanel, an online household panel that is representative for the Dutch population. The process of the annual data collection has been described elsewhere (30). In 2013, the questionnaire was sent to 2,848 panel members ≥18 years, and 2,333 questionnaires were returned. Panel members with incomplete questionnaires (n=27) or a previous cancer diagnosis within 5 years of completing the questionnaire (n = 119) were excluded, and a normative sample (n=541) was matched on age and sex.

Lifestyle data collection

Patients were categorized into current or non-smokers at the time of completing the questionnaire. Smoking status was assessed by asking whether patients smoked at the time of completing the questionnaire (T12wk and T15mo) or if they had ever smoked in the past (T6wk). For the T12wk and T15mo measurements patients were asked whether they had smoked or quit smoking since they filled out the last questionnaire. Fluid intake was measured with a four-day fluid and micturition diary at T12wk and T15mo. Patients filled out how much they drank on those days either in mL or in household measures, and average fluid intake in mL per day was calculated.

Covariables

Educational level of the patients was categorized into low (primary-, secondary-, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), and high (university of vocational education, university). Information on living situation (partner vs. no partner) and employment (paid job vs. no paid job) was also collected.

To assess comorbidities, an adapted version of the Self-administered Comorbidity Questionnaire (SCQ) was used (31), which categorized health problems into heart disease, stroke, high blood pressure, lung disease, diabetes, ulcer, kidney disease, anemia or other blood disease, thyroid condition, depression, osteoarthritis, back pain, rheumatoid arthritis and other medical problems. For analysis, other medical problems were excluded. We constructed a sum score of the number of comorbidities patients reported and categorized this into no comorbidities, one comorbidity, and two or more comorbidities.

Detailed clinical data were collected by trained data managers from IKNL by consulting the medical records and included tumour stage and grade, focality (unifocal, multifocal, unknown), immediate postoperative instillation of chemotherapy (yes, no), and treatment

(TURBT only, TURBT with intravesical chemotherapy, TURBT with intravesical immunotherapy). Patients who received both intravesical chemotherapy and immuno- therapy for their primary tumour were categorized according to which therapy was instilled most often.

Statistical analysis

Sociodemographic characteristics of NMIBC patients were compared with those of the age- and sex-matched normative population using Pearson chi-square tests. We assessed the internal consistency of the multi-item scales with the Cronbach's α coefficient, with >0.70 considered acceptable. In addition, we reported floor and ceiling effects (i.e. the proportion of patients with the lowest and the highest scores, respectively) for all multi-item scales and the number of missing item and scale scores.

We calculated mean scores and standard deviations for all EORTC QLQ-C30 and QLQ-NMIBC24 scales and items at T6wk, T12wk, and T15mo. Comparisons of differences in QLQ-C30 scores between the NMIBC patients and the normative population for each time point were made using independent t-tests, and using analysis of covariance adjusted for educational level and comorbidity. Differences in QLQ-C30 and QLQ-NMIBC24 scores at T12wk and T15mo compared to T6wk were tested using paired t-tests. Analysis of covariance was used to evaluate whether scores differed according to treatment modality, smoking status at the time of filling out the questionnaire, and fluid intake (per 100 mL increase) at the time of filling out the questionnaire, adjusted for age and gender. The analyses for therapy were additionally adjusted for undergoing treatment at the time of filling out the questionnaire, and the analyses for smoking were additionally adjusted for educational level and comorbidity.

The clinical relevance of differences in QLQ-C30 scores was interpreted using the evidence-based guidelines of Cocks et al. (32, 33). They combined systematic review of published literature, expert opinions, and meta-analysis to estimate differences of small, medium, and large clinical relevance as opposed to no clinical relevance for most domains. The Cohen rule of thumb was used for cross-sectional differences in emotional functioning, the summary score, and for the QLQ-NMIBC24 scales, since no guideline was available (34). Here, a difference in effect size (mean difference divided by pooled standard deviation) of 0.2 is regarded as a small, 0.5 as a medium, and 0.8 as a large effect.

Frequency of worries and urinary symptoms that were reported by patients as 'Quite a bit' or 'Very much' in the QLQ-NMIBC24 were calculated for all three time points. Logistic regression analyses was used to assess whether therapy, smoking versus not smoking, and fluid intake per increase of 100 mL per day were associated with the presence of symptoms. All regression analyses were adjusted for age and gender, and the analyses for smoking were additionally adjusted for educational level and comorbidity. All tests were two-sided and a p-value less than 0.05 was considered statistically significant. All data were analysed using IBM SPSS Statistics, Version 22. In future analyses, longitudinal analyses will be performed using a form of mixed models .

Results

Of 1,114 invited NMIBC patients diagnosed up to March 18, 2016, 582 agreed to participate (response rate 52%) (Figure 1). Thereafter, 41 patients were excluded because they had a previous cancer diagnosis in the past five years (n=3), clinical data were not yet collected (n=11), they had metastases at diagnosis (n=2), a tumour stage >T1 (n=6), did not complete their first questionnaire (n=5), filled out T12wk prior to or at the same time as T6wk (n=9), or had missing HRQoL data (n=5), leaving a total of 541 patients for inclusion in the analyses.

Median age of NMIBC patients at diagnosis was 67 years, 79% of patients were men, and 75% had a Ta tumour (Table 1). Compared to the normative population, NMIBC patients were less educated ($p<0.001$) and had more comorbidities ($p<0.001$).

Cronbach's α for the multi-item scales were generally higher than 0.7 and thus considered acceptable. Exceptions were cognitive functioning (0.62) and nausea and vomiting (0.63) in the EORTC QLQ-C30, and bloating and flatulence (0.57) in the EORTC QLQ-NMIBC24 (Supplementary Table I).

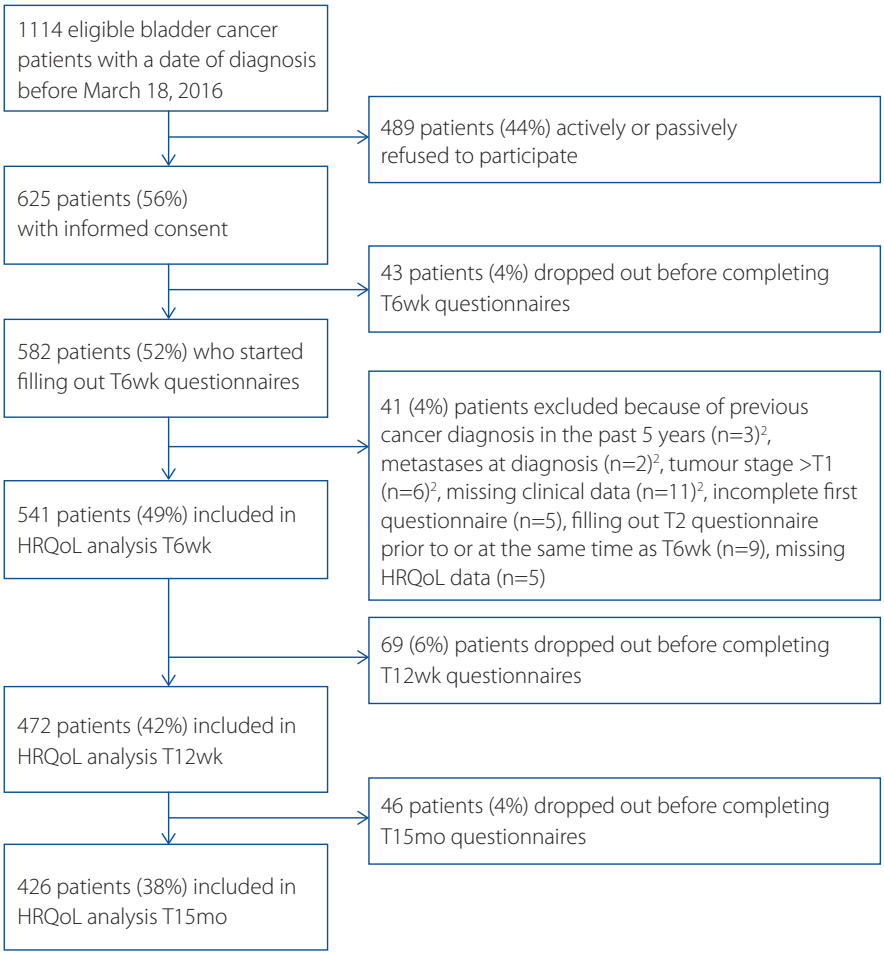
Mean EORTC QLQ-C30 scores for NMIBC patients at T6wk, T12wk, and T15mo and for the normative population are shown in Table 2. In general, statistically significantly lower functioning scores and higher symptom scores were observed for NMIBC patients compared to the normative population. Differences were of small clinical importance for role functioning (T6wk), emotional functioning (T6wk and T12wk), social functioning (T6wk), insomnia (T6wk), appetite loss (T12wk and T15mo), and the summary score (T6wk and T12wk), also after adjustment for educational level and comorbidity (adjusted mean differences not shown). For diarrhea, a difference of medium clinical importance was observed at T12wk and T15mo.

Among NMIBC patients, small clinically important deteriorations over time were seen for appetite loss and diarrhea at T12wk and T15mo. On the other hand, a small clinically important improvement was observed for insomnia at T15mo (Table 2; Figure 2).

Mean EORTC QLQ-NMIBC24 scores for NMIBC patients at T6wk, T12wk, and T15mo are shown in Table 3. Improvements of small clinical importance as compared to T6wk were observed for urinary symptoms (T12wk), future worries (T15mo), sexual functioning (T15mo), intravesical treatment issues (T15mo), and risk of contaminating partner (T12wk). At T15mo, improvements of medium clinical importance were seen for urinary symptoms and female sexual problems.

With regard to treatment, patients undergoing intravesical immunotherapy had more urinary symptoms, future worries, intravesical treatment issues and a higher perceived risk of contaminating their partner during sex at T6wk than patients treated with TURBT only (Table 4; Figure 3). At T12wk, these differences were similar, except for intravesical treatment issues, where no difference was observed. Symptoms reported most often at T6wk were pollakiuria (53%; frequent urination during the day), nocturia (35%; frequent urination during the night), and urge to reach a toilet (34%) (Table 5).

Figure 1 Flowchart of patients included in smoking, fluid intake and HRQoL analyses.



While fewer symptoms were reported at T12wk and T15mo, 40% reported one or more of the urinary symptoms at T15mo. Emotional concerns were reported by 18% (repeated treatments) to 29% (results from tests and examinations) at T6wk, and frequency (almost) halved for all concerns at T15mo, but still 24% reported one or more of the concerns at that time. Patients undergoing immunotherapy reported significantly more symptoms compared to patients treated with TURBT only for several urinary symptoms (T6wk and/or T12wk), sleep disturbance (T12wk), and difficulties leaving home (T6wk and T12wk). No significant differences for patients treated with chemotherapy were observed.

Table 1 Sociodemographic characteristics of the NMIBC patients and the normative population.

	NMIBC patients	Normative population	
***n* (%)**	***n* = 541**	***n* = 541**	***p* value**
Age (years)			
>25 - ≤50	26 (5)	26 (5)	
>50 - ≤60	116 (21)	116 (21)	
>60 - ≤70	212 (39)	212 (39)	
>70 - ≤80	183 (34)	174 (32)	
>80 - ≤85	4 (1)	13 (2)	
Gender			
Male	425 (79)	425 (79)	
Female	116 (21)	116 (21)	
Educational level			<0.001
Low	268 (50)	188 (35)	
Medium	140 (26)	138 (26)	
High	133 (25)	215 (40)	
Living situation			0.07
Partner	458 (85)	435 (80)	
No partner	83 (15)	106 (20)	
Employment			0.19
Paid job	176 (33)	156 (29)	
No paid job	365 (68)	385 (71)	
Comorbidity			
0	87 (16)	154 (29)	<0.001
1	136 (25)	178 (33)	
≥2	314 (59)	209 (39)	
Missing	4 (1)	0 (0)	
Tumour stage			
Ta	403 (75)	n.a.[a]	
T1	120 (22)		
Tis	17 (3)		
Missing	1 (0.2)		
Grade			
1	132 (25)	n.a.	
2	259 (48)		
3	148 (28)		
Missing	2 (0.4)		

Table 1 Continued.

	NMIBC patients	Normative population	
n **(%)**	***n*** **= 541**	***n*** **= 541**	***p*** **value**
Focality			
Unifocal	365 (68)	n.a.	
Multifocal	170 (32)		
Unknown	6 (1)		
Adjuvant therapy			
No	271 (50)	n.a.	
Chemo[b]	138 (26)		
BCG[b,c]	132 (24)		
Single instillation[d]			
No	243 (45)	n.a.	
Yes	298 (55)		

[a] not applicable; [b] Intravesical; [c] Bacillus Calmette-Guérin; [d] Of intravesical chemotherapy.

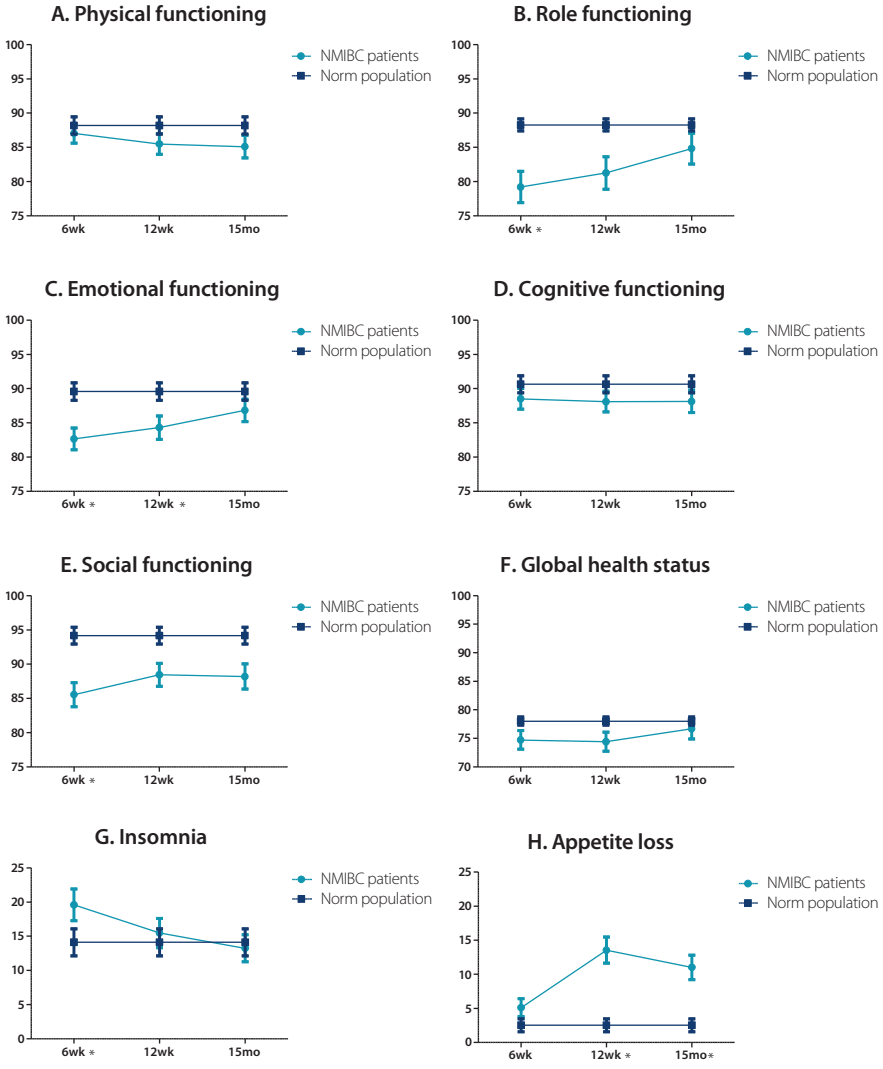
Current smokers had a clinically relevant lower physical functioning (T6wk and T12wk) and global health status (T15mo) than non-smokers (Supplementary Table IIa). No differences were seen at other time points, nor for other subscales. Fluid intake was not associated with the summary score, global health status, or urinary symptoms in a clinically meaningful way (data not shown). Smoking and fluid intake at the time of filling out the questionnaire were not associated with experiencing symptoms, except that patients with a higher fluid intake reported less incontinence at T12wk (Supplementary Table IIb-c).

Table 2 Unadjusted mean scores (± SD) of EORTC QLQ-C30 subscales for NMIBC patients at three time points after diagnosis, and mean differences compared to 6 weeks after diagnosis and compared to a normative population.

	Patient score, mean (SD)			Mean difference (95% CI) over time		Norm score, mean (SD)	Mean difference (95% CI) between patient and norm		
	6 wk	12 wk	15 mo	12 wk vs. 6 wk	15 mo vs. 6 wk		6 wk	12 wk	24 mo
Subscale									
Physical	87 (17)	85 (17)	85 (17)	-1.7 (-2.6, -0.9)	-2.4 (-3.4, -1.3)	88 (15)	-1.2 (-3.1, 0.8)	-2.7 (-4.7, -0.7)	-3.1 (-5.1, -1.1)
Role	79 (27)	81 (26)	85 (24)	1.9 (-0.3, 4.2)	5.6 (2.8, 8.3)	88 (21)	**-9.1 (-11.9, -6.2)[a]**	-7.0 (-9.9, -4.1)	-3.4 (-6.2, -0.6)
Emotional[b]	83 (19)	84 (19)	87 (17)	1.4 (-0.0, 2.8)	3.3 (1.8, 4.8)	90 (15)	**-6.9 (-9.0, -4.9)[a]**	**-5.3 (-7.4, -3.2)[a]**	-2.8 (-4.8, -0.7)
Cognitive	89 (18)	88 (17)	88 (17)	-0.5 (-1.8, 0.7)	-1.5 (-3.0, 0.0)	91 (15)	-2.1 (-4.0, -0.1)	-2.5 (-4.5, -0.6)	-2.5 (-4.5, -0.5)
Social	86 (21)	88 (19)	88 (19)	2.6 (0.9, 4.3)	2.0 (-0.1, 4.2)	94 (15)	**-8.6 (-10.8, -6.5)[a]**	-5.7 (-7.8, -3.7)	-6.0 (-8.1, -3.8)
Global health status	75 (19)	74 (19)	77 (19)	-0.9 (-2.3, 0.5)	1.2 (-0.6, 3.0)	78 (17)	-3.3 (-5.5, -1.1)	-3.6 (-5.8, -1.4)	-1.3 (-3.8, 0.9)
Fatigue	21 (21)	22 (23)	19 (21)	1.1 (-0.6, 2.8)	-0.5 (-2.3, 1.2)	17 (20)	4.6 (2.1, 7.0)	5.1 (2.5, 7.8)	2.8 (0.2, 5.4)
Nausea/ vomiting	2.5 (9.9)	2.0 (6.6)	1.4 (6.0)	-0.5 (-1.4, 0.4)	-0.8 (-1.8, 0.2)	1.9 (7.9)	0.6 (-0.5, 1.7)	0.1 (-0.8, 1.0)	-0.5 (-1.4, 0.4)
Pain	15 (22)	16 (23)	16 (24)	0.3 (-1.5, 2.1)	1.5 (0.7, 3.7)	16 (22)	-1.2 (-3.8, 1.4)	-0.4 (-3.1, 2.4)	-0.1 (-3.1, 2.8)
Dyspnoea	14 (24)	14 (24)	14 (22)	0.9 (-0.8, 2.6)	0.6 (-1.1, 2.3)	8.8 (19)	4.9 (2.4, 7.5)	5.7 (3.0, 8.3)	4.9 (2.3, 7.5)
Insomnia	20 (27)	15 (24)	13 (21)	-3.9 (-6.6, -1.2)	**-5.9 (-8.7, -3.1)[c]**	14 (23)	**5.5 (2.4, 8.5)[a]**	1.4 (-1.6, 4.3)	-0.9 (-3.7, 2.0)
Appetite loss	5.1 (15)	14 (21)	11 (19)	**9.0 (6.9, 11.1)[c]**	**6.5 (4.4, 8.5)[c]**	2.5 (11)	2.6 (1.0, 4.2)	**11.0 (9.0, 13.1)[a]**	**8.5 (6.6, 10.4)[a]**
Constipation	7.0 (17)	9.4 (19)	10 (20)	2.4 (0.3, 4.5)	2.8 (0.6, 5.1)	5.4 (14)	1.6 (-0.3, 3.4)	4.0 (2.0, 6.0)	4.3 (2.2, 6.4)
Diarrhoea	4.9 (14)	14 (23)	14 (23)	**9.3 (7.0, 11.6)[c]**	**9.3 (6.8, 11.8)[c]**	4.3 (13)	0.6 (-1.0, 2.3)	**9.5 (7.2, 11.7)[d]**	**9.5 (7.2, 11.9)[d]**
Financial difficulties	5.7 (18)	6.4 (19)	6.2 (18)	0.6 (-0.6, 1.9)	0.9 (-0.5, 2.4)	3.5 (12)	2.3 (0.5, 4.1)	2.9 (1.0, 4.9)	2.7 (0.8, 4.6)
Summary score[b]	87 (12)	86 (14)	87 (14)	-1.1 (-2.0, -0.3)	-0.4 (-1.4-0.6)	91 (10)	-3.6 (-4.9, -2.3)[c]	**-4.6 (-6.1, -3.1)[a]**	-3.5 (-5.0, -2.0)[c]

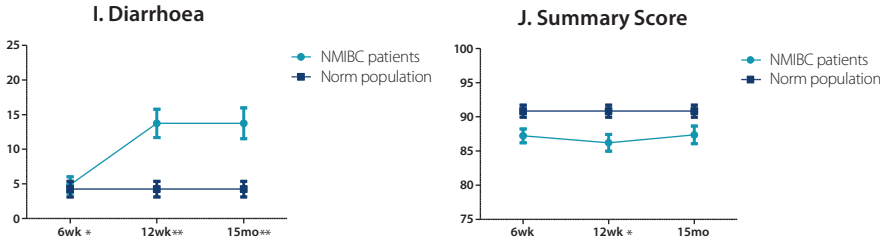
[a] p<0.05 and small clinically important difference, also after adjustment for educational level and comorbidity; [b] Effect sizes interpreted using Cohen's D (mean difference divided by pooled standard deviation); [c] p<0.05 and small clinically important difference; [d] p<0.05 and medium clinically important difference, also after adjustment for education level and comorbidity;

Figure 2 Unadjusted mean scores (± 95% CI) of EORTC QLQ-C30 subscales for NMIBC patients (light blue) and a normative population (dark blue) at three time points: (**A**) Physical functioning; (**B**) Role functioning; (**C**) Emotional functioning; (**D**) Cognitive functioning; (**E**) Social functioning; (**F**) Global health status; (**G**) Insomnia; (**H**) Appetite loss; (**I**) Diarrhoea; (**J**) Summary score.



* p<0.05 and small clinically important difference, also after adjustment for educational level and comorbidity;
** p<0.05 and medium clinically important difference, also after adjustment for education level and comorbidity.

Figure 2 Continued.



* p<0.05 and small clinically important difference, also after adjustment for educational level and comorbidity;
** p<0.05 and medium clinically important difference, also after adjustment for education level and comorbidity.

Table 3 Unadjusted mean scores (± SD) of EORTC QLQ-NMIBC24 subscales for NMIBC patients at three time points after diagnosis and mean differences[a] compared to 6 weeks after diagnosis.

	Patient score, mean (SD)			Mean difference (95% CI) over time	
	6 wk	12 wk	15 mo	12 wk vs. 6 wk	15 mo vs. 6 wk
Subscale					
Urinary symptoms	28 (21)	22 (19)	18 (16)	**-5.4 (-6.8, -4.0)[b]**	**-9.9 (-11.7, -8.1)[c]**
Malaise	3.7 (12)	3.4 (11)	2.5 (9.5)	0.2 (-1.1, 1.4)	-0.8 (-1.9, 0.4)
Future worries	34 (24)	30 (23)	25 (21)	-4.0 (-5.7, -2.2)	**-8.5 (-10.4, -6.6)[b]**
Bloating and flatulence	17 (21)	17 (20)	14 (18)	0.0 (-1.5, 1.5)	-2.8 (-4.8, -0.7)
Sexual functioning	22 (23)	24 (22)	27 (23)	2.6 (1.0, 4.1)	**5.3 (3.4, 7.3)[b]**
Male sexual problems	28 (33)	27 (31)	33 (33)	-0.3 (-3.7, 3.0)	4.0 (0.6, 7.4)
Intravesical treatment issues	10 (19)	9.5 (19)	6.2 (16)	0.2 (-1.9, 2.4)	**-4.0 (-6.2, -1.8)[b]**
Sexual intimacy	14 (22)	10 (20)	10 (19)	-4.1 (-7.1, -1.1)	-5.7 (-9.4, -1.9)
Risk of contaminating partner	19 (27)	14 (23)	10 (21)	**-4.7 (-8.5, -1.0)[b]**	**-11.3 (-16.3, -6.3)[b]**
Sexual enjoyment	55 (30)	57 (26)	58 (29)	3.2 (-0.7, 7.0)	5.3 (0.9, 9.8)
Female sexual problems[d]	33 (26)	19 (36)	13 (25)	-11.2 (-27.6, 5.4)	**-23.3 (-43.0, -3.7)[c]**

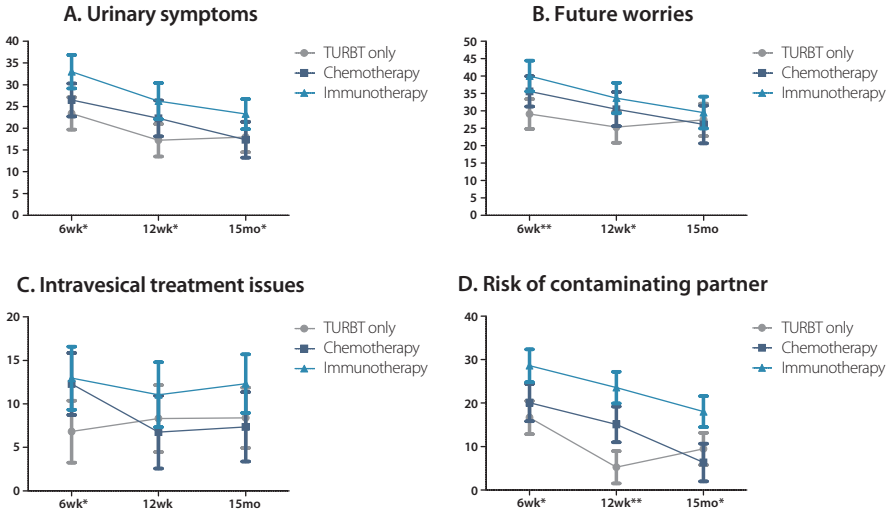
[a] Effect sizes interpreted using Cohen's D (mean difference divided by pooled standard deviation); [b] p<0.05 and small clinically important difference; [c] p<0.05 and medium clinically important difference; [c] Only 21, 16, and 21 women filled out the sexuality questions at T6wk, T12wk, and T15mo, respectively.

Table 4 Adjusted mean scores[a] (± SE) of EORTC QLQ-C30 and EORTC QLQ-NMIBC24 subscales at 6 weeks after diagnosis for NMIBC patients by treatment.

				Mean difference (95% CI)	
	TURBT only[b] (n=271)	**Chemotherapy (n=136)**	**Immunotherapy (n=130)**	**Chemotherapy vs. TURBT only**	**Immunotherapy vs. TURBT only**
Subscales					
Global health status	79 (1.8)	73 (1.8)	75 (1.8)	-6.0 (-12.3, 0.3)	-3.3 (-8.6, 1.9)
Summary score	87 (1.1)	85 (1.1)	87 (1.1)	-1.7 (-5.5, 2.2)	-0.5 (-3.7, 2.8)
Urinary symptoms	23 (1.9)	27 (1.9)	33 (2.0)	3.1 (-3.6, 9.8)	**9.6 (4.0, 15.5)[c]**
Malaise	3.0 (1.1)	4.6 (1.1)	4.0 (1.2)	1.6 (-2.3, 5.5)	1.0 (-2.3, 4.3)
Future worries	29 (2.2)	36 (2.2)	40 (2.3)	6.5 (-1.2, 14.2)	**10.9 (4.5, 17.4)[d]**
Bloating and flatulence	20 (2.0)	17 (2.0)	18 (2.0)	-3.4 (-10.2, 3.5)	-2.2 (-8.0, 3.6)
Sexual functioning	22 (2.0)	16 (2.0)	18 (2.0)	-6.1 (-13.1, 0.9)	-3.5 (-9.4, 2.5)
Male sexual problems	23 (3.3)	36 (3.3)	25 (3.3)	10.4 (-1.7, 22.6)	2.2 (-8.1, 12.6)
Intravesical treatment issues	6.8 (1.8)	12 (1.8)	13 (1.9)	5.5 (-0.9, 11.8)	**6.1 (0.8, 11.5)[c]**
Sexual intimacy	17 (3.3)	17 (3.7)	21 (3.2)	-3.7 (-14.2, 6.9)	4.3 (-4.9, 13.4)
Risk of contaminating partner	17 (3.8)	20 (4.3)	29 (3.8)	3.4 (-9.9, 16.8)	**11.9 (1.1, 22.7)[c]**
Sexual enjoyment	53 (4.2)	48 (5.0)	48 (4.1)	-4.7 (-20.4, 11.0)	-4.8 (-16.7, 7.2)
Female sexual problems[e]	36 (7.4)	33 (13)	25 (13)	-2.6 (-43.0, 37.8)	10.9 (58.3, 41.6)

[a] Adjusted for undergoing treatment at the moment of filling out questionnaire, age and gender; [b] With or without immediate postoperative instillation of chemotherapy; [c] $p<0.05$ and small clinically relevant difference; [d] $p<0.05$ and medium clinically relevant difference; [e] Unadjusted means (± SD) as adjustment was not possible due to small numbers.

Figure 3 Mean scores (± 95% CI) of EORTC QLQ-C30 and EORTC QLQ-NMIBC24 subscales at 6 weeks after diagnosis for NMIBC patients by treatment: (**A**) Urinary symptoms; (**B**) Future worries; (**C**) Intravesical treatment issues; (**D**) Risk of contaminating partner, adjusted for undergoing treatment at the moment of filling out the questionnaire, age and gender.



* p<0.05 and small clinically relevant difference between intravesical immunotherapy and TURBT only;
** p<0.05 and medium clinically relevant difference between intravesical immunotherapy and TURBT only.

Table 5 Frequency of symptoms and worries of NMIBC patients during fifteen months after diagnosis and the association with therapy at 6 and 12 weeks.

Time after diagnosis	6 wk, n (%) (n=541)	12 wk, n (%) (n=472)	15 mo, n (%) (n=425)	OR (95% CI) for chemotherapy vs. TURBT only[b]		OR (95% CI) for immunotherapy vs. TURBT only[b]	
				6 wk	12 wk	6 wk	12 wk
Symptoms[c]							
Pollakiuria	286 (53%)	193 (41%)	132 (31%)	1.53 (0.88, 2.65)	1.20 (0.61, 2.38)	2.31 (1.44, 3.70)	1.69 (0.96, 2.97)
Nocturia	188 (35%)	130 (28%)	102 (24%)	1.26 (0.71, 2.23)	1.13 (0.54, 2.37)	2.03 (1.27, 3.25)	1.57 (0.86, 2.88)
Urge	182 (34%)	114 (24%)	69 (16%)	1.28 (0.73, 2.26)	0.95 (0.43, 2.08)	1.78 (1.12, 2.84)	1.71 (0.92, 3.19)
Dysuria	106 (20%)	48 (10%)	24 (6%)	1.19 (0.60, 2.34)	2.61 (0.94, 7.22)	2.12 (1.23, 3.65)	5.23 (2.42, 11.30)
Sleep disturbance[d]	89 (17%)	52 (11%)	31 (7%)	1.23 (0.60, 2.52)	1.78 (0.66, 4.77)	1.74 (0.97, 3.13)	2.58 (1.20, 5.54)
Difficulties in leaving home[d]	66 (12%)	39 (8%)	23 (5%)	1.35 (0.61, 3.02)	2. 56 (0.87, 7.54)	2.03 (1.08, 3.83)	3.34 (1.45, 7.66)
Incontinence	22 (4%)	28 (6%)	14 (3%)	1.86 (0.51, 6.86)	1.37 (0.29, 6.48)	2.47 (0.92, 6.63)	1.15 (0.41, 3.26)
Emotional concerns							
Results from tests	155 (29%)	97 (21%)	55 (13%)	N/A	N/A	N/A	N/A
Health in the future	140 (26%)	99 (21%)	68 (16%)	N/A	N/A	N/A	N/A
Treatments in the future	138 (26%)	83 (18%)	47 (11%)	N/A	N/A	N/A	N/A
Repeated treatments	96 (18%)	78 (17%)	57 (13%)	N/A	N/A	N/A	N/A

[a] Odds ratio for type of therapy, adjusted for age, gender, and undergoing therapy at the time of filling out the questionnaire using logistic regression; [b] With or without immediate postoperative instillation of chemotherapy; [c] Patients answering 'Quite a bit' or 'Very much'; [d] Because of voiding problems.

Discussion

This study showed that NMIBC patients had a worse self-reported role functioning, emotional functioning and social functioning, and reported more fatigue, dyspnoea, insomnia, appetite loss, and diarrhea than an age- and sex-matched normative population at one or more time points during the fifteen months after diagnosis. Although HRQoL of NMIBC patients improved over time in most domains, more appetite loss and diarrhea at 12 weeks and 15 months compared to 6 weeks after diagnosis were reported, 40% of the patients still had urinary symptoms and 24% had one or more emotional concerns at the end of follow-up. Patients treated with intravesical immunotherapy scored worse on several domains. Smoking and fluid intake did not have a large impact on HRQoL.

NMIBC patients scored worse than a normative population on several HRQoL domains, both shortly as well as a longer period after diagnosis. These results are comparable to other studies, although the use of different questionnaires hampers the comparison (7-9, 14, 35). Among NMIBC patients, differences in HRQoL could possibly be explained by treatment, as approximately 50% of the patients in our study underwent intravesical chemotherapy or immunotherapy. Although in our study, treatment did not seem to have a major impact on domains and symptoms assessed by the QLQ-C30 (data not shown), patients undergoing immunotherapy had more urinary symptoms as compared to patients treated with TURBT only, as expected (5, 36). Also, patients treated with immunotherapy reported more future worries and intravesical treatment issues, which may also be partly explained by the fact that they generally have higher risk disease. A study in 244 NMIBC patients comparing different treatments using the Bladder Cancer Index also found small differences by treatment in subscales only (7). Here, patients treated with chemotherapy improved in the sexual domain, and patients treated with immunotherapy improved in the bowel domain at 6 and 12 months after diagnosis, as compared to patients treated with TURBT only.

To our knowledge, increased appetite loss and diarrhea have not been previously reported in NMIBC patients, and no association with treatment was found (results not shown). The fact that these deteriorations were considered of small or medium clinical importance and were still present at T15mo warrants further research into possible determinants. Even though the frequency of all reported urinary symptoms decreased from T6wk to T15mo, still a substantial part of the patients mentioned suffering from pollakiuria, nocturia or urge 'quite a bit' or 'very much' at T15mo. This was also observed in a study from the UK among 410 NMIBC patients who filled out the QLQ-C30 and QLQ-NMIBC24 four times in the first year after diagnosis (9). Also, the number of patients reporting one or more emotional worries was considerable, with almost 40% and 26% at T6wk and T12wk, respectively, indicating a potential need for psychological support.

We found little evidence for an association of smoking with HRQoL, apart from a lower physical functioning at T6wk and T12wk, and lower global health status at T15mo. Results of other studies are conflicting (15, 25). One study from the US in 586 bladder cancer patients did not find an association of smoking with global health at 2, 5 or 10 years after diagnosis (15), but a small study from the US in 109 NMIBC survivors reported increased fear of recurrence and more psychological distress among current versus non-smokers at approximately 2 years after diagnosis (25). To our knowledge, we are the first to study the association of fluid intake with HRQoL in NMIBC patients. As most symptoms of NMIBC patients are probably related to the urinary domain, an association with fluid intake is plausible.. Other lifestyle factors, such as physical activity may be more important to improve HRQoL and will be incorporated in our analyses in the future (15, 37, 38). Overall, there is not enough evidence to draw conclusions if, and if so, to what extent smoking and fluid intake are associated with HRQoL in NMIBC patients.

Due to the growing number of cancer survivors, patient-reported outcomes such as HRQoL become increasingly important. The integration of statistical significance and clinical relevance is a complicated, but necessary next step in the interpretation of HRQoL data (39-41). Small differences within or between patients can become statistically significant when sample size is sufficiently large, but the important question whether these differences are relevant for patients and clinicians often remains unanswered. Also, the use of different HRQoL indices with corresponding guidelines complicates the comparison with other studies (10). We also used Cohen's d as a more uniform measure of effect size (34). When a guideline was present to determine whether a difference was clinically meaningful, the results were generally in line with the effect sizes as measured with Cohen's d. However, (subtle) differences exist, both between the calculation of Cohen's d in different studies (42) as well as between Cohen's d and the guidelines. Therefore, more effort in a uniform interpretation of HRQoL measures is necessary.

As with all prospective studies, limitations of this study were mainly related to loss to follow-up and missing data. It is possible that patients who had a better health and HRQoL were more likely to participate in the measurements at 12 weeks and 15 months, causing an overestimation of the HRQoL improvement after diagnosis. Indeed, patients in our study who did not complete the second and/or third questionnaires were more likely to have lower scores on some of the HRQoL scales and items at 6 weeks after diagnosis. However, these differences were not considered clinically relevant. Missing data in the HRQoL questionnaires were mainly in the sexuality scales and items, which was not unexpected (9, 12). Further, the Dutch version of the QLQ-NMIBC24 is not yet validated, and no normative data were available. However, validation studies have been performed in Korea and the UK which demonstrated the reliability and validity of the instrument (9, 13). As it is reasonable that the complaints that influence HRQoL of NMIBC patients are mainly

disease-specific, comparison with normative QLQ-NMIBC24 values is recommended. As can be seen in Supplementary Table I, quite some floor and ceiling effects were present, and data were seriously skewed, asking for advanced statistical methods (43). However, there is no consensus yet about which techniques to use. For these preliminary and mainly descriptive analyses of our yet incomplete data, we chose to use t-tests, analysis of covariance and logistic regression. For future analyses, longitudinal analyses using a form of mixed models will be performed. Mixed models have the advantage to be more flexible with regard to non-normally distributed data and are able to handle missing values, instead of leaving all missing values out of the analyses. Lastly, even though we had a reasonable sample size of 541 NMIBC patients, statistical power to detect differences between treatment groups was limited.

Strengths of the current study include the population-based nature, repeated measurements, and the use of a NMIBC-specific module to capture symptoms that may remain unnoticed when only using a broader cancer-specific questionnaire. Also, we made use of Dutch normative data, validated questionnaires, and guidelines to indicate whether differences are considered clinically relevant. High Cronbach's alpha's were observed for most multi-item scales indicating a high internal consistency also in our study.

In conclusion, specific domains of HRQoL of NMIBC patients were worse than that of the general population but generally improved over time. As several symptoms and emotional worries persist for a longer period, caregivers should stay alert. Further research is needed into a more uniform analysis and interpretation of the diverse HRQoL measures that are available, and into the role of lifestyle in HRQoL.

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Supplementary Table I Missing items, floor effects, ceiling effects, and internal consistency of scales of the EORTC QLQ-C30 and QLQ-NMIBC24 at six weeks.

n (%)	Missing items	Floor effect[a]	Ceiling effect[b]	Cronbach's α
EORTC QLQ-C30				
Functioning scales				
Physical	1 (0.2)	0 (0)	225 (42)	0.77
Role	0 (0)	14 (3)	283 (52)	0.89
Emotional	0 (0)	1 (0.2)	185 (34)	0.86
Cognitive	0 (0)	0 (0)	333 (62)	0.62
Social	0 (0)	2 (0.4)	306 (57)	0.77
Global health status	1 (0.2)	1 (0.2)	84 (16)	0.91
Symptom scales				
Fatigue	0 (0)	177 (33)	1 (0.2)	0.81
Nausea/vomiting	0 (0)	489 (90)	2 (0.4)	0.63
Pain	0 (0)	309 (57)	3 (0.6)	0.76
Single items				
Dyspnoea	0 (0)	379 (70)	10 (2)	-
Insomnia	0 (0)	324 (60)	15 (3)	-
Appetite loss	0 (0)	477 (88)	4 (0.7)	-
Constipation	2 (0.4)	450 (83)	4 (0.7)	-
Diarrhoea	1 (0.2)	474 (88)	1 (0.2)	-
Financial difficulties	0 (0)	478 (88)	10 (2)	-
Summary Score	3 (0)	0 (0)	51 (9)	0.92
EORTC QLQ-NMIBC24				
Scales				
Urinary symptoms	1 (0.2)	52 (10)	0 (0)	0.85
Malaise	0 (0)	471 (0)	3 (0.6)	0.72
Future worries	1 (0.2)	78 (14)	10 (2)	0.90
Bloating and flatulence	0 (0)	249 (46)	3 (0.6)	0.59
Sexual functioning	42 (8)	202 (37)	3 (0.6)	0.83
Male sexual problems	43 (10)[c]	163 (38)	32 (8)	0.77
Single items				
Intravesical treatment issues	42 (8)	374 (69)	2 (0.4)	-
Sexual intimacy	301 (56)	164 (30)	2 (0.4)	-
Risk of contaminating partner	303 (56)	139 (26)	10 (2)	-
Sexual enjoyment	303 (56)	41 (8)	26 (5)	-
Female sexual problems	95 (82)[d]	5 (4)	1 (0.9)	-

[a] The proportion of patients with the lowest possible response; [b] The proportion of patients with the highest possible response; [c] 43 out of 425 men; [d] 95 out of 116 women.

Supplementary Table IIa Unadjusted mean scores (± SD) of a selection of EORTC QLQ-C30 and EORTC QLQ-NMIBC24 subscales for NMIBC patients at three time points after diagnosis according to smoking status.

	Non smokers[a,b]	Current smokers[a]	Mean difference (95% CI) Current vs. non smokers[a]
Subscales			
Physical functioning, 6 wk	88 (1.4)	83 (2.0)	**-5.4 (-9.1, -1.7)[c]**
Physical functioning, 12 wk	87 (1.5)	81 (2.2)	**-5.8 (-9.9, -1.6)[c]**
Physical functioning, 15 mo	86 (1.5)	82 (2.3)	-3.4 (-7.9, 1.1)
Global health status, 6 wk	75 (1.7)	72 (2.4)	-2.9 (-7.3, 1.4)
Global health status, 12 wk	75 (1.6)	71 (2.4)	-4.6 (-9.2, 0.1)
Global health status, 15 mo	78 (1.7)	71 (2.6)	**-7.7 (-12.8, -2.5)[c]**
Summary score, 6 wk	87 (1.0)	84 (1.5)	-2.7 (-5.4, -0.1)
Summary score, 12 wk	86 (1.2)	83 (1.8)	-3.4 (-6.9, 0.1)
Summary score, 15 mo	87 (1.2)	86 (1.9)	-0.9 (-4.8, 2.8)
Urinary symptoms, 6 wk	26 (1.8)	25 (2.6)	-0.7 (-5.4, 3.9)
Urinary symptoms, 12 wk	19 (1.7)	21 (2.5)	2.0 (-2.9, 6.8)
Urinary symptoms, 15 mo	16 (1.4)	16 (2.2)	0.3 (-4.1, 4.6)
Future worries, 6 wk	40 (2.0)	37 (2.9)	-2.9 (-8.2, 2.4)
Future worries, 12 wk	32 (2.0)	35 (2.9)	2.8 (-2.9, 8.5)
Future worries, 15 mo	26 (1.9)	27 (2.9)	1.6 (-4.2, 7.4)
Male sexual problems, 6 wk	24 (2.6)	25 (4.4)	0.9 (-8.0, 9.7)
Male sexual problems, 12 wk	24 (2.6)	28 (4.9)	3.5 (-6.4, 13.4)
Male sexual problems, 15 mo	29 (2.7)	37 (5.7)	7.3 (-4.4, 19.0)

[a] Smoking status at the time of filling out the questionnaire; [b] Including former smokers; [c] $p<0.05$ and small clinically important difference, also after adjustment for age, gender, educational level and comorbidities.

Supplementary Table IIb The association of smoking with frequency of urinary symptoms[a] of NMIBC patients during fifteen months after diagnosis.

Time after diagnosis	OR (95% CI) for current smokers vs. non-smokers[b]		
	6 wk	12 wk	15 mo
Pollakiuria	0.95 (0.61, 1.48)	1.06 (0.64, 1.76)	1.12 (0.63, 1.97)
Nocturia	1.04 (0.65, 1.66)	1.32 (0.76, 2.28)	0.91 (0.47, 1.78)
Urge	0.99 (0.62, 1.59)	1.30 (0.74, 2.27)	0.73 (0.34, 1.56)
Dysuria	0.84 (0.47, 1.48)	1.33 (0.60, 2.94)	0.77 (0.22, 2.73)
Sleep disturbance[c]	1.13 (0.63, 2.02)	1.68 (0.82, 3.46)	0.69 (0.23, 2.10)
Difficulties in leaving home[c]	1.02 (0.52, 1.98)	1.43 (0.61, 3.31)	0.96 (0.30, 3.10)
Incontinence	0.78 (0.22, 2.80)	2.00 (0.82, 4.89)	1.55 (0.45, 5.37)

[a] Patients answering 'Quite a bit' or 'Very much'; [b] Odds ratio (OR) for smoking vs. not smoking at time of filling out the questionnaire, adjusted for age, gender, education, and comorbidities using logistic regression; [c] Because of voiding problems.

Supplementary Table IIc The association of fluid intake with frequency of urinary symptoms[a] of NMIBC patients at 12 weeks and 15 months after diagnosis.

Time after diagnosis	OR (95% CI) for 100 ml increase in fluid intake[b]	
	12 wk	15 mo
Pollakiuria	0.99 (0.95, 1.03)	0.99 (0.94, 1.03)
Nocturia	1.00 (0.96, 1.05)	0.99 (0.95, 1.04)
Urge	1.00 (0.96, 1.05)	1.01 (0.95, 1.07)
Dysuria	0.98 (0.92, 1.05)	0.98 (0.88, 1.08)
Sleep disturbance[c]	1.00 (0.94, 1.06)	0.96 (0.88, 1.05)
Difficulties in leaving home[d]	1.00 (0.93, 1.08)	1.10 (1.01, 1.20)[d]
Incontinence	0.86 (0.76, 0.97)[d]	0.94 (0.84, 1.05)

[a] Patients answering 'Quite a bit' or 'Very much'; [b] Odds ratio (OR) per 100 mL increase at time of filling out the questionnaire, adjusted for age and gender using logistic regression; [c] Because of voiding problems; [d] Significant at the $p<0.05$ level.

6

Low awareness of risk factors among bladder cancer survivors: new evidence and a literature overview

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Abstract

Background: Data on urinary bladder cancer (UBC) patients' perceptions about causes of bladder cancer is limited, while this may be important knowledge for health prevention and education. We evaluated self-reported perceptions and beliefs about the causes of bladder cancer among UBC survivors in the Netherlands.

Methods: UBC survivors identified through the Netherlands Cancer Registry from 2007 to 2012 were invited to participate. Patients who consented were asked to fill out a questionnaire, including questions on lifestyle characteristics, occupational and medical history, and family history of cancer. The final question was 'You have been diagnosed with bladder cancer. Do you have any idea what may have been the cause of your cancer?'.

Results: Of 1793 UBC survivors included, 366 (20%) reported a possible cause for their bladder cancer. The most frequently reported suspected causes were smoking (10%), occupational exposure (5%), and heredity (2%). Smoking, occupational exposure and heredity were mentioned only slightly more frequently by participants with these risk factors (11%, 8%, 5%, respectively) compared to the total population.

Conclusions: Most UBC survivors did not suspect any cause that might have contributed to the development of their cancer. Even among participants with established risk factors for bladder cancer, these risk factors were not commonly perceived. This finding probably reflects the superficial knowledge of risk factors for bladder cancer in the population and highlights the importance of effective education on cancer prevention.

Keywords: Urinary Bladder Neoplasms; Survivors; Risk Factors; Qualitative Research; Perception; Questionnaires

Introduction

Urinary bladder cancer (UBC) is the ninth most frequently diagnosed malignancy in the world (1). Due to intensive follow-up and treatment, it has the highest lifetime treatment costs per patient of all cancers (2, 3). Cigarette smoking is the best-established risk factor in the development of UBC and is involved in the etiology of approximately 50% of all cases (4, 5). Other risk factors associated with UBC are occupational exposure to carcinogens like aromatic amines and polycyclic aromatic hydrocarbons, chronic urinary tract infection, schistosomiasis infection, pelvic radiation, cyclophosphamide treatment, family history and specific low-penetrance germline genetic susceptibility (4). Although some studies showed that fluid intake and fruit and vegetable consumption may also influence UBC risk, evidence is inconsistent (6-8).

Knowledge of what cancer survivors perceive as causes of their cancer may provide valuable information for health education and prevention initiatives, especially with regards to modifiable risk factors that are under the control of patients. Awareness of the association between such a risk factor and the disease can enhance the motivation to change it (9). For example, patients' knowledge that tobacco use contributed to their disease can help in their motivation to quit smoking (and advise others to do the same). This information is important, since risk factors for cancer development may also be associated with prognosis (10). Continuation of smoking after diagnosis, for instance, may be related to higher rates of recurrence and increased risk of morbidity and mortality (11, 12), although the literature on this topic is inconsistent (13).

Despite the importance of knowledge on this topic, the literature is sparse. Five previous studies suggested poor knowledge regarding smoking as a risk factor for UBC among urological (9, 14) and, more specific, UBC (9, 15-17) patients. In this study, we evaluated self-reported perceptions and beliefs about the causes of bladder cancer among UBC survivors in the Netherlands. We took a different approach from most of the previous studies and did not ask about knowledge of bladder cancer risk factors in general. Instead we inquired about factors that might have led to the patients' own disease and investigated whether the answers differed according to their reported risk factors.

Materials and methods

Self-reported causes of bladder cancer were evaluated among Dutch UBC survivors. Data from the Nijmegen Bladder Cancer Study (NBCS) were used (18). The population consisted of men and women diagnosed with UBC in one of seven hospitals in the eastern part of the Netherlands between 1995 and 2011 and recruited for the study between 2007 and 2012. Participants had to be younger than 75 years at diagnosis. Patients were identified through the Netherlands Cancer Registry (NCR) held by the Netherlands Comprehensive

Cancer Organisation (IKNL). All eligible UBC survivors received an invitation letter and information brochure. The information brochure highlighted the need for etiological research into risk factors for UBC. Lifestyle factors (e.g. nutrition), smoking and heredity were mentioned as established or probable risk factors for UBC in this information brochure. The response rate to the questionnaire was 65%. The questionnaire included questions on socio-demographic and lifestyle characteristics, physical activity, occupational history, medical history, use of medicines, and family history of cancer. The final question: 'You have been diagnosed with bladder cancer. Do you have any idea what may have been the cause of your cancer?' (No/ Yes, namely…) was evaluated in this study.

Categories of perceived causes were based on answers given by the participants and were presented as groups of risk factors (smoking; passive smoking; environmental and chemical exposure; occupational exposure; heredity; history of bladder polyps; bladder infections; other medical condition/intervention; medication; lifestyle; micturition/fluid intake; stress; treatment delay; don't know/other). Participants were allowed to give multiple answers to the final question. We also stratified the answers by smoking status, family history of UBC, and occupational exposure status to verify whether patients who were 'exposed' to these risk factors acknowledged these as potential causes. We further stratified for sex, age, education and marital status.

The institutional review board approved the NBCS and all participants provided written informed consent. The Statistical Package for Social Sciences (SPSS, version 20.0) was used to create the tables and compare groups using Pearson chi-square test. P-values of less than 0.05 were considered statistically significant.

Results

In this study, 1793 UBC survivors were included and only 366 (20%) participants reported one or more possible causes for their cancer. Table 1 summarizes the sociodemographic and clinical characteristics of the total study population and of patients who did and did not report a suspected cause, separately. The majority of the participants was male (n=1448, 81%) and the median age at completion of the questionnaire was 68 years (interquartile range: 61-74 years). Most of the participants were married (n=1439; 80%), and had a low educational level (n=1388; 77%). Almost two-thirds of the participants were former smokers (n=1164; 65%), 23% (n=417) were current smokers and 12% (n=211) never smoked. Self-reported positive family history of UBC was present in 6% (n=103) and 963 (54%) reported occupational exposure. Comparing participants who did and did not report a causal explanation, those with a causal explanation were younger (median age 64 vs. 69 years) and more likely to have a high educational level (32% vs. 19%). Also, those who reported a causal explanation were more likely to have had occupational exposure (61% vs. 52%).

Table 1 Sociodemographic and clinical characteristics of Dutch bladder cancer survivors included in the study.

	All bladder cancer survivors N=1793	Participants who reported a suspected cause N=366	Participants who did not report a suspected cause N=1427
Age at diagnosis (years)[1]	63 (56-70)	60 (53-66)	64 (57-70)
Age at completion of questionnaire (years)[1]	68 (61-74)	64 (58-71)	69 (62-74)
Time between diagnosis and completion of questionnaire (years)[1]	2 (1-6)	3 (1-7)	2 (1-6)
Body mass index (kg/m^2)[1,2]	25.3 (23.7-27.2)	24.7 (23.2-26.3)	25.4 (23.8-27.5)
Gender			
Female	345 (19%)	78 (21%)	267 (19%)
Male	1448 (81%)	288 (79%)	1160 (81%)
Marital status (%)			
Married	1439 (80%)	290 (79%)	1149 (81%)
Living alone	274 (15%)	51 (14%)	223 (16%)
Living together[3]	80 (5%)	25 (7%)	55 (4%)
Educational level (%)[4]			
Low	1388 (77%)	244 (67%)	1144 (80%)
High	391 (22%)	117 (32%)	274 (19%)
Unknown	14 (1%)	5 (1%)	9 (1%)
Currently employed (%)			272 (19%)
Yes	387 (22 %)	115 (31%)	1155 (81%)
No	1406 (78%)	251 (69%)	
Smoking status[5]			
Never smoked	211 (12%)	44 (12%)	167 (12%)
Former smoker	1164 (65%)	254 (69%)	910 (64%)
Current smoker	417 (23%)	68 (19%)	349 (24%)
Occupational exposure[6] (%)			
Yes	963 (54%)	223 (61%)	740 (52%)
No	830 (46%)	143 (39%)	687 (48%)
Positive family history of bladder cancer[7] (%)	103 (6%)	24 (7%)	79 (6%)

[1] Median and interquartile range; [2] Self-reported average BMI (kg/m^2) during adult life; [3] Cohabiting or living with children; [4] Low (primary education, secondary education and vocational education), high (university and university of applied sciences) or unknown; [5] At the time of filling out the questionnaire; [6] Based on questions regarding regular, current or past exposure to chemicals, radiation, and vapors/gases; [7] At least one reported first-degree family member with UBC.

Table 2 summarizes the categories of causal explanations among the total study population. Smoking (n=184; 10%), occupational exposure (n=85; 5%) and heredity (n=29; 2%) were the three most reported causal explanations among all participants. Environmental and chemical exposure was cited by 2% (n=28) and stress, other medical condition/intervention, medication, lifestyle and micturition/fluid intake were each mentioned by approximately 1% of the participants. Medical condition/intervention comprises answers such as 'The bladder tumors are caused by tumor in one kidney', 'Late-effects of radiotherapy for rectal cancer?'. Lifestyle encompassed answers related to alcohol and food intake as well as physical activity (e.g. 'overuse of coffee', regular alcohol user/often chips eater', 'lack of exercise'). Other causes that were reported by 0.6% or less of the participants are passive smoking, bladder infections, history of polyps, treatment delay, and don't know/other. The category don't know/other contained a variety of answers that could not be placed in other categories, e.g. 'coincidence', 'burns accident at age 3.5' and answers of participants that they did not understand what caused their disease since they lived a healthy life. All answers are included in Appendix I.

Table 2 Categories of perceived causes of bladder cancer among all included Dutch bladder cancer survivors and among those who reported a suspected cause.

Total of participants	No. giving explanation	% of all participants (n=1793)	% of participants who reported a suspected cause (n=366)
Smoking	184	10%	50%
Occupational exposure	85	5%	23%
Heredity	29	2%	8%
Stress	26	1%	7%
Bladder infections	8	0.4%	2%
History of polyps	4	0.2%	1%
Environmental and chemical exposure	28	2%	7%
Medication	22	1%	6%
Other medical condition/ intervention	25	1%	7%
Lifestyle	22	1%	6%
Micturition/Fluid intake	20	1%	6%
Passive smoking	9	0.5%	3%
Don't know/other	11	0.6%	3%
Treatment delay	3	0.2%	1%

Table 3 summarizes the three most cited categories of causal explanations among the total study population, stratified by smoking status, family history of UBC and occupational exposure. Former smokers seemed slightly more likely to suggest smoking (143 out of 1164; 12%) as a cause than current smokers (41 out of 417; 10%) (p=0.18). Among all participants who had occupational exposure (n=963), 83 participants (9%) reported occupational exposure as a cause of their disease. Two participants who reported occupational exposure did not have any occupational exposure according to the questionnaire. Lastly, participants with a positive family history for UBC were more likely to mention heredity as a causal explanation (5 out of 103; 5%) compared to participants with a negative family history (24 out of 1690; 1%) (p=0.02). We also stratified these causal explanations by sex, age (≤67 vs. ≥68), education and marital status (data not shown, all p-values <0.05). Smoking was more often mentioned as a possible cause by younger participants, higher educated participants, and by participants who were living together. Occupational exposure was more frequently mentioned by men and younger participants, and heredity by higher educated participants.

Table 3 Perceived established causes of bladder cancer among Dutch bladder cancer survivors stratified by presence of these causes.

Stratification	Total of participants	Participants giving the risk factor as a causal explanation (%)
Smoking	1792	184 (10%)
Never	211	0 (0%)
Former	1164	143 (12%)
Current	417	41 (10%)
Occupational exposure	1793	85 (5%)
Yes	963	83 (9%)
No	830	2 (0.2%)
Family history of bladder cancer	1793	29 (2%)
Positive	103	5 (5%)
Negative	1690	24 (1%)

Table 4 presents examples of reported causes divided into three categories, 'established risk factors for bladder cancer', 'unknown or unidentified effect on bladder cancer risk' and 'unlikely to have an effect on bladder cancer risk'.

Table 4 Selection of examples of perceived causes of bladder cancer of Dutch bladder cancer survivors.

Perceived causes	Examples of perceived causes given by the participants
Established or probable risk factors for bladder cancer	Smoking According to physician due to smoking Genetically determined I think because of many bladder infections Pipe smoking Late-effects of radiotherapy for rectal cancer Worked with paint for car spraying for 32 years Paint spraying Industrial fabrics exhaust fumes, maybe paints/dyes During my work in the clothing industry, I came into contact with chemical washing products Bad luck Coincidence Because of prolonged use of first an indwelling catheter and then a suprapubic catheter
Unknown or unidentified effect on bladder cancer risk	Hair dye; Working with pesticides Working with silkscreen printers, cleaning products, thinners/ink Cleaning up asbestos Lots of contact with asbestos As a child exposed to "passive smoking" a lot Use of immunosuppressive medication Use of hormones for half a year during menopause transition Stress Use of Selsun shampoo against head lice Used to prepare tics unprotected Worked in roofing Perhaps holding in urine for too long Fears / anxieties Benign polyp Little drinking and urination Prolonged use of medication against bladder spasms As a painter, worked extensively with dilutions especially methylene Laboratory work with the use of many kinds of solvents, e.g. benzene, chloroform, acetone, etc. Spend a lot of time in traffic (20 years) Frequent antibiotics due to inflammations Lifestyle nutrition-related Food Often French fries eater Can the chickenpox virus have had an effect?

Table 4 Continued.

Perceived causes	Examples of perceived causes given by the participants
Unlikely to have an effect on bladder cancer risk	Damage of urethra after prostate surgery Coffee Sedatives (Diazepam) Always worked in a cooling compartment Heart surgery Geneva, where inner penis was damaged. Thereafter several surgeries on penis Too much Erythrocytes/proteins in urine Sunburn Drank a lot of diet sodas with aspartame Sweeteners.

Discussion

In this study, we evaluated self-reported causes of bladder cancer among UBC survivors. Only 20% reported at least one causal explanation for their cancer. The most common causal explanations reported among all participants were smoking (10%), occupational exposure (5%) and heredity (2%), all established risk factors for UBC. Most patients who were exposed to these risk factors failed to report these factors as potential causes of their disease. This is even more striking given the fact that these risk factors were named in the invitation brochure as established risk factors.

Five studies investigated awareness of smoking as a risk factor for UBC among urological (9, 14) and UBC (9, 15-17) patients (Table 5). All studies used a closed question and asked about bladder cancer in general, except for one study (16) that only asked about the patient's own disease. Two studies (9, 15) additionally asked about believes regarding their own bladder cancer. In a study with 280 urological patients (14), the participants were asked to indicate whether smoking, as well as other factors, increased the risk of UBC. Only 36% reported smoking as a risk factor for UBC. In a study with 202 urological patients (9), 118 (58%) of them were aware of the relation between smoking and bladder cancer, and 22 of 39 (56%) of currently smoking UBC patients believed that smoking was related to their disease. In both studies, no difference by smoking status of the patients was observed. Three studies were conducted exclusively among UBC patients (15-17). In a study with 78 participants, 12 of 55 ever smokers (22%) were aware of smoking as a risk factor for their disease (16). A study with 71 participants reported that 85% was aware of smoking as a risk factor for UBC (17). Lastly, a larger study (n=790) showed that 68% of the patients cited tobacco use as a risk factor for UBC in general (90%, 64% and 61% for current, former, and never smokers, respectively) (15). Regarding perceived causes of their own disease, tobacco was mentioned by 84% of the current smokers, 48% of the

Table 5 Overview of literature on perceived causes of bladder cancer in urological and bladder cancer patients.

Author (year), country	Study sample	Bladder cancer in general or own cancer	Open or closed question
Dearing (2005), United Kingdom	55 smoking non-muscle invasive bladder cancer patients, year(s) of diagnosis unknown	Own bladder cancer	Closed
Nieder (2006), USA	280 urological patients presenting in the clinic in 2005	Bladder cancer in general	Closed
Anastasiou (2010), Greece	202 urological patients of whom 39 currently smoking bladder cancer patients, year(s) of diagnosis unknown	Total population: bladder cancer in general Smokers: own bladder cancer	Closed
Guzzo (2012), USA	71 bladder cancer patients diagnosed 2008-2009	Bladder cancer in general	Closed
Bassett (2014), USA	790 non-muscle invasive bladder cancer patients diagnosed 2006-2009	Bladder cancer in general and own bladder cancer	Closed
Current study, The Netherlands	1793 Bladder cancer patients diagnosed 1995-2011	Own bladder cancer	Open

[1] When exact question was not specified in the article, we formulated a question as accurately as possible based on the information provided;

	Question[1]	Main results
	Are you aware of smoking as a risk factor for development of your disease? Are you aware that continued smoking could worsen prognosis?	Answered yes: 22% 13%
	Which of the following factors can increase the risk of bladder cancer? Increasing age, a high fat diet, a low fiber diet, smoking, family history, multiple sex partners, none of these factors and do not know.	Perceived smoking as a risk factor: Bladder: 36%
	All patients: Are you aware of relation between smoking and… … bladder cancer? Smoking bladder cancer patients: Do you believe smoking is related to your present problem?	Answered yes: 55% 56%
	  Smoking is risk factor for bladder cancer. Smoking is leading cause of bladder cancer in the United States.	Answered true: 85% 51%
	Based on what you know or believe, can any of the following cause bladder cancer in anyone? Based on what you know or believe, did any of the following cause your bladder cancer?	Answered yes[2]: Tobacco use: 68% Chemicals: 54% Age: 45% Alcohol: 25% Holding urine: 20% Sexual activity: 12% Answered yes to tobacco use[2,3]: Active smokers: 93% Former smokers: 48% Never smokers: 8%
	You have been diagnosed with bladder cancer. Do you have any idea what may have been the cause of your cancer?	Smoking: 10% Occupational exposure: 5% Heredity: 2% Environmental and chemical exposure: 2% Stress: 1% Medication: 1% Other medical condition/ intervention: 1% Lifestyle: 1% Micturition/fluid intake: 1%

[2] Answer options for both questions: age, family history, alcohol, diet, tobacco use, "holding" urine, chemical exposure, bladder infections or stones, sexually transmitted diseases. No information available for risk factors not mentioned in the table; [3] Information only available stratified for smoking status (never, former, active)

former smokers, and 8% of the never smokers. In our study, we found that a strikingly low percentage of both former and current smokers reported smoking as a causal explanation for their own cancer (12% vs. 9%, respectively). This suggests that the association between smoking and bladder cancer is largely unknown. The open-ended format of the question used in our study might have played a role, as well as the choice of answering 'no', possibly giving participants an easy opportunity to avoid thinking about an explanation. Furthermore, ignoring risk factors that might have been within the patients' control may be a strategy to shield themselves against negative emotions such as self-blame (19).

To date, only two studies examined perceived causes of UBC among urological or UBC patients covering causal explanations other than tobacco (14, 15). Unfortunately, one of these studies did not report these results (14). In the other study (15), tobacco was the most cited risk factor (68%), followed by chemicals (54%) and age (45%). In our study, only 7% of all participants believed chemical or occupational exposure might have caused their disease, and a mere 8% of occupationally exposed participants mentioned this as a cause, even though certain types of occupational exposure are established risk factors. Surprisingly, none of our participants mentioned age or aging even though this is an established risk factor for cancer in general (20). An explanation may be that only patients younger than 75 were recruited. The large difference with the Basset study (15) might be explained by the type of question used (true/false question as opposed to our open question) or the level of education (higher educated as opposed to the low educational level of our study population). Ageing has been reported to be an unknown risk factor in patients with other types of cancer as well, e.g. in only two of 22 studies on breast cancer participants mentioned age as a risk factor (21).

With 2%, heredity was the third most cited explanation, indicating that the role of genetics in bladder cancer etiology is not very well known among UBC survivors either. As expected, the percentage of participants who reported heredity was higher among survivors with a positive family history (5%) compared with participants with a negative family history (1%). Still, 5% is almost negligible. In a similar study that we performed among patients with prostate cancer, the percentage of patients with a positive family history that mentioned heredity was four times higher (19%). In a study that described survivors' beliefs about the causes of prostate, colorectal and breast cancer in general, awareness of heredity was much higher than in our study (>75%) (10). This might be explained by the role of heredity in these types of cancer being more generally known but, again, also by the use of a true/false instead of open question.

For some of the causes mentioned by the participants, there is no or inconsistent evidence for an association with UBC, or an association is unlikely (table 4). An explanation for this might be that the mentioned cause is a well-known risk factor for other cancers or is frequently suggested to be a risk factor for cancer by the media, leading patients to believe that there is a link with UBC as well. This was also found by previous studies on other cancers (10, 22-24). It may be important to proactively address the lack of evidence

for these factors as certain beliefs may prevent patients from changing real risk behaviors (22).

Even though a strikingly low percentage of our participants mentioned a possible cause for their UBC, this is not an unusual finding. In a systematic review on perceived causes of breast cancer among breast cancer survivors (21), the percentage of perceived causes mentioned in the different studies varied greatly, even for well established risk factors. For example, heredity was reported as possible cause by only 4% in one study, while 71% cited it in another study. Comparing two studies on melanoma also reveals a large difference in perceived causes (22, 25). One study. (25) found that only about one-third of the participants thought sun exposure could have caused their melanoma, while in the other study (22) 80% mentioned this as a possible cause. These differences in knowledge may be partly explained by factors such as age, education and country of origin.

In conclusion, the results of this study show that most UBC survivors were not aware of any causal explanation for the development of their cancer. Even among participants with established risk factors for bladder cancer, these established risk factors were not commonly perceived. This finding might reflect the superficial knowledge on risk factors for bladder cancer in the population and highlights the importance of effective education on bladder cancer risk factors.

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Appendix I Perceived causes of bladder cancer reported by Dutch bladder cancer survivors.

Categories of perceived causes	Participants' answers
Smoking	'Smoking', 'According to physician due to smoking', 'Smoking according to my urologist', 'Probably because of smoking', 'According to specialist smoking is one of the causes', 'Doctor claims that smoking could be a cause or at least an important contribution', 'According to the doctor: smoking', 'I think smoking', 'Could be smoking', 'According to my urologist smoking is the primary cause of my mouth disease in 1981 and the bladder polyps in 1994', 'People say because of smoking', 'At the time I smoked ± 20 cigarettes per day', 'Much smoking', 'According to the urologist, smoking might be a cause', 'My wife thinks smoking', 'My smoking behavior', 'Smoked lots of cigarettes', 'Possibly smoking', 'Perhaps smoking behavior', 'Perhaps due to smoking', 'No certainty, but sometimes I suspected an association with smoking home-grown cannabis', 'Cigar / pipe smoking. Did this intensively for many years before the bladder tumor was discovered', 'Smoking in the past', 'Smoking? Haven't smoked much in my younger years, from about the age of 40 to 59 I smoked 1 pack per day. Two weeks before my retirement in 1993 I quit and never smoked again', 'Perhaps smoking', 'Smoking, 9 per day', 'It turns out smoking can be a cause', 'In hindsight my smoking can be a possible cause', 'Smoking can be a cause', 'Smoking is also a cause', 'Not sure, might be smoking', 'According to people in Radboudumc: smoking?', 'Prolonged smoking', 'It is said smoking', 'Probably a lot of smoking', 'According to the doctors it is because of smoking', 'Smoked for too long and too much in my life', 'Maybe smoking?', 'Smoking for about 20 years', 'Too much smoking', 'Pipe smoking causing tar juice to be swallowed (frequently)', 'I suspect by smoking', 'Of course, smoking behavior', 'Presumably smoking', 'Possible contamination of smoking', 'Smoked profusely for 38 years', 'Used to smoke firmly for 26 years', 'Smoked from the age of 16 to 51', 'Long-term smoking', 'Smoked in early childhood', 'Smoking at a younger age'.
Occupational exposure	'At NV Philips we worked with variouspollutants like Clophen (hydrochloric), araldietharders, various solvents', 'Employment history', 'Working with highly toxic substances', 'During my work in the clothing industry, I came into contact with chemical washing products', 'During study (chemistry) and work (paint industry) certain chemicals that I have been in contact with can be the cause', 'Worked with textiles?', 'Worked a lot with arsene, selenium and iodine at the factory', 'Work was not always clean, probably due to my work activities', 'Working with chemicals', 'Working with Bison Kit (glue)', 'Work', 'Working with Bison Kit (glue)', 'Have worked a lot with harmful substances (glue, etc.)', 'As a painter, worked extensively with dilutions especially methylene', 'Perhaps working with asbestos', 'Very carelessly handling photo chemicals', 'Washing hands with benzene (in 1954) + pesticides (1960)', 'Work at the plant nursery, worked a lot with pesticides without protective measures', 'Lots of contact with asbestos', 'Worked many years (± 20) as a project manager in mostly aluminum processing industries (aluminum melting furnaces) and ceramic and metal hardening furnaces', 'My work with toxic substances. Carelessly handling these substances for more than 35 years', 'Worked a lot with unhealthy stuff', 'Welding fumes and metal vapors, lead poisoning', 'Possible contamination due to chemicals during laboratory work', 'Occupation as painter maintenance', 'Worked with photocopier, suffered a lot especially from coughing', 'Cleaning air handling units, working with diesel due to cleaning oil boilers, working with detergents', 'Paints, turpentine, paint thinners, paint removers used as a painter', 'I think the reason for this lies in the period of 1981-1985 (work)', 'During the period (1955-1967) I worked in a graphics company and worked a lot with printing inks stained-solvents such as gasoline, diesel and kerosene', 'Smoking solvents. I spent 15 years on average 8 hours per month making prints in a poorly ventilated area', 'The use of pesticides', 'During home furnishing I worked with Novilon carpet.

	Which contained asbestos and the handling of glue', 'At the age of 16, worked near a paint shop for 6 months.', 'Occupational disease through work', 'Due to autogenous and electric welding work, not the right safety measurements taken (unsafe, low ventilation)', 'Because of my job, daily contact with fuels and auto gas', 'Always worked in a cooling compartment', 'Preparations cytostatic for chemotherapy', 'Use of toxic substances', 'Using gun oil PX10 during period 1965-1995', 'Exposed to trichloroethylene, fine asbestos dust, many other solvents', 'Working with silkscreens printers, cleaning products, thinners/ink', 'Roofing/roof covering', 'Processed asbestos. Sawing in the years 1969-1970. Shielding heaters', 'Preparation and distributing cytostatic', 'Maybe paints/dyes', 'Worked with paint for car spraying for 32 years', 'Worked with hazardous substances (Argon, Eldrin etc.)', 'The use of pesticides', 'Working with pesticides', 'Suggested that this may be related to exposure to chemicals in the laboratory (formaldehyde, etc.). Two colleagues at the lab have been diagnosed with bladder cancer', 'Paint (painting)', 'Radiation, used to prepare cytostatic unprotected', 'Worked with epoxy resin, Perspex adhesives, processing Perspex, solvents (thinner, toluene, turpentine), polystyrene, acrylic', 'Spraying cars without proper protection', 'Paint spraying (lacquer)', 'Handling X-rays in my profession, handling chloralactofinol in my profession', 'Worked in a laboratory from the age of 16 to 26', 'Working with asbestos (which was formerly used in brake lining)', 'Perhaps dyes/colorants (painter)', 'Pesticides or disinfectants', 'Use of spray bottle when ironing', 'Inhaling solvents for ink', 'Chemicals during work', 'Plastic processing vapors (styrene)', 'Working with photo processing chemicals, inhalation of lead-containing substances/gases during the firing of ammo', 'Printing', 'Asbestos', 'Due to profession', 'Chemicals due to spraying and welding', 'Temporarily handling photographic chemicals in poorly ventilated areas', 'Worked with some regularity with duplicator during the job', 'Carelessly working with chemicals', 'Uranium in mission area', 'Prolonged contact with printing inks, adhesives bookbinding', 'Inhaled formaldehyde vapors for 8 years?', 'Electromagnetic radiation (radar equipment)', 'Laboratory work with the use of many kinds of solvents, eg. Benzene, chloroform, acetone etc', 'Work', 'Cleaning up asbestos', 'Paint chemistry (components), industrial fabrics', 'Exposure to hazardous substances', 'Possible cause that I do not rule out: sanding plate with asbestos', 'Welding fumes', 'Laboratory activities'.
Passive smoking	'As a child exposed to "passive smoking" a lot', 'Second-hand smoking, when staying in smoky environments (frequently) it seems that the polyps come back', 'Second-hand smoking for many years', 'During work I was always surrounded by smokers, even after I had quit myself', 'Second-hand smoking', 'Always smoked passively', 'Father was a smoker. Been exposed to smoke a lot via passive smoking', 'Passive smoking in the office', 'Smoked passively for 20 years'.
Environmental and chemical exposure	'Nuclear testing in the years 1945-1980 and spraying pesticides', 'Used to go swimming frequently in the IJsselmeer near iron foundry, a lot of iron in water', 'Chernobyl (radiation), cows had to go inside, was not necessary for us and our children. Or pesticides', 'I have lived on the site of a paint factory from birth until the age of 16', 'Perhaps zinc plant in Budel?', 'I lived in a house at the Schaapsdrift in Arnhem for 36 years. The soil or ground water was contaminated', 'Lived in Heveadorp from birth till the age of 21. We lived near a rubber factory, where I used to play as a child', 'Is drinking water not the cause?', 'Exhaust fumes', 'Exhaust and gasoline fumes', ' Cycled to and from work for 20 years (14 km there and 14km back) along cars, traffic jams and industrial areas (AKZO, BASF, Billiton). Used extra effort right at the place that contained a lot of harmful dust', 'Air pollution, environmental pollution', 'Prolonged exposure to exhaust fumes', 'Asphalt plant in the immediate surroundings', 'Inhaled fireplace fumes for 20 years', 'Exhaust fumes', 'Particulate matter (highway/power plant)', 'Motor/air pollution in Hong Kong. I have lived in Hong Kong for four years', 'The use of chemicals in food such as growth hormones, etc', 'Possibly: have been drinking water (during sports) from a disposable plastic bottle, which was melted in the sauna, for a long time (year)', 'Chemical stuff', 'Chemicals', 'Chemicals darkroom', 'Hair dye (hairdresser denied this)', 'Used cyanide acrylate (superglue) for nails regularly for 30 years'.

Appendix I Continued.

Categories of perceived causes	Participants' answers
Heredity	'Presumably hereditary predisposition; My father died of acute renal failure', 'Genetically determined', 'Heredity, my father had them', 'Grandpa and uncle?', 'My father also had bladder polyps, but my siblings don't', 'Maybe because of the genes (maternal)', 'Possible hereditary', 'Hereditary', 'During the war father in hospital because of bladder. Paternal aunt diagnosed with polyp at age 60 and lived till the age 85. They all used to work in the textile industry. Hereditary?', 'Perhaps inherited father's side?', 'Hereditary, paternal side', 'Hereditary, father and mother', 'Possibly hereditary', 'According to the urologist I was born with it', 'Runs in the family', 'Hereditary: father had stoma because of bladder cancer (deceased from lung cancer)', 'Hereditary defects in DNA', 'Maternal side', 'It runs in the family (grandfather and second cousin)', 'Genetic determination can also be the cause', 'Gene defect', 'Hereditary factors'.
Other medical condition/ intervention	'First kidney and everything that goes with it, and two years later bladder tumor', '1997 first symptoms, physician found no passage from urethra to bladder. Had to wait? 2001 severe bladder bleeding, surgery, cancer (specialist)', 'Heart surgery Geneva, where inner penis was damaged. Thereafter several surgeries on penis', 'Too much Erythrocytes / proteins in urine. Had regular kidney tests from the age of 15', 'Because of prolonged use of first an indwelling catheter and then a suprapubic catheter', 'Dauer catheter (DC)', 'The bladder tumors are caused by tumor in one kidney', 'Diagnosed with cancer of stomach / liver in 1989, by removing the left lobe of the liver, the liver may not be working properly, causing polyps to arise?', 'Damage of urethra after prostate surgery', 'Sensitive membranes?', 'Can the chickenpox virus have had an effect?', 'Kidney cancer?', 'Malignant tumor', 'Maybe because I've had prostate cancer. And after two years 28 radiation treatments', 'Late-effects of radiotherapy for rectal cancer?', 'Violence from the outside on the bladder', 'The residue of my rotten gallbladder', 'Because of large prostate', 'Worm disease associated with living in very primitive conditions', 'Malignant tumor', 'Radiation', 'In 2005, 2/3 of the stomach removed due to malignant cancer. According to dr. at Radboudumc, where I was still under treatment at that time, this is not the cause for the bladder cancer', 'I always had to squeeze urine out, perhaps I never emptied my bladder sufficiently'.
History of polyps	Benign polyp', 'Benign polyp (August 2007)', 'Polyps in the bladder', 'Bladder polyp'.
Bladder infections	'Maybe because of the many bladder infections', 'I think because of many bladder infections', 'I think because of the bladder infections', 'Already had bladder problems (bladder inflammation) as a child', 'Neglect of urinary tract infection', 'Had ± 25 bladder infections', 'Prolonged bladder infections after returning from the tropics'.
Medication	'Used Resdan tar shampoo for 10 years until it became known that it can be carcinogenic', 'Had tuberculosis, used the drug PAS for two years', 'Prolonged use of "temporarily allowed" medication to relax the bladder', 'Medications?', 'Because of the drug Endoxan', 'Used Endoxan daily because of MS (1980-1982)', 'I always had the Yttrium injection into the knee as a possible cause in mind. Just a presumption. Further no idea', 'Due to my urologist I got the idea that it can come from the use of malaria pills', 'The use of acenocoumarol', 'Resistance reduced by using means (Prograf) against organ rejection', 'Medication use?', 'I might be DES-daughter', 'Use of Selsun shampoo against head lice?', 'Sedatives (Diazepam) since 1970', 'Medications for blood pressure', 'Used 50mg of Oxazepam daily for ± 12 years', 'Prolonged use of Denorex R shampoo', 'Medications', 'The use of hormones for half a year during menopause transition', 'Frequent antibiotics due to inflammations', 'Too often antibiotics from GP'.

Lifestyle	'Overuse of coffee', 'In 2002, I used a diet, Super Energy Method without carbs, low fat and high in protein', 'Possibly because of a too limited and too monotonous diet during the war years (1940-1945)', 'Used artificial sweeteners (1975-1979)', 'Lifestyle nutrition-related', 'Regular alcohol user, regular/often chips eater', 'Excessive drinking for a certain period of time', 'Alcoholic beverage', 'Coffee', 'Perhaps biking too much because of commuting', 'Possible contamination of alcohol', 'Not being conscious about your health and healthy lifestyle namely exercise etc', 'Drinking, lack of exercise', 'Sweeteners? Final years before tumor daily drinking of Amstel beer', 'Drank a lot of diet sodas with aspartame', 'Food', 'Alcohol', 'Drinking', 'Overeating', 'Lifestyle'.
Micturition/fluid intake	'Having to hold in urine for prolonged periods of time due to profession', 'Perhaps holding in urine for too long', 'Probably failed to empty bladder often enough', 'During my profession as a truck driver often held off going to the bathroom. I have the idea that that has something to do with it', 'Did not urinate on time', 'Insufficient drinking in the past', 'Probably drinking insufficient water?', 'Take too little fluid', 'Little drinking and urination (long residence time of tar in the bladder', 'Drinking insufficient water', 'Not drinking enough', 'Not enough drinking/concentrated urine', 'Driving 65,000 to 80,000 km per year', 'Insufficient drinking', 'Drinking alcohol in the evening and not urinating at night', 'Driven for more than 1 million kilometers', 'Drinking relatively little, years of living and working in Malaysia (warm climate and little drinking)', 'Spend a lot of time in traffic (20 years) commuting between Leiderdorp and Amstelveen (passing Schiphol)'.
Stress	'Stress', 'Stress, living in Neerbosch-Oost', 'Stress, "a bad disease"', 'With some hesitation I note that a lot of stress and responsibilities could have had an influence', 'Fears/anxieties', 'Stress, uncertain future?', 'When prisoner of war hemorrhage occurred (in feces/urine). Construction Sumatra Airport dragging trunks, earthwork, forest work', 'Can stress be a cause? It happened 4 months after my husband passed away', 'Stress after son getting cancer in 2005 and wife in 2006', 'Survivor guilt', 'Lots of stress', 'Psychosocial factors that we still know little about', 'Worked nightshifts every week. Disruption biorhythm/melatonin deficiency', 'Due to intensively taking care of my husband. An illness of nearly three years (cancer). First bleeding on the day of the funeral', '40 years of living under severe tension', 'Stress and overloaded?', 'Too much work', 'Years of stress due to conflict with boss (since 2000)', 'Less relaxation', 'Very heavy childhood trauma (rape) must also have something to do with it'.
Treatment delay	'Waited too long to visit GP', 'GP should referred me sooner',
Don't know/other	'I live a very healthy lifestyle and cannot understand that I have it', 'Did not smoke, drank very little alcohol, still got cancer', 'Coincidence', 'Bad luck', 'Burns accident at the age of 3,5', 'Sunburn'.

7

Low awareness, adherence and practice but positive attitudes regarding lifestyle recommendations among bladder cancer patients

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Abstract

Background: A healthy lifestyle may reduce the risk of non-muscle-invasive bladder cancer (NMIBC) recurrence. The objective of this study was to obtain insight in whether NMIBC patients are aware of possible risk factors for (bladder) cancer, adhere to lifestyle recommendations for cancer prevention, received lifestyle advice from their physician, and what their attitudes are towards physicians giving lifestyle advice.

Methods: Patients with newly diagnosed NMIBC between 2014-2017 participating in the UroLife cohort study completed questionnaires and a survey at 6 and 12 weeks after diagnosis about awareness of (bladder) cancer risk factors, adherence to lifestyle recommendations, reception of lifestyle advice, and attitudes towards physicians giving lifestyle advice.

Results: A total of 969 NMIBC patients were included. Most patients (89%) were aware that smoking is a risk factor for cancer, but only 44% reported smoking as a risk factor for bladder cancer. Knowledge of other risk factors for cancer varied between 29% (fruit and vegetable consumption) and 67% (overweight). Adherence to cancer prevention recommendations varied between 34% (body weight) and 84% (smoking). Of the smokers, 70% reported they were advised to quit. Only 19% of all patients indicated they received other lifestyle advice. More than 80% of patients had a positive attitude towards receiving lifestyle advice from their physician.

Conclusion: These findings show that awareness of (bladder) cancer risk factors and adherence to cancer prevention lifestyle recommendations among NMIBC patients is low and that physicians' information provision should be improved.

Introduction

Patients with non-muscle-invasive bladder cancer (NMIBC) have a high five-year risk of recurrence (1), necessitating a burdensome and expensive follow-up program (2). A healthy lifestyle has been associated with several positive clinical outcomes in patients with various cancer types, i.e. reduced cancer risk, better prognosis, and reduced risk of secondary malignancies and lifestyle-related comorbidities (3, 4). In bladder cancer, cigarette smoking is responsible for about one-third of all diagnoses (5), and there is limited evidence for an association with overweight (6), physical activity (7), and fruit and vegetable consumption (8). Recent meta-analyses suggest that cigarette smoking (9) and overweight (10) are also associated with an increased risk of NMIBC recurrence.

A cancer diagnosis is often seen as a teachable moment at which the patient is highly motivated to change lifestyle behaviour (11). Also, NMIBC patients have been shown to be more likely to accept smoking as a cancer risk factor when this information was provided by their urologist (12). This highlights the importance of physicians discussing lifestyle with their patients and raising their awareness of known cancer risk factors.

We aimed to obtain more insight in whether NMIBC patients are aware of possible risk factors for (bladder) cancer, adhere to lifestyle recommendations for cancer prevention, received lifestyle advice from their physician, and what their attitudes are towards physicians giving lifestyle advice.

Patients and methods

Participants

This study was part of the population-based, prospective cohort study UroLife (Urothelial cancer: Lifestyle, prognosis and health-related quality of Life), conducted in 22 hospitals in The Netherlands. Before the start of the study, permission was asked from all participating urologists to identify their eligible patients in the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organization (IKNL). Patients diagnosed between April 1, 2014 and April 25, 2017 were identified approximately 4 weeks after diagnosis and invited on behalf of their urologist to participate in this study. Eligible patients were Dutch speaking men and women between 18 and 80 years old and diagnosed with a histologically confirmed primary Ta, T1 or Tis tumour that was surgically removed with a transurethral resection. Patients with a previous cancer diagnosis in the past five years, and those with a positive lymph node or distant metastasis were excluded. Written informed consent was obtained from all participants. UroLife was approved by the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494).

Questionnaires

Patients completed web-based or paper-and-pencil-based questionnaires at approximately six and twelve weeks after diagnosis. Web-based questionnaires were collected using the data collection tool of the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry (13). The baseline questionnaire included questions on socio-demographic characteristics. Both questionnaires included questions on smoking, body mass index (BMI), physical activity, alcohol consumption, and dietary supplement use at the time of filling out the questionnaires.

Smoking status was assessed by asking whether patients smoked or had smoked in the past and, if applicable, the date/age of smoking cessation. Patients were categorized into never, former (quit >6 months before diagnosis; quit £6 months before or after diagnosis), and current smokers. BMI (kg/m^2) was calculated based on self-reported weight and height, and classified as underweight (≤18·4 kg/m^2), normal weight (18·5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2) (14). Habitual physical activity was assessed using the validated *S*hort *QU*estionnaire to *AS*sess *H*ealth-enhancing physical activity (SQUASH), which measures average time and intensity of different activities in a normal week (15). Activities were classified as light, moderate, or vigorous by combining their Metabolic Equivalent of Task (MET) score with their self-reported intensity. Alcohol consumption was assessed by questions about the number of days per week and the average number of drinks per day for week days and weekend days, separately. Dietary supplement use was assessed by asking whether patients (ever) used supplements (at six weeks after diagnosis) or in the previous three months (at twelve weeks after diagnosis). Patients were categorized into never, former, and current users.

We classified former and never smokers as adhering to the guideline of not smoking. Patients adhering to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations for cancer prevention were defined as (1) having a normal weight (BMI 18·5-25 kg/m^2), (2) being moderately active (commuting activities, sports, and leisure activities of 3-4 MET with high intensity, or of ≥4 MET with low, moderate or high intensity) for at least 210 minutes per week, (3) consuming a maximum of two drinks and one drink of alcohol per day for men and women, respectively, (4) former or never using dietary supplements.

Survey

A survey was included in the second questionnaire. Awareness of risk factors for cancer in general was assessed with a prompted list of 13 known risk factors on a four-point Likert scale. An open-ended question was used to ask patients to report which of these 13 or other risk factors were risk factors for UBC. For analysis, responses were categorized into the same categories as for the 13 cancer risk factors, with an additional category for other responses. Furthermore, patients were asked if their physician asked about their smoking behaviour, and gave them advice about smoking cessation, weight loss, physical activity,

and a healthy diet. Patients who stated that they quit smoking after diagnosis were asked to indicate if their physician offered help and their main reason for smoking cessation. Finally, patients' attitudes towards physicians giving advice on smoking cessation, a healthy diet, physical activity, and weight loss were assessed for four positive and four negative attitudes on a four-point Likert scale (16).

Statistical Analysis

Standard descriptive statistics were calculated to describe baseline characteristics of the cohort, and results for awareness, adherence, advice, and attitudes. Multivariable logistic regression analyses were used to determine whether age, gender, and educational level were associated with adherence to the lifestyle recommendations for smoking, body weight, physical activity, alcohol consumption, and supplement use. Also, it was determined whether awareness of smoking, body weight, physical activity, and alcohol use being risk factors for cancer was associated with adherence to these lifestyle recommendations. All tests were two-sided and a p-value less than 0·05 was considered statistically significant. All data were analyzed using IBM SPSS Statistics, Version 22.

Results

Of all 2,134 invited NMIBC patients, 1,193 agreed to participate and 1,117 filled out at least one questionnaire (response rate 52%). Thereafter, 148 patients were excluded because of a previous cancer diagnosis in the past five years (n=4), metastases at diagnosis (n=1), or no completed first (n=10) or second questionnaire (n=133). In total, 969 (87%) patients were included in the current study. Median age at diagnosis was 68 years, the majority of patients were men, and almost half was lower educated (Table 1).

Eighty-nine percent of patients recognized smoking as risk factor for cancer, but other lifestyle factors were known by only 29-67% (Table 2). Sixty-one percent of patients reported one or more possible risk factors for UBC, with smoking being most frequently reported (44%) (Table 2, Appendix Table 1). Patients who reported smoking as a risk factor were younger and higher educated but did not differ according to smoking status (data not shown).

Adherence to lifestyle recommendations for cancer prevention at 6 weeks after diagnosis was lowest for body weight (34%) and highest for smoking (84%) (Table 3). Ninety-one patients (9%) quit smoking in the period of six months before until six weeks after diagnosis. They more often reported smoking as UBC risk factor than patients who continued smoking (78% vs. 60% respectively, data not shown). Their most important reasons for quitting were the NMIBC diagnosis (51%), general health (21%), advice of their physician (13%), or another reason/not applicable/no reason (15%). At 12 weeks after diagnosis, adherence to the lifestyle recommendations was similar, apart from a decrease

Table 1 Sociodemographic characteristics of 969 Dutch non-muscle-invasive bladder cancer patients at baseline.

Variable[1]	
Age at diagnosis (y), median (IQR)	68 (61-73)
Sex, n (%)	
Male	771 (80%)
Female	198 (20%)
Educational level[2], n (%)	
Low	469 (48%)
Medium	257 (27%)
High	242 (25%)
European ancestry, n (%)	953 (98%)
Living situation, n (%)	
Alone	35 (4%)
With partner, with or without children	821 (85%)
Divorced or widow(er)	93 (10%)
Other	20 (2%)
Comorbidities, n (%)	
No comorbidities	106 (11%)
≥1 lifestyle-related comorbidity[3]	107 (11%)
≥1 other comorbidity	303 (31%)
≥1 lifestyle-related and ≥1 other comorbidity	441 (46%)
Weeks between diagnosis and first questionnaire, median (IQR)	6 (5-8)
Weeks between diagnosis and second questionnaire, median (IQR)	13 (12-14)

[1] Where scores do not total 100% this is due to missing values; [2] Low (primary -, secondary -, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university); [3] Heart disease, high blood pressure, diabetes mellitus type II. Abbreviations: IQR: interquartile range; y: year.

for physical activity (from 70% to 60%) and an increase for alcohol consumption (from 42% to 62%). Adherence was generally higher for patients who were older, male, and higher educated (Appendix Table 2). Patients who were aware of overweight, insufficient physical activity, and alcohol as being risk factors for cancer were more likely to meet the corresponding cancer prevention recommendations at baseline (Appendix Table 3). At follow-up, this difference only remained for alcohol.

Table 2 Awareness of risk factors for cancer in general and reported risk factors for bladder cancer among 969 Dutch non-muscle-invasive bladder cancer patients.

Risk factors	Cancer in general[1]		Bladder cancer
	Agree or Strongly agree n (%)	Disagree or Strongly disagree n (%)	Reported by patient as risk factor (yes/no) n (%)[2]
Smoking	866 (89%)	61 (6%)	428 (44%)
Second-hand smoking	802 (83%)	117 (12%)	40 (4%)
> 1 glass alcohol a day	394 (41%)	496 (51%)	109 (11%)
< 5 servings vegetables and fruit a day	285 (29%)	608 (63%)	13 (1%)
Red or processed meat ≥ once a day	468 (48%)	417 (43%)	46 (5%)
Overweight	646 (67%)	262 (27%)	41 (4%)
Sunburn > once as a child	504 (52%)	370 (38%)	10 (1%)
Age > 70 years	464 (48%)	428 (44%)	53 (6%)
First-degree relative with cancer	625 (65%)	268 (28%)	70 (7%)
Infection with Human Papilloma Virus[3]	175 (18%)	115 (12%)	4 (0.4%)
Insufficient physical activity	524 (54%)	373 (39%)	22 (2%)
Using solarium	784 (81%)	133 (14%)	23 (2%)
Exposure to radiation	796 (82%)	94 (10%)	103 (11%)

[1] Where scores do not total 100% this is due to missing values; [2] 16% reported risk factors other than risk factors listed for cancer in general (Appendix II) [3] For Infection with Human Papilloma Virus the option 'I don't know' was added, which was chosen by 638 patients (66%).

Eighty percent of patients indicated that their physician asked about their smoking behaviour (data not shown). Of the 226 patients who smoked at diagnosis, 159 (70%) were advised to quit (Table 4). Forty-three of those (27%) were offered help with smoking cessation, mainly consisting of advice about nicotine replacement (data not shown). Nineteen percent of all patients reported to have received advice on one or more other lifestyle behaviours, mostly on physical activity (Table 4). Noteworthy is that 31% of the overweight patients reported that weight loss advice was not applicable to them.

At least 80% of the patients thought it would be beneficial, helpful, and encouraging if physicians would give lifestyle advice, and approximately 70% agreed that it was the doctor's duty (Table 5). Fifteen percent or less believed it was insensitive, interfering, and unnecessary, and around 25% thought it was placing the blame on the patient.

Table 3 Lifestyle habits of 969 Dutch non-muscle-invasive bladder cancer patients at six and twelve weeks after diagnosis.

Lifestyle factor	Six weeks after diagnosis n (%)[1]		Twelve weeks after diagnosis n (%)[1]	
Smoking status				
Never	173	(**18%**)	173	(**18%**)
Former[2]	549	(**57%**)	547	(**57%**)
Former[3]	90	(**9%**)	87	(**9%**)
Current	150	(16%)	155	(16%)
Body mass index (kg/m²)				
≤18.4	9	(1%)	9	(1%)
18.5-24.9	322	(**34%**)	311	(**32%**)
25.0-29.9	457	(48%)	458	(48%)
≥30.0	171	(18%)	181	(19%)
Physical activity (min/week moderately active)				
≥210	675	(**70%**)	575	(**60%**)
<210	284	(30%)	384	(40%)
Alcohol consumption (glasses/day)				
≤1 (female) or ≤2 (male)	405	(**42%**)	591	(**62%**)
>1 (female) or >2 (male)	552	(58%)	366	(38%)
Supplement use				
Never	534	(**56%**)	502	(**53%**)
Former	94	(**10%**)	177	(**19%**)
Current	324	(34%)	273	(29%)

[1] Only reported for patients who filled out both questionnaires. Percentages in bold indicate adherence to the lifestyle recommendations for cancer prevention; [2] Former smokers who quit more than six months before diagnosis; [3] Former smokers who quit less than six months before diagnosis or shortly after diagnosis.

Table 4 Advice on lifestyle behaviour by physicians as reported by 969 Dutch non-muscle-invasive bladder cancer patients.

	n (%)[1]
Smoking cessation (smokers at diagnosis, n=226)	
Yes	159 (70%)
No	62 (27%)
Not applicable	1 (0.4%)
Physical activity	
Yes	142 (15%)
No	807 (83%)
Healthy diet	
Yes	75 (8%)
No	875 (90%)
Weight loss (patients with BMI>25 kg/m², n=631)	
Yes	39 (6%)
No	381 (60%)
Not applicable	198 (31%)

[1] Where scores do not total 100% this is due to missing values

Table 5 Attitude towards advice to be given by physicians about lifestyle behaviour to improve prognosis in 969 Dutch non-muscle-invasive bladder cancer patients[1]

	Smoking cessation		Healthy diet		Physical activity		Weight loss	
	Agree or strongly agree n (%)	Disagree or strongly disagree n (%)	Agree or strongly agree n (%)	Disagree or strongly disagree n (%)	Agree or strongly agree n (%)	Disagree or strongly disagree n (%)	Agree or strongly agree n (%)	Disagree or strongly disagree n (%)
Beneficial	874 (90%)	42 (4%)	867 (90%)	51 (5%)	864 (89%)	53 (6%)	876 (90%)	38 (4%)
Helpful	823 (85%)	59 (6%)	839 (87%)	61 (6%)	820 (85%)	71 (7%)	848 (88%)	46 (5%)
Encouraging	780 (81%)	90 (9%)	790 (82%)	97 (10%)	803 (83%)	82 (9%)	814 (84%)	69 (7%)
The doctor's duty	706 (73%)	173 (18%)	647 (67%)	237 (25%)	624 (64%)	252 (26%)	729 (75%)	149 (15%)
Insensitive	132 (14%)	699 (72%)	108 (11%)	736 (76%)	88 (9%)	753 (78%)	96 (10%)	738 (76%)
Interfering	80 (8%)	782 (81%)	81 (8%)	789 (81%)	76 (8%)	791 (82%)	84 (9%)	775 (80%)
Unnecessary	147 (15%)	721 (74%)	131 (14%)	738 (76%)	115 (12%)	748(77%)	100 (10%)	758 (78%)
Placing the blame	285 (29%)	584 (60%)	200 (21%)	661 (68%)	198 (20%)	663 (68%)	237 (24%)	618 (64%)

[1] Where scores do not total 100% this is due to 'don't know' responses (2-7%) or missing values (3-8%)

Discussion

In this large cohort of NMIBC patients, most patients recognized smoking as risk factor for cancer. Other cancer risk factors, and smoking as a risk factor for UBC, were less well-known. Adherence to the lifestyle recommendations for cancer prevention varied, with lowest adherence for a healthy body weight and highest adherence for not smoking. Patients indicated that they were not routinely advised about a healthy lifestyle by their physician, except for smoking cessation. However, the majority of patients had a positive attitude towards receiving lifestyle advice from their physician.

Awareness of cancer risk factors in NMIBC patients in our study is fairly comparable with that in the general population (17). Thus, a cancer diagnosis by itself does not seem to increase awareness of risk factors. This may be of concern, because cancer recurrence, the development of a second primary cancer, or lifestyle-related comorbidities (e.g., cardiovascular disease, diabetes) may be partly caused by the same risk factors that were involved in the etiology of the primary cancer (3). Moreover, awareness of risk factors and perception of one's own cancer risk may be important in the motivation to change unhealthy behaviours (18).

Awareness of smoking as a UBC risk factor greatly differs between studies, ranging from 10-85% (19). These differences can be explained by age, educational level, the type of question posed (open versus closed), and whether the question referred to UBC in general or to the patients' own disease. For example, our recent study in 1,793 Dutch UBC survivors asked about possible causes of their own UBC, and only 12% of ever smokers reported smoking as a possible cause (19). In our previous and current study, patients also reported non-established risk factors for UBC. Therefore, it remains important to educate NMIBC patients about established risk factors, to prevent them from focusing on causes or behaviours that do not influence disease (20).

Information on awareness in combination with information on adherence to lifestyle recommendations provides insight into whether knowledge is put into practice. The majority of patients did not smoke, which is similar to the findings of a Canadian study in 586 UBC patients (21). However, it is important to be aware that former smokers are prone to start smoking again as a coping mechanism in stressful situations (22). Only about one-third of the patients had a healthy body weight, which is similar to findings in cancer survivors as well as in a healthy population (23). Since the time between the two questionnaires was short, we did not expect large changes in BMI categories. The shifts we found were mainly caused by patients who had a BMI on the border of the categories and thus had a plausible weight loss or gain, although the possibility of misreporting cannot be excluded. The majority of patients adhered to the physical activity recommendation. However, physical activity is frequently over-reported (24). In the Canadian study in UBC patients, only one-third adhered to the physical activity recommendation (21), but a different questionnaire and different criteria for adherence were used. The increased

adherence to the lifestyle recommendation on alcohol from baseline to follow-up was also found in studies in other cancer survivors (25). Lastly, two-third of the patients adhered to the recommendation not to use supplements, which was higher than in US cancer survivors (26). Patients who were aware of smoking, overweight, insufficient physical activity, and alcohol as risk factors for cancer were more likely to quit smoking or adhere to the corresponding lifestyle recommendations. Awareness of risk factors may thus be of importance for actual behaviour.

Knowing whether and what kind of advice is given by physicians about risk factors and lifestyle can be used to improve provision of lifestyle advice in clinical practice. Although the majority of patients were asked about their smoking behaviour and the majority of smokers were advised to quit, still not all physicians follow the EAU guideline for NMIBC (27). Given the fact that a cancer diagnosis is seen as a teachable moment (11), and that advice from a physician greatly increases the chances of success with smoking cessation (12), all physicians should be encouraged to advise smoking cessation. Patients were not routinely informed about other lifestyle factors, possibly because convincing evidence for an association with UBC prognosis is still lacking.

The positive attitudes of NMIBC patients towards lifestyle advice observed are in line with those found in a similar survey in cancer survivors conducted in the UK(16). Since patients sometimes agreed with both a positive (e.g., 'helpful') and negative attitude (e.g., 'placing the blame'), discretion in providing lifestyle advice is required. Training of health care professionals in this area may be needed, since physicians have been shown not to feel well equipped to deliver smoking cessation interventions (28), and this likely also applies to providing advice on other lifestyle factors.

The UroLife study is the first to extensively investigate the combination of awareness, adherence, practice, and attitudes regarding lifestyle recommendations. This provides valuable information for physicians and health promotion initiatives. Furthermore, patients were included shortly after diagnosis and followed up prospectively, minimizing the reliance on memory. Also, much effort was put into complete retrieval of the data by follow-up telephone calls.

Limitations include the reliance on self-reported questionnaires that are inherently accompanied by the risk of bias such as over- or underestimation because of social desirability. Furthermore, the prompted question format for the question about cancer risk factors as opposed to an open question may have led to an overestimation of awareness (29), but made our study comparable to most previous research. Lastly, follow-up measurements are needed to determine whether durable lifestyle changes have been made.

Conclusions

Many cancer risk factors were relatively unknown among NMIBC patients and adherence to cancer prevention recommendations varied widely. Although patients generally have a positive attitude towards receiving lifestyle advice, they were not routinely informed about risk factors and a healthy lifestyle by their physician. Therefore, information provision on lifestyle recommendations for cancer prevention to NMIBC patients by urologists and other health professionals should be improved.

Author contributions

Alina Vrieling had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Vrieling, Kiemeney, Kampman, Witjes.
Acquisition of data: Westhoff.
Analysis and interpretation of data: Westhoff, Vrieling.
Drafting of the manuscript: Westhoff, Hendriks.
Critical revision of the manuscript for important intellectual content: Vrieling, Kampman, Kiemeney, Witjes.
Statistical analysis: Westhoff.
Obtaining funding: Vrieling, Kiemeney, Witjes.
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Supervision: Vrieling, Kampman, Kiemeney, Witjes.
Other: None.

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8

General discussion

General discussion

The aim of this thesis was to investigate the association of smoking, fluid intake, and dietary patterns with risk of recurrence and HRQoL in NMIBC patients. Additionally, we aimed to investigate patients' awareness of and adherence to lifestyle recommendations for cancer prevention, whether they received lifestyle advice, and what their attitudes are towards receiving lifestyle advice from their physician. In a review of the literature, we found that evidence for an association of pre- and post-diagnostic dietary and lifestyle factors with bladder cancer prognosis is limited, with some evidence that NMIBC patients who were overweight or obese at diagnosis had a higher risk of recurrence compared to those with a healthy weight. In a cohort of US NMIBC patients with data on dietary intake in the year before diagnosis, we found a higher risk of recurrence in patients who adhered most to a so-called Western diet, which is high in fried food, and red and processed meat. In preliminary analyses within the UroLife study, smoking at diagnosis and post-diagnostic fluid intake were not markedly associated with risk of recurrence nor with HRQoL in a fifteen-month period after diagnosis. HRQoL of NMIBC patients in the UroLife study was worse than HRQoL of a normative population for multiple domains, both directly as well as 15 months after diagnosis. Also, we found that complaints of appetite loss, diarrhea, urinary symptoms, and emotional concerns persisted until the last measurement at 15 months after diagnosis. Lastly, we showed that awareness of (bladder) cancer risk factors and adherence to cancer prevention lifestyle recommendations among NMIBC patients is low and that physicians' information provision with respect to lifestyle should be improved.

In the current chapter, our findings are placed in a broader perspective by elaborating on eleven statements. Also, recommendations for policy makers, clinical practice, and future research are provided.

An association between lifestyle and bladder cancer prognosis is mechanistically plausible

Even though the biologic mechanisms underlying the association of lifestyle factors with urinary bladder cancer (UBC) prognosis are not yet completely understood (1), there are numerous hypotheses how lifestyle habits can influence UBC (2). Potentially harmful substances from food and cigarettes, such as polycyclic aromatic hydrocarbons and heterocyclic aromatic amines, are excreted through the urinary tract. These substances are known to have a carcinogenic effect on the entire urinary system (2). They come into close contact with urothelial cells and may directly act on the urothelium, causing DNA damage and promoting pathogenesis (3-9). Further, components of tobacco smoke are involved in immune modulation (10, 11), and may induce specific mutations in genes related to DNA repair or tumor suppression such as *ERCC2* (12) and *TP53 (13)*. Through the same mechanisms known or hypothesized to be involved in etiology, smoking is thought to be associated with more aggressive tumours with a less favourable prognosis (14-21).

However, other studies did not find an association of smoking with tumours with a worse prognosis (22-30) and more research is needed into the exact mechanism through which smoking may be associated with worse prognosis. A recent study in MIBC patients found that smoking was associated with a more aggressive molecular subtype (31). This finding has not yet been replicated in NMIBC patients, and deserves further research.

Fluid intake could potentially act as an effect-modifier or intermediate in the excretion of carcinogens through the urinary tract. A larger fluid volume intake is thought to dilute carcinogens in the urine, and decreases contact time with the urothelium through an increased micturition frequency (6). However, the role of fluid intake is complicated and dependent on micturition frequency, the types of fluid consumed, and the nutritional content of both diet and fluids. Together, they influence the concentrations of carcinogenic and anti-carcinogenic substances in the urine and the transit time and this could be associated with both risk and prognosis of NMIBC (6, 32).

Overweight and obesity may increase the risk of recurrence in NMIBC by inducing systemic and local biochemical and immunological changes, including altered levels of insulin, insulin-like growth factor-1, leptin, adiponectin, steroid hormones, and cytokines (33, 34). For example, a higher amount of body fat leads to elevated secretion of pro-inflammatory cytokines which induces chronic inflammation. Inflammation causes an increased cell proliferation and a decreased insulin sensitivity (35). In NMIBC patients, markers of systemic inflammatory response have indeed been associated with increased risk of recurrence and progression (36). Also, potential difficulties in performing a complete transurethral resection of the bladder in obese patients may play a role (37, 38).

Conclusion: The association of lifestyle with bladder cancer prognosis is mechanistically plausible. Because of the good survival but relapsing nature, NMIBC is an excellent model to investigate the association of lifestyle with disease outcome.

There is not sufficient evidence that dietary and lifestyle factors influence bladder cancer prognosis

To date, research has primarily focused on the role of diet and lifestyle in cancer etiology. Due to earlier diagnosis, more effective treatments and an ageing population, the number of patients in the Western world is rapidly increasing (39). However, research on the effects of lifestyle on cancer prognosis lags behind. Most studies on lifestyle and prognosis in bladder cancer were focused on pre-diagnostic smoking (40-42). Evidence is increasing that current and former compared to never smokers have a higher risk of tumour recurrence (40-42), and possibly a higher risk of cancer-specific mortality as well (41, 42). Evidence for an association between smoking and disease progression is weak (42) and results of studies on smoking cessation are inconsistent (40, 43-46). Especially the impact of smoking cessation shortly before or after diagnosis remains unclear (46-50). Two historical cohort studies (47, 48) found a protective effect of quitting smoking after

diagnosis, but this has not yet been confirmed by prospective cohort studies (46), including our own study (**chapter 3)**. The lack of an association in our study, as well as in some other studies, may support the hypothesis of 'field cancerization' (51, 52). Long term exposure to carcinogens in e.g. tobacco can cause genetic alterations in stem cells, which can result in the replacement of fields of normal mucosa with preneoplastic cells. When only the primary tumour has been removed, the remaining fields of precancerous cells may eventually lead to disease recurrence, independent of whether someone quits smoking or not.

Our systematic review and meta-analysis of the available evidence regarding the impact of body mass index (BMI), diet and dietary supplements complemented the reviews on smoking (**chapter 2**). An increased risk of recurrence was found for overweight and obese compared to normal weight NMIBC patients in a meta-analysis of three studies. Observational studies on diet and intervention studies with dietary supplements showed inconsistent results. Some reported protective associations of single foods and supplements with risk of recurrence or cancer-specific mortality, but others did not find evidence of an association. Studies on physical activity were not available.

In general, studies performed to date had methodological shortcomings and no firm conclusions can be drawn. Many studies were retrospective, small, based on single pre-diagnostic measurements, and did not report patient characteristics and methods in a clear way. Also, analyses were often not stratified by stage and grade, although risk of recurrence, progression, and mortality are known to differ by stage and grade (53). Therefore, possible associations with lifestyle and disease outcomes could have been masked.

Conclusion: Evidence-based recommendations with respect to diet and lifestyle cannot be given to NMIBC patients yet. Until conclusive evidence is available, patients should be advised to quit smoking based on the association with several comorbidities and possibly the risk of second primary cancers. Further, patients should be referred to the general lifestyle recommendations for cancer prevention of the World Cancer Research Fund / American Institute for Cancer Research (54).

A Western dietary pattern may increase the risk of NMIBC recurrence

In a large ongoing cohort study performed at the M.D. Anderson Cancer Center and Baylor College of Medicine, we found that adhering most to a Western dietary pattern was associated with a higher risk of recurrence in NMIBC (**chapter 4**). There seemed to be a trend for higher risk of progression as well. Our findings are in line with a study on bladder cancer risk (55), with a study on colorectal cancer recurrence (56), and with a meta-analysis on breast and colorectal cancer and overall mortality (57).

A classical Western dietary pattern is high in animal products, especially red and processed meat, refined grains, and high-fat and high-sugar snacks (57-59). These food items contain several potentially carcinogenic compounds (N-nitroso-compounds, polycyclic aromatic hydrocarbons and heterocyclic aromatic amines) that are excreted through the urine (5, 60). Nevertheless, it is not yet possible to draw firm conclusions.

Foods and nutrients may be correlated and potentially interact with each other (61). Analysis of dietary patterns instead of single foods or nutrients takes into account the multidimensionality of the diet and resembles a more real-life situation (62-64). However, it is important to consider the complexity of this type of analysis. At several times during the analysis, rather subjective choices have to be made, e.g. which foods to include, whether and how to group foods, how many factors to retain, and what cut-off point to choose to decide which foods or food groups contribute to the retained factors. These choices influence the rest of the analysis and thus the results. Therefore, it is recommendable that at least two researchers perform this analysis separately, to compare the outcomes, and to discuss and resolve any disagreements. Depending on the aim of the research, it might be also an option to use an existing diet quality index and score patients accordingly, instead of using a data-driven approach like factor analysis.

Conclusion: Evidence-based recommendations with respect to diet cannot be given to patients yet. Since a classical Western diet is generally high in unhealthy products, replacing foods typical for the Western diet by e.g. fruits, vegetables, and high-fibre products can be advised for general health benefits.

Prospective cohort studies with repeated lifestyle measurements are needed to obtain more insight in the role of dietary and lifestyle factors in NMIBC prognosis and HRQoL

Because of methodological shortcomings of available studies, there is an urgent need for prospective cohort studies specifically designed to study dietary and other lifestyle factors in relation to NMIBC prognosis and HRQoL. There are several considerations with regard to the design of such studies. First of all, newly diagnosed NMIBC patients should be recruited as shortly after diagnosis as ethically and logistically possible. In that way, an assessment of pre-diagnostic dietary and lifestyle habits is still possible. Preferably, this assessment is followed by multiple post-diagnostic assessments of lifestyle until at least five years after diagnosis to be able to capture any (long-term) changes. With this study design, the most relevant question for the patient can be addressed, i.e. whether lifestyle changes at the time of, or after diagnosis can favourably alter disease prognosis and HRQoL.

Since lifestyle habits may be correlated and (un)healthy habits may be clustered within persons (65-68), it is important to assess multiple lifestyle habits. Preferably, measurement of habitual dietary intake should be combined with measurements of smoking, physical activity, sedentary behaviour, and a measure of abdominal obesity. Waist circumference,

waist-hip ratio, or waist-height ratio should be considered as a more suitable measure of abdominal obesity than the often used BMI (69-72).

Objective measurements should complement self-reported questionnaires where possible These can overcome issues inherently associated with self-reported measures, including socially desirable answers, over- and underreporting of food intake, and misinterpretation of questions, and prevent bias. Examples of more objective measures are blood samples to investigate biomarkers of fruit and vegetable intake, and accelerometers as a measure of physical activity and sedentary behaviour. Naturally, these measures have other disadvantages to take into account. Therefore, a combination of both self-reported measures and objective measurements should be strived for.

Conclusion: Prospective studies with self-reported and objective lifestyle measurements, taking into account lifestyle factors before and after diagnosis, are needed to obtain more insight in their role in NMIBC prognosis and HRQoL.

The Netherlands Cancer Registry is an essential partner for the recruitment of patients and clinical data collection for a prospective cohort study

With almost complete coverage, the Netherlands Cancer Registry (NCR) is an excellent infrastructure for population-based patient recruitment. The objective of the NCR is to record, report, improve and regulate information about every patient with cancer (73). However, in our opinion the NCR is in the perfect position to be, and should also function as, a logistic framework to recruit patients and to collect both clinical and patient-reported data.

In our study UroLife, we asked permission from all urologists of the participating hospitals to identify their eligible patients in the NCR. Patients were then identified and invited by the NCR on behalf of their urologist to participate in the study. In this way, patients were invited as quickly as possible after their diagnosis, with no additional effort for the urologists, resulting in a satisfactory response rate of around 50%. An alternative would be that patients are directly invited by their physician. However, this will likely have negative consequences for accrual for studies that do not focus on treatment interventions (74). It has been shown that physicians experience multiple barriers to recruiting patients for research, such as additional workloads without compensation, conflicts of interest when multiple studies are being performed at the same time, beliefs and/or attitudes toward clinical research, protection of their patients, and a lack of knowledge about the study (74-76). Therefore, it is essential that the NCR remains involved in the recruitment of patients. Low recruitment rates can hamper the validity of the results because of possible selection bias, reduce the statistical power to detect associations, and extend the study duration (77).

The recording and reporting of data by the NCR is currently focused on tumour-specific clinical data. Given the increasing number of cancer survivors, patient-reported

outcomes (PRO) such as HRQoL and quality of care are becoming more important and constitute a prominent research area (78-80). A PRO captures the patients' perspectives on how disease, therapy, and the provided care are impacting their well-being. When routinely collected, it can be used to work towards evidence-based, personalised health care (78).

Conclusion: The NCR is in a unique position to recruit patients for prospective studies and to routinely collect PRO on almost all patients diagnosed with cancer in the Netherlands.

The optimal statistical analysis of prospective cohort studies with repeated measurements and multiple outcomes is still unclear

Apart from our study UroLife, several prospective cohort studies in the field of lifestyle and bladder cancer are being performed at this moment (81-84). Even though some of them are in the phase of (preliminary) data analysis, methods for the statistical analysis of such studies still need to be improved. It is especially challenging how to make optimal use of the repeated measurements to evaluate lifestyle changes in relation to prognosis. E.g. what time span should be kept as a minimum between the lifestyle measurement and the outcome? How to deal with patients with fluctuating lifestyle behaviour? Joint efforts are needed from both lifestyle researchers and statisticians to resolve these issues.

Also, the starting point of follow-up of patients is not always clear. Follow-up should start when a patient is at risk of the outcome of interest. In many studies this is immediately after diagnosis or removal of the primary tumour. However, NMIBC patients are theoretically not immediately at risk of a recurrence after the transurethral resection of the bladder tumour (TURBT) for the primary tumour when a re-TURBT is planned. Therefore, in case a re-TURBT was carried out, we started follow-up at the date of the re-TURBT. Also, we considered all tumour tissue found within 90 days of the resection of the primary tumour to be part of the primary tumour, as this is standard practice in the NCR. Thus, theoretically a NMIBC patient would not be at risk of a recurrence within 90 days after the first resection. This time period of 90 days is nonetheless quite arbitrary and should be reconsidered.

Lastly, many NMIBC patients have multiple recurrences. Traditionally, either time to first recurrence or the number of recurrences is assessed as an outcome. However, time to first recurrence does not take into account what happens subsequently, and the number of recurrences does not take into account how much time there is between multiple recurrences. For example, two patients who both have their first recurrence at 9 months after diagnosis will be treated equally in the analysis, but might have a totally different course of disease after their first recurrence. Similarly, a patient with a recurrence at 2 and 5 years after diagnosis might be different from a patient with two recurrences within the first year after diagnosis who is lost to follow-up thereafter. This information should be better addressed in the statistical analyses.

Conclusion: Currently available statistical methods are not being used in an optimal way. Improvements can be made especially by better defining when a patient is at risk, and by using multiple lifestyle measurements and including multiple outcomes.

Urinary symptoms and future worries can persist for a longer time and are dependent on adjuvant treatment

Even though overall scores in the urinary symptoms domain improved, the presence of one or more individual urinary symptoms was still reported by 40% of the patients at the end of follow-up. Pollakiuria and nocturia were the most common complaints. The improvement in the urinary domain was observed in other studies as well (85, 86), but individual symptoms were not reported. As we showed that a substantial number of patients still has symptoms, this should not be neglected by only taking into account overall scores. Twenty-four percent of the patients had one or more emotional concerns at the end of the fifteen-month follow-up period, of which health in the future was the main concern. The persistence of emotional concerns for a longer period was also observed in studies performed in the UK and Korea (87, 88). Despite the good prognosis of NMIBC, the considerable number of patients with concerns indicates a potential need for psychological support. Scores on all other domains of both the EORTC QLQ-C30 and the disease-specific EORTC QLQ-NMIBC24 improved over time or remained constant, as was also observed in other studies (85-88).

Patients treated with intravesical immunotherapy or chemotherapy reported more future worries and intravesical treatment issues compared to patients treated with TURBT only. This may be partly due to their generally more aggressive disease. A Spanish study comparing different treatments in 244 NMIBC patients also found differences with regard to treatment. Here, patients treated with intravesical chemotherapy improved over a 12 month period in the sexual domain compared to patients treated with TURBT only, and patients treated with immunotherapy improved in the bowel domain (86). Additionally, patients in our study who received bacillus Calmette-Guérin immunotherapy had more urinary symptoms as compared to patients treated with TURBT only, as observed in other studies (85, 89, 90). However, neither in our study, nor in most other studies (85, 86, 91), immunotherapy had an impact on other aspects of HRQoL that are often worse in other cancer survivors, such as fatigue and functioning scales (92, 93). This indicates that intravesical immunotherapy, outside of NMIBC-specific complaints, is generally well tolerated.

Conclusion: HRQoL of NMIBC patients improved in most domains after diagnosis, but attention should be paid to persistent urinary symptoms and future worries, especially in patients treated with intravesical immunotherapy.

Awareness of (bladder) cancer risk factors and adherence to cancer prevention recommendations among bladder cancer patients is low

We found that most NMIBC patients recognized smoking and passive smoking as risk factors for cancer in general, but other established lifestyle-related factors were less well known **(chapter 7)**. Low levels of awareness of lifestyle risk factors other than smoking were also observed in other studies (94-99). Even though around one-third of all bladder cancer cases is attributable to smoking, this was mentioned as a risk factor for bladder cancer by less than 50% in our study. Only 11% of ever smokers reported smoking as a perceived cause for their own disease **(chapter 6)**.

Ignoring risk factors that might have been within the patients' control may be a strategy to shield themselves against negative emotions, such as blame from self or others (100). Also, it is known that people tend to attribute causes for negative events externally (100, 101). We also observed that many patients thought that environmental or chemical exposures that were out of their control could be a cause of bladder cancer in general (**chapter 7**) or of their own disease (**chapter 6**). External attribution often goes together with a fatalistic view that nothing can be done to prevent cancer or improve prognosis (102). These beliefs are important to address, since they may decrease the probability of a patient engaging in healthy behaviours (102, 103). Further, the way of questioning may play a role in the response given by patients. An open-ended format combined with the possibility of answering 'no', as we used in **chapter 6**, possibly gave patients the opportunity to avoid thinking about possible causes for their disease (104). This may have led to an underestimation of their actual awareness. In contrast, a prompted list of risk factors as in **chapter 7** may have led to an overestimation of awareness. As just recognizing a risk factor when it is prompted is less likely to translate into behaviour change, open-ended questions may give a more useful indication of accessible knowledge that might influence more direct predictors of behaviour and behaviour change (104).

As awareness of risk factors and perception of one's own cancer risk may be important in engaging in healthy behaviours (105), it is not surprising that we found a low adherence to lifestyle recommendations for cancer prevention except for smoking (**chapter6**). Our findings are in line with other studies in cancer patients with regard to smoking (106), body weight (107, 108), and alcohol (107). However, in our study a higher percentage of NMIBC patients was adhering to the recommendation for supplement use, i.e. not to take supplements for cancer prevention (109). For the physical activity recommendation, results are highly diverse and seem to vary with, among others, age, gender, and socio-economic status (106, 107, 110-112). In our study, adherence to cancer prevention recommendations was generally higher for patients who were older, male, and higher educated. Also, patients who were more aware of overweight, insufficient physical activity, and alcohol as being risk factors for cancer were more likely to meet the corresponding cancer prevention recommendation. It should be kept in mind though that patients could have given socially desirable answers that may have led to an overestimation of adherence (113).

Conclusion: Clearly, although awareness of cancer risk factors does not automatically translate into adherence to cancer prevention recommendations, it is an important element of behaviour change.

Low awareness and adherence but positive attitudes towards lifestyle advice among NMIBC patients highlights the need for effective education

The low levels of awareness and adherence with regard to lifestyle in our study indicate a need for education. Awareness of the association between a risk factor and the disease can enhance the motivation to change it (114) and is thus essential when increased adherence to recommendations is the ultimate goal. Mass media campaigns focused on smoking for example have been proven to be successful in altering smoking behaviour (115, 116). The knowledge that has been gathered over the years of what bladder cancer survivors perceive as causes of their cancer (114, 117-119) also provides valuable information for health education and prevention initiatives. The reporting of risk factors that are not associated with risk or for which there is no evidence (yet) also highlights the importance of effective education to debunk myths. Focusing on factors that are not really risks may withhold patients from addressing behaviour that really matters (120).

Even though patients' lifestyle habits were often unhealthy, they had positive attitudes towards receiving lifestyle advice. Attitude is an important indicator of how receptive patients are for health promotion initiatives and how willing they are to make changes (121, 122). The government also has a role in providing clear, evidence-based and easily accessible information, as conflicting messages in the media cause uncertainty about what is true.

Conclusion: The existing evidence on the association between lifestyle and (bladder) cancer should be used to educate patients, since their awareness of risk factors is low and their attitudes towards lifestyle advice are positive.

Urologists and other health care professionals should be better equipped to inform bladder cancer patients about a healthy lifestyle

Although NMIBC patients have a positive attitude towards receiving lifestyle advice, they were not routinely informed by their physicians (**chapter 7**). About 20% of patients indicated that physicians did not ask about their smoking behaviour. Thus, information provision by physicians should be improved. There are several reasons for physicians not to give lifestyle advice to patients, as has been shown in different studies (123, 124). Barriers include time constraints, doubt of effectiveness, a lack of skills in the behavioural change field, and doubt about whether it is appropriate to interfere in patients' lives, (123, 124). Further, they do not want to give patients the feeling that they are blamed for their own disease. This delicate balance needs skills of the physician that might not receive sufficient

attention during their education. Further, another barrier may be the lack of evidence for the effectiveness of lifestyle changes for the specific disease. Although there is no direct evidence for an association of lifestyle with NMIBC prognosis yet, advice on a healthy lifestyle already is relevant for these patients. Lifestyle-related comorbidities such as diabetes mellitus type II and cardiovascular disease are highly prevalent among cancer patients. In our study, more than half of the patients had at least one of these comorbidities. A better physical condition is advantageous when surgery or multiple treatments are necessary. Also, smoking cessation greatly reduces the risk of peri- and post-operative complications in case a cystectomy is necessary (125-127).

Despite these barriers, the need for training of urologists and other health care professionals in this field is evident, since NMIBC patients have been shown to be more likely to accept smoking as a cancer risk factor when this information was provided by their urologist (128), and that a cancer diagnosis could be a teachable moment (129).

However, it takes a village to change. Behaviour change is a complicated process in which patients often need repeated personal appointments to be successful. This support cannot only be expected from urologists, but should also be provided by other health care professionals. Provision of lifestyle advice also does not change the environment patients live in, their social network, or the amount of support they receive.

Conclusion: A systems approach to promote behaviour change is needed, and additional policy measures to support health promotion initiatives are necessary.

Setting up and obtaining valid results on cancer-specific outcomes from a prospective cohort study within the time frame of a PhD project is not feasible

Setting up and obtaining valid results on cancer-specific outcomes from a multi-center prospective cohort study is like a long and winding road. The study first needs to be approved by the ethics committee and then by the executive boards of all participating hospitals (or local committees on behalf of them). For UroLife, local committees of participating hospitals often did not only review the feasibility of the study, as they should (130), but also reviewed the protocol again. Together with delays due to a lack of clarity about the procedure, this made the local approval procedures very time consuming (average time 5 months, range 1.5-12 months).

After the introduction of the General Data Protection Regulation (131) in May 2018, setting up multi-center prospective cohort studies may become even more complicated. The new law may seriously interfere with doing epidemiological research and, among others, slow down the process of getting ethical and local approval (132-134). For example, currently patients often give permission to be approached again for future research. At that time, it is usually unclear what the future research exactly entails, because it is partly dependent on findings of the current research. With the new privacy law, the informed

consent needs to be more specific and if that is not possible, consent has to be obtained again. Also, rules concerning depersonalisation are much stricter. Where pseudonimisation of personal data used to be considered safe, it is not anymore. Further, changing privacy laws are a danger to complete coverage of the NCR (132), especially when the current opt-out system will be changed into opt-in (135-139). The balance between the improvement of health (care) through research and personal data protection appears to move in favour of the latter. Researchers, clinicians, and policy makers should join forces and cooperate to find the best solution for all parties.

In order to be able to evaluate associations of diet and lifestyle with appropriate clinical disease outcomes, sufficient participants and a minimum duration of follow-up are necessary to observe sufficient outcomes to ensure sufficient statistical power. In NMIBC patients, tumour recurrence occurs relatively shortly after diagnosis (140), but still a follow-up time of at least two years and preferably five years is needed.

Conclusion: Because of the lengthy local approval procedures and the prolonged recruitment period, it is evident that this four-year PhD project was not long enough to complete such a study. Since we could only include 550 instead of the initially planned 1000 NMIBC patients in our preliminary analysis, with a median follow-up time of 19 months, true associations between lifestyle and risk of recurrence may have been overlooked because of a lack of statistical power. Future analyses of the complete cohort will yield more information.

Recommendations for policy makers

To be able to make full use of the potential effects of lifestyle to improve health, and to increase research possibilities in the future, several recommendations for policy makers can be made.

Through policy the government can and has to give direction to the solution of social problems. One of these is the burden of Western diseases, in which the role of lifestyle is evident. The government has several tools to improve lifestyle behaviour and thereby reduce healthcare costs by primary, secondary *and* tertiary prevention. Through stricter policy around tobacco, alcohol and unhealthy food, the burden of many diseases can be reduced. For example, higher taxes on tobacco, and bans on advertising, promotion and sponsorship (116, 141). A topical issue in this field is the sugar-sweetened beverage tax. Taxes in different forms have been implemented in over twenty countries and have been shown to be effective in lowering sugar consumption (142).

A less far-reaching tool is nudging, which is the use of positive reinforcement and indirect suggestions to guide behaviour in the desirable direction without limiting freedom of choice (143-147). Examples of nudging are footsteps directing people to the stairs instead of the elevator, placing a sign with "most sold in this supermarket" above the shelf with broccoli, and changing the default side order to vegetables instead of fries.

In contrast to the new privacy law, it should be considered to use the citizen service number for research purposes, as is now common practice in the Scandinavian countries (148). Use of the citizen service number would allow linkage between medical registers, preferably without explicit approval of the patients. The protection of the patients' privacy is of utmost importance, but so is improving health and health care through research. Among others, this linkage enables researchers to estimate morbidity and mortality in various patient populations, perform high powered analyses, and evaluate sensitivity and specificity of new diagnostic techniques (148).

Recommendations for clinical practice

This thesis underlined the need for and necessity of better information provision with regard to lifestyle. Urological practice would look different if we start treating lifestyle as a medicine in addition to regular treatment. Lifestyle should be a standard topic of conversation within urological practice, as smoking is the most important risk factor. However, knowledge of urologists how to approach such a sensitive topic, and more general knowledge about lifestyle, is suboptimal and should be improved. A prominent argument not to discuss lifestyle is the lack of convincing evidence for the association between lifestyle factors and the specific disease. For bladder cancer, only smoking has been consistently associated with risk, but evidence is still limited for an association with prognosis. Nevertheless, the WCRF/AICR lifestyle recommendations for cancer prevention (54) and the Dutch guidelines for healthy nutrition (149) are beneficial for everybody. Especially cancer patients, who often have a more unhealthy lifestyle predisposing them to several comorbidities, could benefit. We recommend that physicians register their patients' lifestyle and eventual intentions to change it in a standardized way in the medical chart. In this way, all medical specialists have access to the same information and can use it to start a conversation on lifestyle. Further, prevention is not only a task of municipalities, Public Health Services, and the National Institute for Public Health and the Environment. It should be viewed and treated as a joint responsibility of aforementioned parties *and* general practitioners and medical specialists. As urological practice is not always the right place to give patients the support they need, referral to primary care is often desirable. Proper feedback between all parties is however essential to make prevention initiatives succeed, and improve patients' health.

Lastly, clinicians need to be alert to individual impairments in HRQoL. We observed several clinically relevant differences between NMIBC patients and a normative population over a fifteen-month period after diagnosis. Most of these differences became less prominent over time, but complaints about appetite loss and diarrhea became present after 3 months after diagnosis and were still present at 15 months after diagnosis. Additionally, a substantial number of patients still reports urinary symptoms or emotional worries at 15 months after diagnosis.

Recommendations for future research

During this PhD project, we experienced a number of difficulties that made the performance of this research challenging. To avoid similar situations in the future, several recommendations can be made.

During the recruitment phase of UroLife, we often heard that patients were already participating in another study, or felt overwhelmed by numerous requests to participate in trials. For them, this could be a reason to refuse participation to UroLife, or to any study they were invited for. Also, patients participating in more than one study at a time often had difficulties understanding why questionnaires overlapped so much, or why they had to give blood multiple times. Sometimes these studies indeed had partly overlapping research aims. Cooperation in the form of better alignment or (partial) integration of studies would not only decrease the burden on patients but also highly increase the efficiency of research and the use of materials and budget. Another benefit of more cooperation between studies is to obtain a larger sample size and more statistical power to study progression, or detect associations that only exist in subgroups, and would remain undetected in smaller study samples.

Future studies should investigate associations between lifestyle and NMIBC prognosis by molecular subtype, as relevant disease outcomes are clearly different for these subgroups (150). Three molecular subtypes of NMIBC have been identified, i.e. urobasal, genomically unstable, and squamous-cell-carcinoma-like bladder cancer (151-153). T1 tumours are mostly of the genomically unstable and squamous-cell-carcinoma-like subtypes and have a high risk of progression (152). Also, a study in MIBC patients found that former and current versus never smoking was more strongly associated with the genomically unstable than with the urobasal subtype (31). Therefore, future studies should collect tumour tissue to be able to investigate whether molecular subtypes can be seen as intermediate variables in the associations of smoking and possibly other lifestyle factors and NMIBC prognosis.

As we experienced, numerous definitions of recurrence and progression are being used, making comparison between studies complicated (154, 155). It is recommended to let an expert panel decide upon the critical elements in the definitions so that all studies can report the same clinical endpoints in the future. In this way, integration of studies will be easier, which will allow high powered subgroup analyses. Similarly, more effort should be put into the standardization of other clinical data and into the standardization of the interpretation and comparison of HRQoL scores. Statistically significant HRQoL differences between groups or over time are too often being reported as the main outcomes of a study. However, when study size is large enough, these differences may be so small that they will not be relevant to the patient. The determination of how large the difference should be to be considered relevant for the patient and in clinical practice is difficult. Several HRQoL instruments have their own guidelines, but these are hard to compare and the distinction between a 'small' and a 'medium' clinically relevant difference is still hard

to grasp for both researchers and clinicians. The highly subjective nature of HRQoL further complicates the interpretation. A way to transfer HRQoL scores of different instruments in one uniform and easily interpretable scale should be a high priority on the research agenda.

Concluding remark

With UroLife, we have an enormous potential to discover what we can do with lifestyle to improve the HRQoL and prognosis of NMIBC patients. An exciting time lies ahead of us. With the collection of questionnaire data and blood samples at different time points, and tumor tissue for molecular subtyping, we are working towards a goldmine of information and possibilities to give the best possible support to the patients.

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9

Summary
Samenvatting

Summary

Urinary bladder cancer (UBC) is a common malignancy, which ranks ninth in worldwide cancer incidence. The most important risk factor for UBC is smoking. Smoking cigarettes is associated with an over three-fold increased risk of developing UBC, while smoking cessation can decrease the risk. The World Cancer Research Fund / International American Institute for Cancer Research concluded that there is limited suggestive evidence for a protective effect of fruit, vegetables, and tea. No conclusions could be drawn for other dietary factors, physical activity, or body mass index (BMI). However, recent meta-analyses also found a small increased UBC risk with a higher BMI, and a decreased risk with higher levels of physical activity and vitamin E.

Approximately 75% of UBC patients present with non-muscle-invasive bladder cancer (NMIBC). NMIBC has a high five-year recurrence rate (28-52%), necessitating an intensive follow-up and potentially multiple treatments. Lifestyle factors have been linked to the prognosis of several cancer types, but the role of lifestyle in NMIBC prognosis has scarcely been investigated. Studies conducted to date were mostly focused on smoking. Both former and current smokers may be at an over 20% higher risk of disease recurrence than non-smokers.

Apart from a potential effect on NMIBC prognosis, lifestyle may have an effect on health-related quality of life (HRQoL). NMIBC patients have been shown to have a worse mental and/or physical health compared to a normative population. As several health behaviours have been linked to HRQoL in survivors of other cancer types, a healthy lifestyle may improve HRQoL in NMIBC patients as well. Until now, there is only suggestive evidence for an association of higher physical activity levels with better HRQoL in UBC survivors.

Besides the role of lifestyle before diagnosis, it is of great interest to know whether changes made after diagnosis can still beneficially alter the course of disease or have an impact on HRQoL. These questions are yet unanswered, leaving urologists with only general lifestyle advice when patients ask what they can do themselves to improve their prognosis. Ultimately, the development of evidence-based lifestyle advice specifically for NMIBC could aid urologists in giving lifestyle advice, and could give patients some control over their disease by involving them in their disease management.

The aim of this thesis was to investigate the association of smoking, fluid intake, and dietary patterns with risk of recurrence and HRQoL in NMIBC patients. Additionally, we aimed to investigate patients' awareness of, adherence to, and interest in lifestyle recommendations for cancer prevention.

This thesis starts with a general introduction on UBC etiology and prognosis, the role of lifestyle factors in the development and prognosis of UBC, HRQoL of patients and the association of lifestyle with HRQoL, and it introduces the complexity of behaviour change after diagnosis (**Chapter 1**). The aim and outline of the thesis is also presented.

In **Chapter 2**, we give an overview of the existing evidence on the associations of BMI, diet, and dietary supplements with bladder cancer recurrence, progression, and mortality in the form of a systematic review and meta-analysis. We included 31 studies published until May 2017, 13 of which were focused on BMI. We found that evidence for an association of lifestyle factors with bladder cancer prognosis is limited. In a meta-analysis of three studies in NMIBC patients we showed that overweight and obesity compared to normal weight were associated with increased risk of recurrence. No association with risk of progression to muscle-invasive bladder cancer (MIBC) was found. Results of studies on BMI in relation to prognosis in NMIBC and MIBC patients combined, or restricted to MIBC patients, were inconsistent and sometimes even opposite. Some observational studies on diet and dietary supplementation studies found a potentially protective effect on recurrence, cancer-specific-, or all-cause mortality, but only for single foods and supplements. However, most studies had (severe) methodological shortcomings. Prospective cohort studies with repeated measurements focusing on appropriate clinical outcomes, and covering the entire diet are needed to develop evidence-based guidelines.

In **Chapter 3**, we studied the association of self-reported smoking status at diagnosis, time since smoking cessation, cumulative smoking exposure, and post-diagnostic fluid intake with risk of NMIBC recurrence in our prospective cohort study UroLife. We included 550 newly diagnosed NMIBC patients who completed a questionnaire on smoking at 6 and 12 weeks after diagnosis and a 4-day diary on fluid intake at 12 weeks after diagnosis. Median follow-up time was 19 months, and 103 patients (19%) developed at least one recurrence. Most patients were former (58%) or current (26%) smokers and median average fluid intake was 1840 mL (interquartile range 1500 – 2215). In these preliminary analyses, smoking and fluid intake were not statistically significantly associated with risk of recurrence. Risk of recurrence was non-statistically significantly increased among former smokers. Among ever-smokers, having smoked the highest versus lowest amount of pack-years was associated with a non-statistically significant increased risk of recurrence. Future analyses with a larger sample size and longer follow-up time are needed before definitive conclusions can be drawn. However, smoking cessation should still be recommended based on its well-established general health benefits.

Evaluation of the association of different empirically derived dietary patterns with risk of recurrence and progression in NMIBC was described in **Chapter 4**. Food-frequency questionnaire and clinical data from 595 newly diagnosed NMIBC patients from a large

ongoing cohort study performed at M.D. Anderson Cancer Center and Baylor College of Medicine were used. We identified four dietary patterns ("fruits and vegetables", "Western", "low-fat", and "Tex-Mex"), which together explained 37% of the total variance. Patients adhering most to the Western dietary pattern had a 1.5 times higher risk of recurrence compared to patients adhering least. No statistically significant associations with risk of progression were found, or of the other dietary patterns with risk of recurrence and progression. As a Western diet is high in fried food, and red and processed meat, the harmful substances present in these foods may directly exert a carcinogenic effect on the urothelium when excreted in the urine. Our study thus supports the more general hypothesis that a Western diet plays a role in the etiology and prognosis of cancer. However, further research is needed to confirm our findings and elucidate the association of diet with NMIBC prognosis.

Chapter 5 describes the HRQoL of 541 NMIBC patients participating in the UroLife study over a fifteen month period after diagnosis and compared it with the HRQoL of an age- and sex-matched normative population. Further, we investigated whether HRQoL of patients was associated with treatment, smoking behaviour and fluid intake. HRQoL was assessed with the EORTC QLQ-C30 and the EORTC QLQ-NMIBC24. We showed that NMIBC patients had a worse self-reported role functioning, emotional functioning and social functioning, and reported more fatigue, dyspnoea, insomnia, appetite loss, and diarrhea than a normative population. Differences were of small clinical importance. Although HRQoL improved over time in most domains, complaints of appetite loss, diarrhea, urinary symptoms, and emotional concerns persisted in many patients until 15 months after diagnosis. Patients treated with intravesical chemotherapy or immunotherapy scored worse on several NMIBC-specific domains compared to patients treated with a transurethral resection of the tumour only. Patients treated with intravesical immunotherapy also had a higher urinary symptom burden. Smoking and fluid intake did not have a relevant impact on HRQoL. Caregivers should be alert as specific domains of HRQoL of NMIBC patients are worse than that of the general population, and symptoms and emotional worries may be present for a longer period of time.

UBC patients' perceptions about what they believe contributed to the development of their own disease is described in **Chapter 6**. For this purpose, data of the Nijmegen Bladder Cancer Study was used. The question 'You have been diagnosed with bladder cancer. Do you have any idea what may have been the cause of your cancer?' was evaluated. Of 1793 included patients, 366 (20%) reported a possible cause for their bladder cancer. Only 10% of all patients suspected that smoking could be the cause, followed by occupational exposure (5%), and heredity (2%). Even among ever smokers, only 11% perceived smoking as a possible cause of their disease. This is important knowledge for health prevention and education initiatives as it reflects the superficial knowledge about

smoking as risk factor for UBC. Also the fact that patients reported factors that are known to be not involved in (bladder) cancer etiology deserves attention. Focusing on these factors might prevent patients from focusing on changing real risk behaviours.

In **Chapter 7**, we investigated whether NMIBC patients are aware of (bladder) cancer risk factors, and whether they adhere to several lifestyle recommendations for cancer prevention. Also, we evaluated whether they received lifestyle advice, and their attitudes towards receiving lifestyle advice from their physician. A total of 969 NMIBC patients participating in the UroLife were included. We showed that awareness of risk factors for cancer in general varied between 29% for fruit and vegetable consumption and 89% for smoking. Only 44% of the patients were aware of smoking as risk factor for UBC. Adherence to the cancer prevention recommendations varied between 34% for body weight and 84% for smoking. Seventy percent of the smokers was advised to quit, but only 19% of all patients reported to have received other lifestyle advice. However, over 80% of the patients had a positive attitude towards receiving lifestyle advice from their physician. Therefore, information provision by physicians on a healthy lifestyle should be improved.

This thesis ends with a general discussion of the studies described in this thesis in the context of relevant existing literature, including recommendations to policy makers, clinicians, and researchers (**Chapter 8**). In conclusion, we gathered valuable data on lifestyle in relation to different aspects of NMIBC: prognosis, HRQoL, and patients' awareness. We found evidence for a higher risk of recurrence in NMIBC patients with a higher BMI in a meta-analysis of the literature, and with a Western diet in a US cohort. In preliminary analyses of UroLife, with repeated lifestyle and HRQoL measurements smoking and fluid intake were not markedly associated with risk of recurrence nor with HRQoL. HRQoL of NMIBC patients in our study was worse than that of a normative population in multiple domains and complaints of appetite loss, diarrhea, urinary symptoms, and emotional concerns persisted until 15 months after diagnosis. Finally, we showed that awareness of (bladder) cancer risk factors and adherence to cancer prevention lifestyle recommendations among NMIBC patients is low and that physicians' information provision should be improved.

Samenvatting

Blaaskanker is de negende meest veelvoorkomende vorm van kanker wereldwijd. De meest belangrijke risicofactor voor het krijgen van blaaskanker is roken. Het roken van sigaretten kan het risico op het ontwikkelen van blaaskanker met meer dan drie keer verhogen, maar stoppen met roken kan de schade gedeeltelijk ongedaan maken. Wat betreft andere leefstijlfactoren is er volgens het World Cancer Research Fund / International American Institute for Cancer Research beperkt suggestief bewijs voor een beschermend effect van de consumptie van fruit, groente en thee. Recente meta-analyses vonden daarnaast een licht verhoogd risico op het krijgen van blaaskanker bij een hogere body mass index (BMI) en een verlaagd risico bij meer fysieke activiteit en een hogere inname van vitamine E.

De meeste patiënten worden gediagnosticeerd met niet-spierinvasieve blaaskanker (non-muscle-invasive bladder cancer; NMIBC). NMIBC heeft een goede vijfjaarsoverleving (89-99%), maar een hoog risico op recidivering van de tumor binnen vijf jaar (28-52%) waardoor een intensieve follow-up en mogelijk meerdere behandelingen nodig zijn. Er zijn associaties gevonden van verschillende leefstijlfactoren met meerdere vormen van kanker, maar de rol van leefstijl in NMIBC prognose is nog nauwelijks onderzocht. De studies die tot op heden zijn uitgevoerd waren vooral gericht op roken en vonden dat zowel voormalige als huidige rokers een meer dan 20% hoger risico op recidief kunnen hebben. Vochtinname, een leefstijlfactor die vaak verondersteld wordt geassocieerd te zijn met het ontstaan van blaaskanker, is tot op heden nog niet onderzocht in relatie tot prognose.

Afgezien van een potentieel effect op NMIBC prognose kunnen verbeteringen in leefstijl ook een positief effect hebben op gezondheidsgerelateerde kwaliteit van leven (health-related quality of life; HRQoL). Het is aangetoond dat NMIBC patiënten een slechtere mentale en/of fysieke gezondheid hebben ten opzichte van een normatieve populatie. Aangezien verschillende leefstijlgewoonten geassocieerd zijn met HRQoL in overlevenden van andere vormen van kanker, is het waarschijnlijk dat een gezonde leefstijl ook HRQoL van NMIBC patiënten kan verbeteren. Tot nu toe is er alleen suggestief bewijs voor een positieve associatie tussen meer fysieke activiteit en HRQoL in NMIBC overlevenden.

Naast de rol van leefstijl vóór diagnose is het van groot belang om te weten of veranderingen in leefstijl die gemaakt zijn na diagnose nog steeds het verloop van de ziekte, of HRQoL positief kunnen beïnvloeden. Deze vragen zijn vooralsnog onbeantwoord, waardoor urologen alleen algemeen leefstijladvies kunnen geven wanneer patiënten vragen wat zij zelf kunnen doen. Uiteindelijk zal de ontwikkeling van zogenaamde 'evidence-based' richtlijnen specifiek voor NMIBC patiënten urologen helpen bij het geven van leefstijladvies en patiënten enige controle over hun ziekte teruggeven en hen meer betrekken in de behandeling.

Het doel van het onderzoek beschreven in dit proefschrift was daarom de associatie tussen roken, vochtinname en voedingspatronen en risico op recidief en HRQoL in NMIBC

patiënten te onderzoeken. Daarnaast hadden we als doel te onderzoeken of patiënten zich bewust zijn van risicofactoren voor (blaas)kanker, of zij zich houden aan richtlijnen voor kankerpreventie, of zij op dit moment leefstijladvies ontvangen en wat hun houding is ten opzichte van het ontvangen van leefstijladvies van hun arts.

Dit proefschrift begint met een algemene introductie over blaaskanker etiologie en prognose, de meest belangrijke bevindingen op het gebied van leefstijl en HRQoL tot nu toe en de complexiteit van gedragsverandering na diagnose (**Hoofdstuk 1**). Tevens wordt het doel van dit onderzoek gegeven, alsmede een kort overzicht van de opbouw van dit proefschrift.

Daarna geven we een overzicht van de literatuur over de associaties tussen BMI, voeding en voedingssupplementen en blaaskankerrecidief, progressie en mortaliteit door middel van een systematische literatuurstudie en meta-analyse (**Hoofdstuk 2**). We includeerden 31 studies gepubliceerd tot mei 2017 waarvan de meeste zich focusten op BMI. Uit deze literatuurstudie bleek dat het bewijs voor een verband tussen leefstijlfactoren en het verloop van blaaskanker beperkt is. Een meta-analyse van drie studies in NMIBC patiënten vond dat overgewicht en obesitas, in vergelijking met een gezond gewicht, geassocieerd waren met een verhoogd risico op recidieven. Er was ook een voorzichtige trend te zien voor een hoger risico op progressie naar spierinvasieve blaaskanker (muscle-invasive bladder cancer; MIBC) in patiënten met obesitas. De resultaten van onderzoeken naar het effect van BMI in een gecombineerde groep van NMIBC en MIBC patiënten, of in MIBC patiënten alleen was inconsistent en soms zelfs tegengesteld. Een meta-analyse van drie studies in NMIBC en MIBC patiënten gecombineerd liet echter een trend zien voor een lagere kankerspecifieke mortaliteit in patiënten met overgewicht in vergelijking met patiënten met een gezond gewicht. Sommige observationele studies naar voeding en voedingssupplementen vonden een potentieel beschermend effect op recidief, kankerspecifieke mortaliteit of mortaliteit in het algemeen. Dit gold echter alleen voor afzonderlijke voedingsmiddelen en supplementen. Het feit dat de meeste studies (ernstige) methodologische tekortkomingen hadden was misschien wel onze belangrijkste bevinding. Prospectieve cohortstudies met herhaalde metingen, die het hele dieet in beschouwing nemen en gericht zijn op geschikte klinische uitkomsten zijn nodig om evidence-based richtlijnen te ontwikkelen.

In **Hoofdstuk 3** beschrijven we de associatie tussen door de patiënt gerapporteerde rookstatus, tijd sinds stoppen met roken, cumulatieve blootstelling aan rook en postdiagnostische vochtinname met risico op NMIBC recidief in de prospectieve cohortstudie UroLife. We includeerden 550 patiënten met een primaire NMIBC diagnose. Deelnemers vulden 6 en 12 weken na diagnose een vragenlijst in over hun rookgedrag. Daarnaast hielden ze 12 weken na diagnose een vierdaags vocht- en urinedagboekje bij. Patiënten

werden opgevolgd voor een mediaan van 19 maanden. Hierin ontwikkelden 103 (19%) patiënten op zijn minst één recidief. De meeste patiënten hadden vroeger gerookt (58%) of rookten nog op het moment van invullen van de eerste vragenlijst (26%) en de mediane vochtinname was 1840 mL (interkwartielafstand 1500 – 2215 mL). Roken en vochtinname waren niet duidelijk geassocieerd met risico op recidief in deze voorlopige analyses van de UroLife studie. Een niet-statistisch significant verhoogd risico op recidief werd gevonden in voormalig rokers en in voormalig of huidig rokende patiënten met de hoogste versus de laagste cumulatieve blootstelling aan rook. Analyses in grotere studies met een langere follow-up zijn nodig voordat we definitieve conclusies kunnen trekken. Echter, stoppen met roken moet zeker worden aanbevolen op basis van de algemeen bekende en bewezen gezondheidsvoordelen.

De evaluatie van de associatie tussen verschillende empirisch afgeleide voedingspatronen en het risico op recidief en progressie van NMIBC wordt beschreven in **Hoofdstuk 4**. Hiervoor gebruikten we voedselfrequentievragenlijsten en klinische gegevens van 595 patiënten met primaire NMIBC uit een grote lopende cohortstudie uitgevoerd in M.D Anderson Cancer Center en Baylor College of Medicine. Uit de data identificeerden we vier voedingspatronen ("fruit en groente", "Westers", "vetarm" en "Tex-Mex"), die samen 37% van de totale variantie verklaarden. Patiënten die het meest volgens het Westerse voedingspatroon aten hadden een 1.5 keer hoger risico op recidief dan mensen die het minst volgens dit voedingspatroon aten. Er leek ook een trend te zijn voor een hoger risico op progressie bij een Westers voedingspatroon. Voor de andere voedingspatronen werden er geen associaties met recidief of progressie gevonden. Een Westers voedingspatroon is rijk aan voedingsmiddelen met veel schadelijke stoffen zoals gefrituurd voedsel en rood en bewerkt vlees. De schadelijke stoffen uit deze voedingsmiddelen zouden, wanneer ze via de urine worden uitgescheiden, een direct carcinogeen effect kunnen hebben op de urotheelcellen in de blaas. Onze studie ondersteunt dus de meer algemene hypothese dat een Westers eetpatroon een rol speelt in zowel het ontstaan als de prognose van kanker. Er is echter verder onderzoek nodig om onze bevindingen te bevestigen en deze complexe associatie tussen voeding en ziekte in meer detail te onderzoeken.

Hoofdstuk 5 beschrijft de HRQoL van aan UroLife deelnemende NMIBC patiënten over een periode van vijftien maanden na diagnose. Ook vergelijken we de HRQoL van patiënten met de HRQoL van een normatieve populatie die gematcht is op basis van een vergelijkbare leeftijd en geslacht. Het laatste doel van deze studie was te onderzoeken of de HRQoL van onze patiënten afhing van het type behandeling, rookgedrag en vochtinname. De HRQoL is gemeten met de EORTC QLQ-C30 en EORTC QLQ-NMIBC24 in 541 NMIBC patiënten binnen UroLife. We toonden aan dat NMIBC patiënten een slechter rol-, emotioneel- en sociaal functioneren rapporteren dan een normatieve populatie.

Daarnaast gaven ze aan meer klachten te ervaren op het gebied van vermoeidheid, benauwdheid, slapeloosheid, verlies van eetlust en diarree. Hoewel de HRQoL in de loop van de tijd verbeterde in de meeste domeinen, bleven klachten op het gebied van verlies van eetlust, diarree, urinewegsymptomen en emotionele zorgen bij veel patiënten aanwezig tot 15 maanden na diagnose. Patiënten die werden behandeld met intravesicale spoelingen met chemotherapie of immunotherapie scoorden slechter op een aantal ziekte-specifieke domeinen dan patiënten die alleen een transurethrale resectie van de tumor hadden ondergaan. Patiënten die werden behandeld met immunotherapie hadden daarnaast meer last van urinewegsymptomen. Rookstatus en vochtinname hadden geen relevant effect op HRQoL. Al met al is het belangrijk dat zorgverleners alert blijven op een slechtere HRQoL van NMIBC patiënten, ook voor een langere periode na diagnose. Tijdens deze studie ondervonden we dat de analyse van HRQoL uitdagend is vanwege de subjectieve aard van de gegevens. Er moet naar meer eenheid worden gestreefd in zowel de analyse als de interpretatie van deze zelfgerapporteerde uitkomsten.

Welke factoren volgens overlevenden van blaaskanker hebben bijgedragen aan de ontwikkeling van hun eigen ziekte is beschreven in **Hoofdstuk 6**. Hiervoor werden gegevens van de Nijmegen Blaaskankerstudie (NBCS) gebruikt en de vraag "Bij u is een relatief goedaardige poliep of een kwaadaardige tumor in de blaas vastgesteld. Heeft u zelf enig idee wat hiervan de oorzaak zou kunnen zijn?" werd geëvalueerd. Van de 1793 geïncludeerde patiënten rapporteerden slechts 366 (20%) patiënten een mogelijke oorzaak van hun tumor. Een opvallend lage 10% van alle patiënten vermoedde dat roken de oorzaak geweest zou kunnen zijn, gevolgd door beroepsmatige blootstelling aan toxische stoffen (5%) en erfelijkheid (2%). Zelfs onder rokers rapporteerde maar 11% dat roken mogelijk de oorzaak van hun ziekte zou kunnen zijn. Deze kennis is belangrijk voor initiatieven op het gebied van gezondheidspreventie en educatie, omdat het de geringe kennis over roken als risicofactor voor blaaskanker weergeeft. Ook het feit dat patiënten bepaalde risicofactoren als mogelijke oorzaak rapporteerden waarvan bekend is dat deze niet betrokken zijn bij het ontstaan van (blaas)kanker verdient aandacht. Wanneer patiënten zich op deze factoren richten, kan dit hen ervan weerhouden ongezonde leefgewoonten te veranderen.

Om onze kennis van bewustzijn en andere determinanten van gedragsverandering uit te breiden, hebben we onderzocht of NMIBC patiënten zich bewust zijn van risicofactoren voor (blaas)kanker en of zij zich houden aan richtlijnen voor kankerpreventie op het gebied van leefstijl in **Hoofdstuk 7**. Ook evalueren we in deze studie of patiënten advies over leefstijl kregen van hun arts en hoe zij ertegenover zouden staan leefstijladvies te krijgen van hun arts. In totaal werden 969 NMIBC patiënten die aan UroLife deelnamen in dit onderzoek geïncludeerd. Onze bevindingen tonen aan dat het bewustzijn van risicofactoren voor kanker in het algemeen varieerde tussen 29% voor consumptie van

fruit en groente en 89% voor roken. Slechts 44% van de patiënten was zich ervan bewust dat roken een risicofactor is voor het krijgen van blaaskanker. Het verschil met de studie die is beschreven in **Hoofdstuk 6** wordt waarschijnlijk veroorzaakt door het verschil in het type vraagstelling (gesloten versus open vraag) en omdat er in deze studie werd verwezen naar blaaskanker in het algemeen, in tegenstelling tot de eigen ziekte in **Hoofdstuk 6**. Of patiënten zich hielden aan de richtlijnen voor kankerpreventie varieerde tussen 34% voor lichaamsgewicht en 84% voor roken. Zeventig procent van de rokers gaf aan te zijn geadviseerd te stoppen met roken, terwijl slechts 19% van alle patiënten rapporteerde dat zij advies hadden gekregen over andere leefstijlfactoren. Meer dan 80% van de patiënten had echter een positieve houding ten aanzien van het ontvangen van leefstijladvies van hun arts. Deze bevinding, in combinatie met het lage bewustzijn van risicofactoren en slechte leefstijlgewoonten, zouden artsen moeten aanmoedigen om hun patiënten vaker te adviseren over een gezonde leefstijl.

Dit proefschrift eindigt met een algemene discussie van de studies die zijn beschreven waarbij zij in de context van relevante literatuur worden geplaatst (**Hoofdstuk 8**). Ook worden aanbevelingen gedaan aan beleidsmakers, clinici en onderzoekers.

Samengevat hebben we waardevolle gegevens verzameld over leefstijl in verschillende aspecten van NMIBC: prognose, HRQoL en het bewustzijn van patiënten. We vonden dat het risico op recidivering van NMIBC hoger is in patiënten met een hoger BMI (in de literatuur) en in patiënten met een Westers voedingspatroon (in patiënten uit de VS). Met UroLife startten we de hoognodige prospectieve studie met herhaalde metingen van leefstijl en HRQoL. In voorlopige analyses waren roken en vochtinname niet duidelijk geassocieerd met het risico op recidief, noch met HRQoL. HRQoL van NMIBC patiënten in onze studie was echter wel slechter dan HRQoL van een normatieve populatie in meerdere domeinen. Ook bleven klachten op het gebied van verlies van eetlust, diarree, urineweg-symptomen en emotionele zorgen vaak aanhouden tot 15 maanden na diagnose. Ten slotte tonen onze bevindingen aan dat patiënten zich maar matig bewust zijn van risicofactoren voor het krijgen van (blaas)kanker. Daarnaast houden zij zich slecht aan de richtlijnen voor kankerpreventie op het gebied van leefstijl en moet voorlichting door artsen op dit gebied worden verbeterd.

PhD portfolio

Name:
PhD student: P. Westhoff
Department:
Health Evidence
Graduate School:
Radboud Institute for Health Sciences

PhD period:
15-11-2013 – 14-08-2018
Promotor(s):
Prof. dr. L.A.L.M. Kiemeney, Prof. dr. E. Kampman, Prof. dr. J.A. Witjes
Co-promotor(s):
Dr. A. Vrieling

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- RIHS Introduction course, RIHS, Nijmegen	2014	1.4
- Management voor Promovendi, RUN, Nijmegen	2014	3.0
- Introductie tot de klinische en fundamentele oncologie, NVvO, Ellecom	2014	1.4
- Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK), Radboudumc, Nijmegen	2015	1.4
- Scientific integrity, RIHS, Nijmegen	2016	1.0
- Introduction to R, Radboudumc, Nijmegen	2016	0.3
- Exposure assessment in nutrition research, VLAG, Wageningen	2016	1.5
- Survival analysis, Erasmus MC, Rotterdam	2016	1.9
- Loopbaanmanagement voor promovendi, RUN, Nijmegen	2017	0.6
- Netwerken en solliciteren, RUN, Nijmegen	2017-2018	0.9
b) Seminars & lectures		
- Seminars and colloquia at the Department for Health Evidence, Radboudumc, Nijmegen	2013-2018	NA
c) Symposia & congresses		
- RIHS Science Day, RIHS, Nijmegen (laptop presentation)	2014	0.3
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON), Leiden (poster presentation)	2014	0.6
- Masterclass Diet and Cancer, Wageningen (oral presentation)	2014	1.3
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON), Maastricht (poster presentation)	2015	0.6
- Global Cancer, Occurrence, Causes and Avenues to Prevention, IARC, Lyon, France	2016	1.3
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON), Wageningen (poster presentation)	2016	0.6
- Voorjaarsvergadering Nederlandse Vereniging voor Urologie, Den Bosch (oral presentation)	2017	0.3
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON), Antwerpen (oral presentation & poster presentation)	2017	0.6
- RIHS PhD Retreat, RIHS, Den Bosch (oral presentation)	2017	0.3

- First Annual Conference Lifestyle as Medicine, LUMC, Leiden - German Cancer Research Center (DKFZ) Conference on Preventive Oncology, Heidelberg, Germany (poster presentation)	2017 2018	0.3 0.6
d) Other		
- Weekly epidemiology journal club at the Department for Health Evidence	2014-2018	3.6
- RIHS PhD Council – Workshop and Retreat committee	2014-2016	2
- Co-organizing a 2-day PhD retreat	2014-2016	6
TEACHING ACTIVITIES		
e) Lecturing		
- Different teaching activities	2015-2017	NA
f) Supervision of internships / other		
- Co-supervision internship Brazilian exchange student Medicine (Julia Neumayer)	2015	1.0
- Co-supervision science internship Medicine (Inge Hendriks)	2016	1.0
- Supervision Meet your PhD (Susanne Broekhuis, Sanne van Oosterhout)	2016	1.0
- Co-supervision BSc internship Biomedical Sciences (Babette de Geest)	2017	1.0
- Co-supervision MSc internship Nutrition and Health (Manette Dinnessen)	2017	1.5
- Co-supervision Science Project Biomedical Sciences and Medicine (Sanne van Oosterhout, Meilin Schaap, Jessie Swarts)	2017	1.0
- Supervision Science Project Biomedical Sciences and Medicine (Anna Groeneveld, Monique Jasperse, Sophie van Kessel)	2017-2018	1.0
TOTAL		39.3

About the author

Ellen Westhoff (born December 29th, 1988 in Bennekom) obtained her pre-university degree at the Marnix College in Ede in 2006. She went on to earn her Bachelor (2011) and Master (2013) of Science degrees in the field of Nutrition and Health at Wageningen University. During her Master specialisation Epidemiology and Public Health, she wrote a master thesis about the evaluation of an intervention to prevent overweight in primary school children at TNO, and completed an internship at the community health service of Gelre-IJssel. After a short period as a research assistant at TNO, Ellen started as a PhD candidate at the Department for Health Evidence in 2013. The research was focused on the association between dietary and lifestyle factors and the prognosis and quality of life of patients with non-muscle-invasive bladder cancer. For this, a large and still ongoing cohort study called UroLife was set up. Until now, over 1200 patients diagnosed in 22 hospitals have participated in the study. In the third year of her PhD, from November 2015 to January 2016, she was a visiting scientist at the epidemiology group of MD Anderson Cancer Center in Houston, Texas, led by professor Xifeng Wu. The research was conducted between November 2013 and August 2018, and resulted in several publications, all of which can be found in this thesis. The findings described here have been presented at (inter)national scientific meetings, including the annual WEON. Currently, Ellen is working as a researcher and consultant at Significant Groep in Utrecht.

List of publications

Westhoff E, Witjes JA, Fleshner NE, Lerner SP, Shariat SF, Steineck G, Kampman E, Kiemeney LA, Vrieling A. *Body mass index, diet-related factors, and bladder cancer prognosis: a systematic review and meta-analysis.* Bladder Cancer 2018;4:91-112.

Westhoff E, Wu X, Kiemeney LA, Lerner SP, Ye Y, Huang M, Dinney CP, Vrieling A, Tu H. *Dietary patterns and risk of recurrence and progression in non-muscle invasive bladder cancer.* Int J Cancer 2018;142:1797-1804.

Westhoff E, de Oliveira-Neumayer JM, Aben KK, Vrieling A, Kiemeney LA. *Low awareness of risk factors among bladder cancer survivors: New evidence and a literature overview.* Eur J Cancer 2016;60:136-45.

Peer-reviewed conference abstracts

Westhoff E, Kampman E, Aben KA, Hendriks I, Witjes JA, Kiemeney LA, Vrieling A. *Awareness of, adherence to, and interest in lifestyle recommendations for cancer prevention among bladder cancer patients.* DKFZ, 2018, Heidelberg, Duitsland.

Westhoff E, Wu X, Kiemeney LA, Ye Y, Huang M, Dinney CP, Vrieling A, Tu H. *Dietary patterns and risk of recurrence and progression in non-muscle invasive bladder cancer.* WEON, 2017, Antwerpen, België.

Westhoff E, Hendriks I, Kampman E, Witjes JA, Kiemeney LA, Vrieling A. *Awareness of, adherence to, and interest in lifestyle recommendations for cancer prevention among bladder cancer patients.* WEON, 2017, Antwerpen, België.

Westhoff E, Hendriks I, Kampman E, Witjes JA, Kiemeney LA, Vrieling A. *Leefstijl en blaaskanker: bewustzijn en gedrag van pati*ënten en advies van de uroloog. Voorjaarsvergadering van de Nederlandse Vereniging voor Urologie, 2017, Den Bosch, Nederland.

Westhoff E, de Oliveira-Neumayer JM, Aben KK, Vrieling A, Kiemeney LA. *Low awareness of risk factors among bladder cancer survivors.* WEON, 2016, Wageningen, Nederland.

Westhoff E, Kampman E, Witjes JA, van der Heijden AG, Kiemeney LA, Vrieling A. *Lifestyle factors and bladder cancer prognosis: a systematic review.* WEON, 2015, Maastricht, Nederland.

Westhoff E, Kampman E, Witjes JA, van der Heijden AG, Kiemeney LA, Vrieling A. *Dietary and lifestyle factors potentially influence bladder cancer prognosis: a systematic review*. Masterclass Diet and Cancer, 2014, Wageningen, Nederland.

Westhoff E, Kampman E, Witjes JA, Kiemeney LA, Vrieling A. *UroLife (Urothelial cell cancer: Lifestyle, prognosis, and quality of life)*. WEON, 2014, Leiden, Nederland.

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Ellen

There is a crack in everything, that's how the light gets in. (Leonard Cohen, 1934-2016)

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