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Lifestyle and nutritional modifiable factors in the prevention and treatment of bladder cancer

Marilyn L. Kwan, Ph.D.[a,*], Brandon Garren, M.D.[b], Matthew E. Nielsen, M.D., M.S.[b,c], Li Tang, Ph.D.[d]

[a] *Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612*
[b] *Department of Urology, University of North Carolina, Chapel Hill, NC 27599*
[c] *Departments of Epidemiology and Health Policy & Management, University of North Carolina, Chapel Hill, NC 27599*
[d] *Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263*

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Abstract

Bladder cancer is one of the top 5 most common cancers diagnosed in the U.S. It is also one of the most expensive cancers to treat through the life course given its high rate of recurrence. While cigarette smoking and occupational exposures have been firmly established as risk factors, it is less certain whether modifiable lifestyle factors such as diet and physical activity play roles in bladder cancer etiology and prognosis. This literature review based on a PubMed search summarizes the research to date on key dietary factors, types of physical activity, and smoking in relation to bladder cancer incidence, and discusses the potential public health implications for formalized smoking cessation programs among recently diagnosed patients. Overall, population-based research in bladder cancer is growing, and will be a key platform to inform patients diagnosed and living with bladder cancer, as well as their treating clinicians, how lifestyle changes can lead to the best outcomes possible. © 2018 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Diet and nutrition; Physical activity; Smoking and smoking cessation; Lifestyle factors

Introduction

In the U.S., bladder cancer is among the top 5 most common cancers, with an expected 76,960 newly diagnosed cases in 2016 and 16,390 deaths [1,2]. It is also the most expensive cancer, per patient, from diagnosis to death [3], due in part to its extraordinarily high rate of recurrence [4,5]. Established risk factors for bladder cancer encompass 3 general areas: genetic and molecular abnormalities (specific oncogenes and tumor suppressor genes), chemical or environmental exposures (primarily cigarette smoke), and chronic irritation (such as pelvic irradiation or indwelling catheters) [6]. To date, the associations of diet and physical activity with bladder cancer risk are unclear, yet point to possible beneficial effects of these modifiable lifestyle factors. This targeted literature review will summarize the current evidence on the roles of diet, physical activity, and cigarette smoking with risk of bladder cancer, as well as any implications for potential interventions after bladder cancer diagnosis. A PubMed search was conducted using key words of bladder cancer, urothelial cancer or urothelial carcinoma, diet, nutrition, physical activity, exercise, smoking, and tobacco.

Diet and bladder cancer

Dietary behaviors may reduce exposure to known bladder cancer carcinogens or block the carcinogenic process, subsequently preventing or delaying bladder cancer occurrence. Fluid intake and vegetable and fruit consumption are of great interest in line with this notion.

Total fluid intake is expected to affect urine output and frequency of voiding, therefore modifying urinary concentrations of carcinogens and altering duration of carcinogen exposure to the bladder epithelium [7]. In a randomized trial of 65 smokers, increasing water intake for 50 days significantly decreased urinary mutagenicity [8].

*Corresponding author. Tel.: +1-510-891-3521; fax: +1-510-891-3836.
E-mail address: Marilyn.L.Kwan@kp.org (M.L. Kwan).

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Epidemiological studies on total fluid intake and bladder cancer risk have yielded conflicting results. In the Health Professionals Follow-up Study, high fluid intake (>2,531 ml/d) was associated with a 49% reduction in bladder cancer risk when compared with the lowest intake (<1,290 ml/d) (relative risk, RR = 0.51, 95% CI: 0.32–0.80) [9]. In contrast, a case-control study conducted in the U.S. reported a 41% increase in bladder cancer risk with high total fluid intake (≥2,789 ml/d) compared to low intake (<1,696 ml/d) [10]. A recent meta-analysis by Bai et al. summarized findings from 17 case-control and 4 cohort studies, and found no associations between total fluid intake and bladder cancer risk (overall odds ratio = 1.06, 95% CI: 0.88–1.27), yet subgroup analyses revealed significant inverse associations between intake of green tea and black tea and bladder cancer risk [11]. This finding was confirmed by the latest meta-analysis of cohort studies on tea consumption and bladder cancer risk. The meta-analysis showed a dose-dependent inverse association with an increase of every 1 cup of tea consumed per day, although the association was restricted to studies in Western countries (RR = 0.95, 95% CI: 0.91–0.98) with a mixed tea drink, instead of specifically green or black tea [12]. Similar inconsistent results were also observed for coffee and milk consumption in relation to bladder cancer risk [13,14]. Many factors could contribute to such inconsistencies, and frequency of urination may play a critical role in determining contact time of the carcinogen with the bladder epithelium, rather than fluid intake itself. A multicenter case-control study in Spain found an inverse trend between bladder cancer risk and nighttime voiding frequency in both men and women regardless of amount of fluid consumption [15]. Examining both fluid intake and urination in a case-control study in China, Zhang et al. [16] reported that subjects with more than 1,500 ml of total fluid intake and at least 6 times of urination per day had a significant reduction in bladder cancer risk (odds ratio = 0.43, 95% CI: 0.25–0.74), compared to those who drank less than 750 ml of total fluid and urinated 3 times or less daily.

Vegetables and fruits contain many micronutrients and phytochemicals, which may block or suppress carcinogenesis to modify cancer risk [17]. One of these mechanisms is modulation of the phase I/II enzyme system to alter carcinogen metabolism and facilitate detoxification [17,18]. This may be particularly important for the bladder due to altering exposure to carcinogens. Additionally, nutrients and phytochemicals from fruits and vegetables have been shown to have multifacet anticancer activities. They can inhibit cancer cell proliferation and invasion via targeting signaling pathways and boosting the antitumor microenvironment by inhibiting angiogenesis and reducing inflammatory responses [17,19,20]. Therefore, phytochemical-rich vegetables and fruits may not only be cancer-preventive, but also have cancer-therapeutic potential [19]. A meta-analysis of 27 observational studies published through August 2014 reported a dose-dependent reduction of bladder cancer risk with every 200 g/d increment in vegetable (RR = 0.92, 95% CI: 0.87–0.97) and fruit (RR = 0.91, 95% CI: 0.83–0.99) consumption [21]. However, these associations were primarily driven by findings from the case-control studies. A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)-compliant study summarized results from 14 cohort studies and found that bladder cancer risk was not associated with either vegetable or fruit intake [22]. Significant inverse associations with bladder cancer risk have also been reported from pooled case-control studies but not cohort studies for individual food items, such as cruciferous vegetables [23] and citrus fruits [24]. One important factor often neglected in observational studies is cooking style. Many micronutrients and phytochemicals are heat sensitive and may be destroyed or inactivated during the cooking process. In a hospital-based case-control study that examined effects of raw vs. cooked cruciferous vegetables separately, significant inverse associations were only observed for raw cruciferous vegetable intake but not total or cooked counterparts [25].

Although studies have examined dietary factors and bladder cancer risk, data on dietary factors and bladder cancer survivorship are sparse. One study examined numbers of days for which consumption was at least 5 servings of fruits and vegetables per week in relation to a general health score in cancer survivors; the study found no associations among bladder cancer survivors [26]. Another study examined cruciferous vegetable intake in relation to bladder cancer survival and observed strong inverse associations for broccoli intake, particularly raw broccoli, with overall survival (hazard ratio, HR = 0.57, 95% CI: 0.39–0.83) and bladder cancer-specific survival (HR = 0.43, 95% CI: 0.25–0.74) [27]. This finding is well supported by preclinical data on isothiocyanates, a group of promising chemopreventive phytochemicals primarily found in cruciferous vegetables [18], however, the result was obtained from a small retrospective study with further validation required. During the early 1980s and 1990s, several clinical trials were conducted on specific micronutrients such as etretinate (a vitamin A analog), pyridoxine (vitamin B6), and a megadose multivitamin combination [28–31]. All studies reported a significant delay or prevention of recurrence with these supplements in patients diagnosed with non–muscle-invasive bladder cancer (NMIBC). Although severe side effects were also observed for these micronutrients, which limited their application, these positive results shed light on improving bladder cancer prognosis with diet or food items enriched in micronutrients or phytochemicals. Considering the high recurrence rate of NMIBC [32], dietary studies with a focus on bladder cancer prognosis could have a significant effect on bladder cancer outcomes.

Overall, there is no conclusive evidence to support or dispute the notion of potential beneficial roles of dietary factors in bladder cancer prevention and survival. Well-designed prospective studies are needed in this field.

Physical activity and bladder cancer

Physical activity may protect against bladder cancer. Plausible mechanisms include physical activity being associated with biologic pathways that can directly influence cancer development. These include enhanced immune function, reduced chronic inflammation, increased detoxification of carcinogens, enhanced DNA repair, modified cell proliferation, differentiation, and apoptosis [33,34]. It has also been hypothesized that physical activity might indirectly decrease the risk of bladder cancer by reducing weight and helping to maintain a healthy weight [35]. Two recently published studies, 1 a meta-analysis [36] and the other a pooled analysis [37], reported statistically significant decreased risks of bladder cancer associated with physical activity. To note, a systematic literature review of physical activity and obesity found no associations of physical activity with bladder cancer risk in the literature, including 6 prospective and 2 retrospective studies [38].

The meta-analysis included 15 studies published from January 1975 to November 2013, which represented nearly 5.5 million subjects and 27,784 bladder cancer cases [36]. High vs. low levels of physical activity were associated with a 15% reduction in risk of bladder cancer (RR = 0.85, 95% CI: 0.74–0.98). When examined by type of physical activity, the reduction in risk persisted. For recreational activity, there was a 19% RR (RR = 0.81, 95% CI: 0.66–0.99), and for occupational activity, there was a 10% RR (RR = 0.90, 95% CI: 0.76–1.07). In addition, when examining by intensity of physical activity, results were comparable. For both moderate (RR = 0.85, 95% CI: 0.75–0.98) and vigorous activity (RR = 0.80, 95% CI: 0.64–1.00), the risk reductions ranged from 15% to 20%, respectively. Increasing duration of physical activity was also suggestive of decreasing bladder cancer risk; 10%, 14%, and 17% significant reductions at 25th, 50th, and 75th percentiles of physical activity levels. Overall, associations by sex (male vs. female) and study design (cohort vs. case-control) were similar.

The pooled analysis combined data from 12 prospective U.S. and European cohorts representing 1.44 million subjects to examine the association of leisure-time physical activity with risk of various types of cancer [37]. Leisure-time physical activities were defined as activities done at an individual's discretion that improve or maintain fitness or health. There were a total of 9,073 bladder cancer cases included. High levels (90th percentile) compared with low levels (10th percentile) of leisure-time physical activity were associated with a moderate 13% reduction in risk of bladder cancer (HR = 0.87; 95% CI: 0.82–0.92; *P* for heterogeneity = 84). The association changed very minimally after adjustment for body mass index (HR = 0.88; 95% CI: 0.83–0.94). Finally, the associations were examined among current, former, and never smokers, and results were very similar across these 3 groups (*P* for effect modification>0.99).

To our knowledge, only 1 recent study has investigated the effect of physical activity on bladder cancer prognosis or survival [39]. This large study using data on 222,163 participants and 83 bladder cancer-specific deaths from the National Health Information Survey (NHIS) found that any exercise (light, moderate, or vigorous in ≥10-min increments) was associated with a 47% decreased risk of death compared to those who reported no exercise. Results were based on a multivariable model adjusting for body mass index and smoking. One limitation of this study was reduced statistical power to comprehensively examine the association between physical activity and bladder cancer death, given that the majority of participants (78%) were less than 60 years of age. Future prospective, population-based studies of bladder cancer survivors should examine specific type, duration, frequency, intensity, and timing of physical activity in relation to bladder cancer diagnosis, as well as collect more detailed physical activity data with standardized instruments measuring activity levels.

Smoking and bladder cancer

Tobacco smoking has long been recognized as perhaps the single most important behavioral/lifestyle risk factor associated with the development of bladder cancer, and nearly half of all bladder cancer cases in the U.S. are attributable to smoking [40].

Historical studies and landmark meta-analyses from the early 2000s demonstrate a quantifiable risk of bladder cancer in those who smoke tobacco compared to those who do not. These studies show more than 3-fold increased risk in current smokers and approximately 2-fold increased risk in former smokers [41]. Smoking is higher than any other known risk factor for bladder cancer. These findings were validated in a 2016 meta-analysis of 89 observational studies in the last 50 years [42]. Bladder cancer risk was also associated in a dose-dependent manner with number of cigarettes smoked, with a peak risk around 15 cigarettes smoked per day. Interestingly, smoking greater than 15 cigarettes per day did not confer a significantly additive overall risk, suggesting an underlying saturation phenomenon.

Though the prevalence of tobacco smoking within the U.S. has been decreasing, the age-adjusted incidence rate of bladder cancer has remained relatively stable [43]. A 2011 study of the NIH-AARP cohort demonstrated increased risks of tobacco smoking and bladder cancer compared to earlier prospective studies in the 1960s to 1980s. This suggests an increase in the intensity of the association over time. The authors hypothesize that the chemical makeup of cigarettes might be increasing in carcinogenicity [44]. Cigarette composition has changed since the 1950s, containing less nicotine and tar, but higher concentrations of nitrates and known carcinogenic N-nitrosamine byproducts [45].

Bladder cancer has historically been more common in males vs. females with an almost 3:1 predominance. Early studies, particularly from the 1970s to 1990s, attribute this

finding to known variance in smoking prevalence. Newer studies, performed in populations with more comparable sex-specific smoking prevalence show a convergence in cancer incidence. These findings indicate that males and females share comparable risk after smoking similar amounts. However, a 2009 meta-analysis suggested that tobacco smoking only partially explains the male excess in bladder cancer incidence. An explanation for this difference has not been well-elucidated, but theories suggest stronger occupational influences, as well as biogenetic susceptibilities [46].

Given the large body of evidence outlined above, public health awareness of bladder cancer as a tobacco-related disease is poor and is notably lower compared to other tobacco-related illnesses. In a survey of 535 urology patients, 94% of patients recognized the association of smoking and lung cancer, yet only a quarter of those patients understood the association between smoking and bladder cancer [47].

In addition to tobacco smoking's association with bladder cancer risk, it is also associated with bladder cancer prognosis. Current and former smokers diagnosed with NMIBC exhibit increased recurrence and progression rates than never smokers, perhaps as a function of their total cumulative exposure [48–50], and are 4 and 3 times more likely, respectively, to die of bladder cancer compared with never smokers [39]. Current smokers additionally tend to fare worse than former smokers and nonsmokers after similar treatments with transurethral resection and intravesical chemotherapy. In the context of muscle-invasive disease, current smokers experience higher rates of treatment-related complications and morbidity, and a 1.4-fold increased risk of bladder cancer-specific mortality [51].

Health care providers, particularly urologists, have an opportunity to assume a key role in the secondary prevention of bladder cancer, as well as other cancers and medical conditions associated with tobacco smoking, through smoking cessation counseling. Exceptionally high cessation rates of 40% to 96% observed among patients with new diagnoses of lung or oropharyngeal cancers [52–59] speak to the potential efforts in this context. One population-based study found smokers with a new diagnosis of bladder cancer were approximately 5 times more likely to quit as smokers in the general population. Patients cited the bladder cancer diagnosis and the advice of their urologist as the most common reasons for cessation [60]. Evidence suggesting potentially decreased recurrence rates among patients with NMIBC [48,61] may be particularly relevant in the reinforcement of bladder cancer diagnosis as a "teachable moment." Nevertheless, greater attention is needed on this topic in the bladder cancer clinic. American urologists are particularly deficient in cessation counseling, with a majority of practitioners never addressing tobacco cessation, and almost 40% expressing the belief that it would not affect disease course or alter treatment outcomes [62]. In one study demonstrating the gaps in

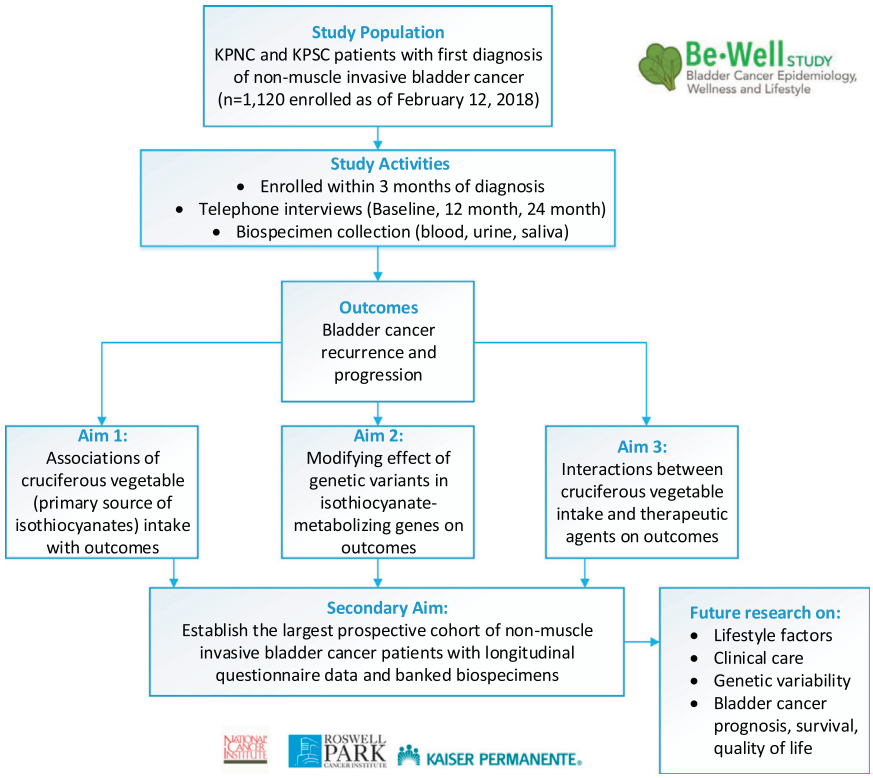

Fig. Overview of Bladder Cancer Epidemiology, Wellness, and Lifestyle Study (Be-Well Study), Funded by the National Cancer Institute, R01CA172855. (colour version of the figure available online.)

current practice, almost 95% of active smokers newly diagnosed with tobacco-related urologic cancer were not counseled in tobacco cessation at the time of their initial visit, despite the fact that as few as 5 minutes of cessation intervention can increase the likelihood of quitting by 4 fold [63]. Greater attention to this component of patient counseling may provide benefits not only in terms of bladder cancer outcomes, but overall health.

The Bladder Cancer Epidemiology, Wellness, and Lifestyle Study (Be-Well Study)

As this review suggests, the evidence on the role of several lifestyle and nutritional factors and bladder cancer prognosis and survival is sparse. To address these gaps, the Be-Well Study, a prospective cohort study of patients with newly diagnosed NMIBC, began in 2014 with funding from the National Cancer Institute (R01CA172855; MPI: Kwan, Tang, Kushi). The overall aim of Be-Well is to examine the role of nutritional, lifestyle, and genetic factors in bladder cancer treatment and outcomes (Fig). Patients are being actively recruited from Kaiser Permanente (KP), the largest integrated health delivery system in the U.S., in KP Northern and Southern California. Prospective data are being collected at 3 points postdiagnosis on self-reported lifestyle and nutritional factors, along with confirmed recurrence, progression, and survival outcomes. Blood, urine, and saliva are also being obtained in a prospective manner to provide accompanying genetic and biomarker data. It is anticipated that Be-Well will establish one of the largest, most comprehensive prospective cohort studies of bladder cancer patients with NMIBC to help answer critical questions related to prognosis, quality of life, and care in patients diagnosed with early-stage bladder cancer.

Conclusion and future steps

Potentially modifiable lifestyle factors and health behaviors including diet, physical activity, and smoking have been associated with bladder cancer carcinogenesis to varying degrees [64]. These include increased fluid intake, more vegetable and fruit consumption, and regular physical activity. The effect of these factors on prognosis has been relatively unexplored, especially for diet and physical activity. More well-designed studies with precise behavioral measurements are necessary to investigate possible beneficial effects of lifestyle on incidence and outcomes. Results from the ongoing Be-Well Study of bladder cancer survivors could inform future interventions in this area. Encouragingly, a pilot intervention study found that telephone- or Skype-based dietary counseling is able to increase total vegetable intake among bladder cancer patients diagnosed with NMIBC, showing the feasibility of dietary intervention programs among bladder cancer survivors [65]. Finally, while primary prevention from continued broad-based tobacco control policies are important, evidence suggests potentially high effect opportunities for secondary prevention through a more systematic implementation of smoking cessation in the clinic as a component of bladder cancer care. In conclusion, population-based, observational research in bladder cancer is growing, which will contribute to further knowledge on how patients diagnosed and living with bladder cancer can modify their lifestyle to ensure the best outcomes possible.

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