EDITORIAL

Unraveling the Dietary Puzzle: Exploring the Influence of Diet, Nutraceuticals, and Supplements on Bladder Cancer Risk, Outcomes, and Immunotherapy Efficacy: Insights from the BLOSSOM Study and Beyond

Carlo Buonerba · Concetta Ingenito · Rossella Di Trolio · Francesca Cappuccio · Roberta Rubino ·
Arianna Piscosquito · Antonio Verde · Ferdinando Costabile · Michela Iuliucci · Felice Crocetto ·
Francesco Chiancone · Antonio Nacchia · Antonio Campitelli · Luca Scafuri · Roberto Sanseverino ·
Giuseppe Di Lorenzo

ABSTRACT

Bladder cancer is considered a global health concern characterized by significant morbidity and mortality rates. The complex relationship between diet and bladder cancer is examined, with a specific focus on the role of diet in risk, outcomes, and treatment efficacy. Attention is drawn to the burgeoning field of immunotherapy in bladder cancer treatment, and the possible influence of diet on its outcomes is explored. While evidence remains limited, prior

C. Buonerba · C. Ingenito · F. Cappuccio ·
R. Rubino · A. Piscosquito · A. Verde · F. Costabile ·
M. Iuliucci · L. Scafuri · G. Di Lorenzo (✉)
Oncology Unit, "Andrea Tortora" Hospital, ASL
Salerno, Presidio Ospedaliero A.Tortora, Via Alcide
de Gasperi, 59, 84016 Pagani, SA, Italy
e-mail: direttoreuocpagani@gmail.com

C. Buonerba · A. Verde · F. Costabile · L. Scafuri ·
G. Di Lorenzo
Associazione O.R.A. ETS-Oncology Research
Assistance, Somma Vesuviana, Italy

C. Buonerba
Department of Public Health, "Federico II"
University, 80131 Naples, Italy

R. Di Trolio
Unit of Melanoma, Cancer Immunotherapy and
Development Therapeutics, Istituto Nazionale
Tumori Istituto di Ricovero e Cura a Carattere
Scientifico Fondazione G. Pascale, Naples, Italy

F. Crocetto
Department of Neurosciences, Reproductive and
Odontostomatological Sciences, Urology and
Andrology Unit, University of Naples Federico II,
Via Pansini No. 5, 80131 Naples, Italy

F. Chiancone
Department of Urology, AORN A. Cardarelli, Naples,
Italy

A. Nacchia
Urology Unit, Ospedale Sant'Andrea, 'Sapienza'
University of Rome, 00191 Rome, Italy

A. Campitelli · R. Sanseverino
Department of Urology, Umberto I, Nocera
Inferiore, Salerno, Italy

G. Di Lorenzo
Department of Medicine and Health Sciences
"Vincenzo Tiberio", University of Molise,
Campobasso, Italy

studies in other cancer types have suggested a potential connection between diet and immunotherapy response. To address this knowledge gap, the ongoing BLOSSOM study is presented, which aims to investigate the link between dietary factors, lifestyle, and the effectiveness of immunotherapy in patients with non-muscle-invasive bladder cancer. Ongoing efforts to decipher the intricate relationship between diet and bladder cancer care are highlighted, emphasizing the quest to unravel the dietary puzzle for the improvement of bladder cancer management.

Keywords: Bladder neoplasms; Diet; Risk factors; Treatment outcomes; Immunotherapy; Micronutrients; Epidemiology; Dietary patterns

Key Summary Points

Bladder cancer is a global health concern with significant morbidity and mortality rates.

The study explores the intricate relationship between diet and bladder cancer, focusing on its role in risk, outcomes, and treatment efficacy.

The field of immunotherapy in bladder cancer treatment is highlighted, with an examination of the potential impact of diet on its outcomes.

Limited evidence suggests a potential connection between diet and immunotherapy response in other cancer types.

The ongoing BLOSSOM study aims to investigate the link between dietary factors, lifestyle, and the effectiveness of immunotherapy in patients with non-muscle-invasive bladder cancer, addressing a knowledge gap in the field.

INTRODUCTION

Bladder cancer remains a significant global health burden, affecting millions of individuals each year. Despite advances in diagnosis and treatment, bladder cancer remains associated with considerable morbidity and mortality rates. Thus, understanding the factors that influence bladder cancer risk, outcomes, and treatment efficacy is crucial for devising effective preventive and therapeutic strategies. The impact of diet on human health has been the subject of numerous epidemiological studies [1]. Dietary patterns play a pivotal role in the development and progression of various diseases, including cancer. In the context of bladder cancer, understanding the role of specific dietary components and patterns becomes crucial in unraveling the dietary puzzle that may influence bladder cancer risk [2].

Over the years, research has demonstrated that certain dietary factors may contribute to the development of bladder cancer, while others may have protective effects [3]. Diets low in fruit intake were associated with an increased risk of bladder cancer, while diets low in vegetable intake showed a slightly elevated risk. Conversely, diets high in fat intake were linked to an increased risk, but no significant associations were found for diets high in meat intake or low in retinol and beta-carotene intake [2].

Additionally, research has shown that certain nutraceuticals and supplements possess bioactive compounds that may impact bladder cancer biology, potentially influencing tumor growth and response to therapies. As an example, potential protective effects of certain micronutrients against bladder cancer emerged in a case–control study, with higher intakes of vitamin E, carotenoids, vitamin D, thiamin, and niacin showing inverse relationships with bladder cancer risk, especially among heavy smokers and older individuals [4].

Diet is increasingly recognized as a significant factor that can influence the treatment outcomes of bladder cancer, particularly immunotherapy. This recognition stems from the intricate interplay between diet and various critical components, such as the immune

system, the host's overall health status, the tumor microenvironment, and the gut microbiome. A diet rich in these nutrients may improve the immune system's ability to identify and eliminate cancer cells, potentially enhancing the response to immunotherapy, while the overall health and nutritional status of the host can significantly impact the success of cancer treatment [5].

Immunotherapy is used to treat both early and advanced bladder cancer. In early, localized bladder cancer, bacillus Calmette-Guérin (BCG) immunotherapy is a widely used treatment for non-muscle-invasive bladder cancer [6]. In advanced urothelial carcinoma, immune checkpoint inhibitors (ICIs) have emerged as effective therapeutic agents [7, 8]. Understanding the interplay between dietary components and BCG treatment may offer insights into the optimization of this therapy and enhance its effectiveness in managing early-stage bladder cancer.

As we embark on the BLOSSOM study, an ongoing prospective study which will be summarized in this article, and beyond, aiming to unravel the impact of diet, nutraceuticals, and supplements on bladder cancer risk, outcomes, and immunotherapy efficacy, it is crucial to recognize the growing evidence of diet's influence on immune function. With this understanding, investigating the potential interplay between diet and ICI response in patients with bladder cancer becomes imperative. By achieving a deeper comprehension of these relationships in the context of changing bladder cancer epidemiology and therapeutic opportunities, we can devise targeted prevention strategies and adapt treatment approaches to address the complexities of this disease landscape. This holistic approach holds the key to resolving the dietary puzzle and harnessing the potential benefits of diet and nutritional interventions in the pursuit of improved bladder cancer management.

The purpose of this article is to underscore the critical role of diet in bladder cancer, examining its influence on risk, outcomes, and treatment efficacy. By summarizing existing research and introducing the ongoing BLOSSOM study, we aim to highlight the significance of understanding the intricate relationship between dietary factors and bladder cancer. Our ultimate goal is to contribute to the development of effective preventive and therapeutic strategies, fostering a holistic approach to bladder cancer management that harnesses the potential benefits of diet and nutritional interventions.

INFLUENCE OF DIETARY FACTORS ON BLADDER CANCER RISK

Several systematic reviews and meta-analyses have explored the relationships between diet and bladder cancer risk. Al-Zalabani et al. conducted a systematic review of meta-analyses on modifiable risk factors for primary bladder cancer. They found statistically significant associations between bladder cancer and factors such as current (RR 3.14) or former (RR 1.83) cigarette smoking, pipe (RR 1.9) or cigar (RR 2.3) smoking, antioxidant supplementation (RR 1.52), obesity (RR 1.10), higher physical activity levels (RR 0.86), higher body levels of selenium (RR 0.61) and vitamin D (RR 0.75), and higher intakes of processed meat (RR 1.22), vitamin A (RR 0.82), vitamin E (RR 0.82), folate (RR 0.84), fruit (RR 0.77), vegetables (RR 0.83), citrus fruit (RR 0.85), and cruciferous vegetables (RR 0.84). They calculated the probability of causation for individual factors, ranging from 4% to 68%, and the combined probability of causation was 81.8% [9]. Taylor et al. investigated the impact of plant-based diets on bladder cancer risk and outcomes. Although only two studies were included, they found that a lower risk of bladder cancer diagnosis was associated with vegetarian diets [10]. Dianatinasab et al. focused on dietary patterns and their association with bladder cancer risk. Their meta-analysis revealed that the Mediterranean diet had a protective effect on bladder cancer risk in both case–control (OR 0.73, 95% CI 0.52–0.94) and cohort studies (RR 0.93, 95% CI 0.88–0.97). However, the Western diet showed a direct association with bladder cancer risk in cohort studies (RR 1.53, 95% CI 1.37–1.70), but not in case–control studies (OR 1.33, 95% CI 0.81–1.88). There was no significant association between the dietary

inflammatory index (DII) and bladder cancer risk in cohort studies (RR 1.02, 95% CI 0.93, 1.12), but a strong direct association was found in case–control studies (RR 2.04, 95% CI 1.23–2.85) [11]. Dai et al. examined the association between coffee consumption and bladder cancer risk. Their meta-analysis of 16 prospective studies, comprising 2,122,816 participants and 11,848 bladder cancer cases, did not find a significant link between coffee consumption and bladder cancer risk (RR high-vs-low 1.07, 95% CI 0.96–1.20). They suggested that direct associations observed in some studies may be a result of residual confounding by smoking [12]. Conversely, it is important to note that both coffee and caffeic acid, a bioactive compound found in various herbs, vegetables, and fruits, hold promising anticancer potential. As an example, coffee consumption has been associated with a reduced risk of hepatocellular carcinoma [13]. Similarly, caffeic acid exhibits antitumor actions by exerting pro-oxidant and antioxidant properties, inhibiting reactive oxygen species formation, and suppressing angiogenesis and matrix metalloproteinases, suggesting its therapeutic implications for cancer treatment and prevention [14]. Xenou et al. performed a systematic review and meta-analysis of prospective cohort studies to examine the association between fruit and vegetable consumption and bladder cancer risk. They found that vegetable consumption (pooled RR 0.95, 95% CI 0.87–1.04) as well as combined fruit/vegetable consumption were not associated with bladder cancer risk. Regarding fruit intake, the overall protective trend did not reach significance (pooled RR 0.91, 95% CI 0.81–1.02); however, they found a significant association in East Asians. A trend toward a protective association with citrus fruit consumption was also noted (pooled RR 0.83, 95% CI 0.69–1.01), once again with a significant effect in East Asians. Moreover, no association was found regarding the subgroups of leafy vegetables, dark green vegetables, and berries. Single studies pointed to a reduced bladder cancer risk in never smoking male individuals consuming cruciferous vegetables and East Asians consuming yellow vegetables [15].

These systematic reviews and meta-analyses provide valuable insights into the role of diet in bladder cancer risk and outcomes. While smoking remains a significant risk factor, dietary factors, including certain nutrients, food groups, and dietary patterns, may also influence bladder cancer risk. Adopting a plant-based diet and avoiding certain dietary habits, such as high-fat and processed meat intake, may be beneficial in reducing bladder cancer risk.

INFLUENCE OF DIETARY FACTORS ON TREATMENT SENSITIVITY: LACK OF DATA AND THE BLOSSOM STUDY

There is currently a lack of specific evidence regarding how diet can impact immunotherapy efficacy in bladder cancer. Golčić et al. [16] analyzed the gut microbiome and dietary habits in patients with metastatic melanoma and a complete and sustained response to immunotherapy. Patients who exhibited a late complete response had a significantly different gut microbiome composition, with higher abundance of certain bacterial species and lower abundance of others compared to early responders. Late responders also exhibited a different diet profile, with lower intake of proteins and sweets and higher intake of flavones. Bolte et al. [17] conducted a multicenter cohort study to investigate the association between habitual diet and response to immune checkpoint blockade (ICB) treatment in patients with advanced melanoma. They found a positive linear association between a Mediterranean dietary pattern, high in whole grains, fish, nuts, fruits, and vegetables, and the probability of overall response rate (ORR) and progression-free survival at 12 months (PFS-12).

Both studies provide valuable insights into the potential relationship between diet and immunotherapy efficacy in patients with cancer, which prompted us to start the BLOSSOM trial, a prospective, observational study designed to investigate the potential interaction of nutritional and psychological aspects with the most clinically relevant outcomes in

patients with non-muscle-invasive bladder cancer (NMIBC) who are scheduled to receive intravesical BCG therapy as part of standard clinical practice.

The multicenter study promoted by ASSOCIAZIONE ORA ETS and conducted at several Italian centers coordinated by the Oncology Unit of the Tortora Hospital of ASL of Salerno aims to assess the impact of dietary factors and lifestyle variables on treatment sensitivity and disease progression in this specific patient population. Patient selection for the BLOSSOM trial includes BCG-naïve individuals with high-risk NMIBC, as determined by the American Urological Association (AUA) risk classification and the 2016 World Health Organization (WHO) Classification of Tumors of the Urothelial Tract. The evaluation timetable includes multiple visits throughout the 12-month observation period, and various parameters will be assessed at each visit, including demographic information, medical history, physical examination variables, laboratory tests, dietary variables, distress levels, functional assessment of cancer therapy, adverse events, and more. Of particular interest is the FOODCONS method for dietary assessment. This method involves the 24-h dietary recall method, where trained field workers will interview patients on three separate occasions during a 14-day period. The dietary assessment will be conducted using an ad hoc web-based software database called FOODCONS, which allows for precise data coding and processing of recorded food and recipe information, including weight, energy intake, macronutrients, vitamins, minerals, and other dietary variables. To ensure the study's statistical power, a sample size of 148 patients will be enrolled, with the goal of detecting associations between specific food or food group consumption and the risk of bladder cancer recurrence. Overall, the BLOSSOM trial will provide valuable insights into the potential influence of dietary factors on the efficacy of BCG immunotherapy in patients with NMIBC, shedding light on the role of nutrition and lifestyle in the context of bladder cancer treatment.

CONCLUSIONS

Understanding the impact of dietary factors on bladder cancer risk, outcomes, and treatment efficacy is crucial for developing effective preventive and therapeutic strategies. Research has shown that certain dietary components and patterns may contribute to the development of bladder cancer, while others may have protective effects. Diets low in fruit intake and vegetables were associated with increased risk, while diets high in fat intake were linked to an increased risk. Certain nutraceuticals and supplements have bioactive compounds that may impact bladder cancer biology, potentially influencing tumor growth and response to therapies. Several flavonols, like quercitrin [18], kaempferol, myricetin, and fisetin [19] hold the potential to function as advantageous nutrients in the prevention of bladder cancer, and they could be administered through supplements or even pharmaceutical agent [20]. Diet quality and adherence to certain dietary patterns, such as cruciferous vegetable intake and avoidance of sugar-sweetened beverages, may impact bladder cancer survival. Currently, there is a lack of specific evidence regarding how diet can impact immunotherapy efficacy in bladder cancer. In this regard, it is essential to emphasize certain limitations. The available evidence, while suggestive, is largely observational, and causation cannot always be established. Additionally, dietary assessments are subject to recall bias, and the influence of confounding variables can affect study outcomes. The ongoing BLOSSOM study will contribute to shed light on the role of nutrition in bladder cancer treatment outcomes and its findings are awaited. The impact of diet on immunotherapy outcomes in bladder cancer remains an area of ongoing investigation and requires more comprehensive research to better understand the potential mechanisms and implications.

contributed to the finalization of the draft and approved the final version.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Giuseppe Di Lorenzo is an Editorial Board member of *Oncology and Therapy*. Giuseppe Di Lorenzo was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Cespedes EM, Hu FB. Dietary patterns: from nutritional epidemiologic analysis to national guidelines. Am J Clin Nutr. 2015;101:899–900. https://doi.org/10.3945/ajcn.115.110213.

2. Steinmaus CM, Nuñez S, Smith AH. Diet and bladder cancer: a meta-analysis of six dietary variables. Am J Epidemiol. 2000;151:693–702. https://doi.org/10.1093/oxfordjournals.aje.a010264.

3. Jubber I, Ong S, Bukavina L, et al. Epidemiology of bladder cancer in 2023: a systematic review of risk factors. Eur Urol. 2023;84:176–90. https://doi.org/10.1016/j.eururo.2023.03.029.

4. Brinkman MT, Karagas MR, Zens MS, Schned A, Reulen RC, Zeegers MP. Minerals and vitamins and the risk of bladder cancer: results from the New Hampshire Study. Cancer Causes Control. 2010;21:609–19. https://doi.org/10.1007/s10552-009-9490-0.

5. Zhang X, Li H, Lv X, et al. Impact of diets on response to immune checkpoint inhibitors (ICIs) therapy against tumors. Life. 2022;12:409. https://doi.org/10.3390/life12030409.

6. Mukherjee N, Wheeler KM, Svatek RS. Bacillus Calmette–Guérin treatment of bladder cancer: a systematic review and commentary on recent publications. Curr Opin Urol. 2019;29:181–8.

7. Ferro M, Crocetto F, Tataru S, et al. Predictors of efficacy of immune checkpoint inhibitors in patients with advanced urothelial carcinoma: a systematic review and meta-analysis. Clin Genitourin Cancer. 2023. https://doi.org/10.1016/j.clgc.2023.05.017.

8. Barone B, Calogero A, Scafuri L, et al. Immune checkpoint inhibitors as a neoadjuvant/adjuvant treatment of muscle-invasive bladder cancer: a systematic review. Cancers (Basel). 2022. https://doi.org/10.3390/cancers14102545.

9. Al-Zalabani AH, Stewart KFJ, Wesselius A, Schols AMWJ, Zeegers MP. Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses. Eur J Epidemiol. 2016;31:811–51. https://doi.org/10.1007/s10654-016-0138-6.

10. Taylor J, Gupta N, Blanck J, Loeb S. A systematic review of plant-based diets and bladder cancer: a call for further research. Soc Int Urol J. 2022;3:240–4. https://doi.org/10.48083/GBMA2534.

11. Dianatinasab M, Forozani E, Akbari A, et al. Dietary patterns and risk of bladder cancer: a systematic review and meta-analysis. BMC Public Health.

2022;22:73. https://doi.org/10.1186/s12889-022-12516-2.

12. Dai Z-W, Cai K-D, Li F-R, Wu X-B, Chen G-C. Association between coffee consumption and risk of bladder cancer in a meta-analysis of 16 prospective studies. Nutr Metab (Lond). 2019;16:66. https://doi.org/10.1186/s12986-019-0390-3.

13. Fan FS. Coffee reduces the risk of hepatocellular carcinoma probably through inhibition of NLRP3 inflammasome activation by caffeine. Front Oncol. 2022;12:1029491. https://doi.org/10.3389/fonc.2022.1029491.

14. Alam M, Ashraf GM, Sheikh K, et al. Potential therapeutic implications of caffeic acid in cancer signaling: past, present, and future. Front Pharmacol. 2022;13: 845871. https://doi.org/10.3389/fphar.2022.845871.

15. Xenou D, Tzelves L, Terpos E, Stamatelopoulos K, Sergentanis TN, Psaltopoulou T. Consumption of fruits, vegetables and bladder cancer risk: a systematic review and meta-analysis of prospective cohort studies. Nutr Cancer. 2022;74:2003–16. https://doi.org/10.1080/01635581.2021.1985146.

16. Golčić M, Simetić L, Herceg D, et al. Analysis of the gut microbiome and dietary habits in metastatic melanoma patients with a complete and sustained response to immunotherapy. Cancers (Basel). 2023;15:3052. https://doi.org/10.3390/cancers15113052.

17. Bolte LA, Lee KA, Björk JR, et al. Association of a Mediterranean diet with outcomes for patients treated with immune checkpoint blockade for advanced melanoma. JAMA Oncol. 2023;9:705–9. https://doi.org/10.1001/jamaoncol.2022.7753.

18. Mirto BF, Scafuri L, Sicignano E, et al. Nature's hidden gem: quercitrin's promising role in preventing prostate and bladder cancer. Future Sci OA. 2023;9:FSO67. https://doi.org/10.2144/fsoa-2023-0041.

19. Crocetto F, di Zazzo E, Buonerba C, et al. Kaempferol, myricetin and fisetin in prostate and bladder cancer: a systematic review of the literature. Nutrients. 2021. https://doi.org/10.3390/nu13113750.

20. Buonerba C, De Placido P, Bruzzese D, et al. Isoquercetin as an adjunct therapy in patients with kidney cancer receiving first-line sunitinib (QUASAR): results of a phase I trial. Front Pharmacol. 2018. https://doi.org/10.3389/fphar.2018.00189.