Introduction

Among all urological cancers, Bladder Cancer (BC) is the tenth most common type of cancer worldwide, with approximately 549,000 new cases per year and 200,000 mortality. It is four times more common in males than females and is frequently seen in the sixth and seventh decades [1]. In addition to its negative effects on public health, BC is one of the cancer types with the highest cost of treatment due to its frequent recurrence [2]. For these reasons, the role of dietary factors, especially vitamins, in preventing BC has been studied frequently. In this mini review, we aimed to summarize that experimental and epidemiological studies investigating the relationship between vitamin A and BC.

Vitamin A is a fat-soluble micronutrient and must be taken with dietary or supplementary since it cannot be produced in the human body. When taken in excess, it can be stored in the liver and adipose tissue. The vitamin A family exists in two forms: preformed vitamin A (retinaldehyde, retinol, and retinoic acid) and provitamin A carotenoids (α-carotene, β-cryptoxanthin, and β-carotene). Provitamin A is the precursor of retinol, the most active metabolite. Retinol is found in high amounts in eggs, dairy products, and fish oils. Carotenoids are found in high amounts in orange and yellow fruits and dark green leafy vegetables. Although lycopene, lutein, and zeaxanthin are carotenoids, they do not have vitamin A activity biologically. In contrast, synthetic retinoid compounds have vitamin A activity [3].

Many studies have used human tumor xenografts in nude mice or human cancer cell lines to investigate the effects of vitamin A metabolites and synthetic retinoids on BC and other types of cancer [4]. The results report that these compounds have chemo preventive, therapeutic, or anticancer effects through cell differentiation, regulation of apoptosis, or cell growth arrest [5,6]. Because of their antioxidant activity, carotenoids have prompted researchers to investigate their modulatory effects on carcinogen metabolism [7], and the potential benefits of carotenoids in heavy smokers BC patients are often debated.

One of the oldest studies examining the relationship between BC and vitamin A was conducted by Toyoshima et al. [8]. The researchers, in their studies using the NBT-II rat urinary bladder cell line, showed that adding 1UI/mL of vitamin A to the medium did not alter cell proliferation and aggregation, but inhibited keratinization reversibly [8]. A later study by Tchao et al. [9] was shown that vitamin A prevents keratinization in NBT-II cell aggregates but does not have an inhibitory effect on aggregate formation [9]. Cohen et al. investigated the effects of vitamin A level on N-[4-(5-Nitro-2-furyl)-2-thiazolyl] formamide-induced BC in rats and they reported that vitamin A deficient rats seemed to speed up the carcinogenic process, with Urinary Bladder Tumor (UBT) emerging earlier. In contrast, hypervitaminosis A-rats, UBT development occurred more slowly, and squamous metaplasia and squamous cell neoplasia did not occur [10]. In the study conducted by Squire et al. [11], they reported that 13-cis-retinoic acid is protective on the development of N-methyl-N-nitrosourea-induced BC in rats and inhibits the development of preneoplastic or neoplastic lesions in the bladder epithelium [11]. The study by Grubbs et al. [12] reported that 13-cis-retinoic acid inhibits the N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced BC in rats [12]. Similarly, Sporn et al. [13]...
was reported that 13-cis-retinoic acid inhibited the development of N-methyl-N-nitrosourea-induced BC in rats [13]. In the study by Becci et al. [14] was reported that 13-cis-retinoic acid inhibited N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced BC in C57BL/6 mice [14]. In the study of Miyata, et al. was stated that rats with hypervitaminosis A have increased resistance to N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced BC [15]. In a study conducted by Becci et al. [14] with a different approach, BC was formed with N-butyl-N-(4-hydroxybutyl)-nitrosamine in 344 rats, and the effect of delay in the administration of 13-cis-retinoic acid on BC inhibition was investigated. The results showed that the ability of 13-cis-retinoic acid to prevent bladder carcinogenesis was not weakened even by a nine-week delay in initiating retinoid feeding [16].

Mathews-Roth et al. [17] investigated the effect of supplementary β-carotene on N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced BC in male B6D2F1 mice. Researchers reported that mice taking supplementary β-carotene developed significantly fewer tumors than untreated mice [17]. After experimental studies have shown its protective effects on BC, there has been an increase in epidemiological studies examining the relationship between vitamin A and BC. In the study conducted by Risch et al. [18] on 826 BC patients and 792 healthy control groups, it was reported that dietary β-carotene or retinol had no protective effect on bladder cancer [18]. In the study conducted by Steineck et al. [19] on 418 BC patients and 511 healthy control groups, no relationship was found between BC and dietary vitamin A levels, but it was reported that intake of vitamin A supplements may reduce the risk of BC [19]. In the study conducted by Nomura et al. [20] on 261 BC patients and 522 healthy control groups, it was reported that dietary and supplementary (total) carotenoids, retinol, and vitamin A were not associated with BC risk [20]. In the study conducted by Brümmemer et al. [21] on 262 BC patients and 405 healthy control groups, it was shown that total vitamin A and retinol may have a protective effect on BC, unlike dietary β-carotene [21]. In the study of Michaud et al. on 320 BC patients, no significant relationship was found between vitamin A and BC risk [22]. In the study conducted by Wakai et al. [23] on 297 BC patients' retinol and vitamin A could be protective on BC. Besides, dietary carotene has been reported to have a protective and 295 healthy control groups, it was shown that dietary effect only in BC patients who are heavy smokers [23]. In the study conducted by Zeegers et al. [24] on 569 BC patients and 3123 healthy control group, the relationship between retinol, α-carotene, β-carotene, and β-cryptoxanthin intake and BC was evaluated and it was stated that only β-cryptoxanthin intake could have a protective effect on BC [24]. In a study conducted by Michaud et al. on 344 BC patients, the relationship between dietary vitamin A, α-carotene, β-carotene and β-cryptoxanthin intake and BC was investigated, and none of them were reported to show a statistically significant level of protection. However, the researchers stated that their findings could not be generalized to non-smokers [25]. Nomura et al. [20] investigated the levels of retinol, α-carotene, β-carotene, and β-cryptoxanthin from serum samples of 111 BC patients and 111 healthy control groups using HPLC. The researchers saw that α-carotene, β-carotene, and β-cryptoxanthin were statistically significant inverse correlated with BC, but they reported the following the adjustment for the smoking pack-year, none of the reverse patterns remained significant [26].

In the study conducted by Castelo et al. [27] on 1592 BC patients and 1592 healthy control group, a statistically significant inverse relationship was found between dietary total carotenoid intake and BC [27]. Schabath et al. [28] investigated dietary total carotenoid intake in 423 BC patients and 467 healthy controls and found that there was a statistically significant lower carotenoid intake in BC patients. Then, they investigated DNA damage from peripheral blood lymphocytes of BC patients and healthy controls by comet analysis. As a result of the study, the researchers reported that there is a statistically significant inverse relationship between carotenoid intake and DNA damage and that carotenoid intake may have a protective effect against DNA damage [28]. Holick et al. [29] in their study including 237 women with BC, investigated the relationship between BC intake with total vitamin A, dietary α-carotene, β-carotene, and β-cryptoxanthin, and it was reported that there was no statistically significant relationship [29]. Hung et al. [30] analyzed the plasma retinol, α-carotene, β-carotene, and β-cryptoxanthin levels by HPLC in their study on 242 BC patients and 204 healthy control groups. The researchers stated that α-carotene and β-cryptoxanthin could have a statistically significant protective effect on BC, and pointed out that BC could be prevented, especially in smokers, through diet [30].

Ozasa et al. [31] as a result of HPLC analysis of serum samples of 42 BC patients and 124 healthy control groups, reported that total carotenoids, especially β-carotene, were statistically significantly associated with a reduced risk of BC, in contrast to serum retinol levels [31]. In the study of Garcia-Closas et al. [32] on 912 BC patients and 873 healthy control groups, it was reported that there was no statistically significant relationship between dietary retinol intake and BC [32]. Similarly, the study Kellen et al. [33] on 178 BC patients and 362 healthy control groups stated that there was no statistically significant relationship between dietary retinol intake and BC [33]. In contrast to these two studies, Liang et al. [34] investigated retinol levels by HPLC from the plasma of 386 BC patients and 389 healthy controls and reported that the plasma retinol level was statistically significant protective for BC [34]. In the study conducted by Roswall et al. [35] on 322 BC patients, it was stated that unlike supplementary β-carotene, dietary β-carotene could be statistically significant protective for BC [35]. In the study conducted by Brinkman et al. [36] on 322 BC patients and 239 healthy controls, a statistically significant inverse relationship was found between total carotenoids intake and BC among elderly individuals [36]. In the study conducted by Hotaling et al. [37] on 330 BC patients, it was reported that taking supplementary β-carotene and retinol does not reduce the risk of BC [37]. In the study conducted by Ros et al. [38] on 856 BC patients, plasma carotenoid levels were analyzed by HPLC and it was reported that high plasma carotenoid levels could reduce the risk of BC. The researchers also stated that β-carotene level and Urothelial
Cell Carcinoma (UCC) were statistically significant inverse related [38]. In the study conducted by Wu et al. [39] on 1177 BC patients and 1418 healthy controls, no statistically significant relationship was found between dietary vitamin A, α-carotene and β-carotene intake and BC [39]. In a multiethnic study by Park et al. [40] on 581 BC patients (152 women and 429 men), it was stated that high dietary vitamin A, α-carotene, β-carotene, and β-cryptoxanthin intake reduced the risk of BC among women, but the same results were not seen in male BC patients [40]. On the other hand, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study conducted by Virtamo et al. [41] in Finland, it was reported that long-term supplementary β-carotene intake had no protective effect on urinary tract cancers in middle-aged male smokers [41].

Epidemiological studies indicate that vitamin A may have preventive effects on BC development, but the findings are inconsistent. For this reason, it will be more informative to examine meta-analysis. In the meta-analysis conducted by Tang et al. [42] in 2014, it was found that total vitamin A intake (OR: 0.82; 95% CI: 0.65, 0.95), total retinol intake (OR: 0.88; 95% CI: 0.73, 1.02), and high blood retinol levels (OR: 0.64; 95% CI: 0.38, 0.90) have been reported to have a protective effect on BC. Researchers also stated that there is an inverse relationship between carotenoids and BC risk [42]. In the meta-analysis conducted by Wu et al. [43] in 2019, dietary β-cryptoxanthin intake (OR: 0.58; 95% CI: 0.36, 0.94), high blood α-carotene (OR: 0.24; 95% CI: 0.08, 0.67) and β-carotene levels (OR: 0.73; 95% CI: 0.57, 0.94) has been reported to be inversely related to BC risk [43].

Conclusion

Although studies conducted in animal experimentation clearly show the inhibitory effect of vitamin A on bladder carcinogenesis, epidemiological studies are inconsistent. As a result, it seems that most of the studies state that vitamin A intake is associated with a reduced risk of BC in humans. The findings of studies dealing with the relationship between retinol and BC are variable. When the relationship between BC and α-carotene, β-cryptoxanthin, and β-carotene are considered one by one, the results are inconsistent. However, there may be an inverse relationship between total carotenoid intake or serum carotenoid levels and BC risk. Using vitamin A and other dietary factors might have effects on reducing BC risk, however, the number of studies that have investigated circulating concentration of micronutrients and other food components are limited. Therefore, further studies are needed with a larger sample.

Competing Interests

The authors declared they have no competing interests.

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