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How dairy food affects prostate cancer?- a literature review

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Abstract:
Introduction: Prostate cancer is one of the most common type of tumors. Potential factors influencing this neoplasm are subject of many scientific studies as a scarce number of risk variables have been well-established so far.

Purpose of the work: The objective of this review is to collect and interpret recent findings regarding dairy food and its influence on prostate cancer.

Materials and method: A systematic research was conducted using the PubMed database. Articles in English published from 2015 to 2024 were selected using keywords: dairy products, dairy, milk, prostate cancer.

State of knowledge: There is an overall positive association between total dairy products, milk and prostate cancer risk. Although whole milk is not considered as a risk factor, it has been reported that high-fat milk has a positive association with fatality rate and recurrence.

Several studies presented a new potential pathomechanisms of dairy's influence on prostate tumors. Casein, IGF-1 and exosomes are labeled as mediators between high dairy food intake and prostate cancer occurrence.

Summary: As of now, there is not strong enough evidence to limit dairy food intake in the whole population. Further research is needed to explore the relationship between dairy consumption and prostate cancer. Men with diagnosed prostate tumors are suggested to eat food according to the Mediterranean diet as it has been reported that it decreases cancer-specific and overall mortality.

Keywords: dairy products, dairy, milk, prostate cancer

1. Introduction

Prostate cancer is one of the main health challenges for men. According to the WHO 2022 report it is the 4th most common type of cancer with over 1.4 million diagnoses and nearly 400.00 deaths worldwide [1]. The incidence for prostate tumors varies in different parts of the world. There is a limited number of acknowledged prostate cancer risk factors such as advanced age, disease-related family history, ethnicity (especially African heritage), genes variations and BMI [2]. Diet has been linked with carcinogenesis long since. One of the focuses of the scientists has been largely analyzed dairy food, especially milk. Milk is an agricultural product consisting mainly of water, milk sugar - lactose, fats, proteins, vitamins and minerals. It is an important component of a balanced diet and source of bioactive compounds [3]. Although, beneficial effects of milk are well-known, especially in infancy, there have been studies that described dairy food as a prostate cancer risk factor.

The objective of this review is to collect and interpret recent findings regarding dairy food and its influence on prostate cancer.

2. Materials and method

A systematic literature search was conducted using the PubMed database. Studies were selected using keywords: dairy products, dairy, milk, prostate cancer. Articles in English published from 2015 to 2024 were included, then evaluated for their significance and suitability for inclusion.

3. State of knowledge

Milk products as a prostate cancer risk factor

The overall positive association between milk and prostate cancer risk has been well-documented in many epidemiological studies [4], however, data from cohort and case-control studies have been inconsistent [5, 6], so meta-analyses were conducted to provide more unambiguous conclusions. According to the 2014 and 2018 World Cancer Research Fund Report dairy might be linked with an increased risk of prostate cancer, but data were limited and suggestive [7,8]. A large, prospective population-based cohort study in Sweden, did not contribute any major negative or positive effects of consuming dairy products regarding prostate cancer prevention. Dairy products were divided into subgroups: non-fermented milk, fermented milk, cheese, and butter.

Most results rendered null, except for significant positive association between high intake of cheese and prostate cancer risk [9]. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial analysis results on total dairy food consumption and prostate neoplasm risk did not find a relevant correlation either. Statistically significant positive association was found between 2% fat milk consumption and risk of advanced tumor. Additionally, there was a linkage between late stage prostate cancer and increased regular fat dairy food intake, noted that these findings were with no difference in the association by clinical stage or advancement [10]. A research performed by Larsson et al. included groups of patients from European data bases. The selected lactase gene variants were used as a proxy for milk consumption. As no overall statistically significant association between milk intake and prostate tumor occurrence was observed (OR 1.01; 95% CI 0.99–1.02; $p = 0.389$), analysis of Finnish data base alone demonstrated positive association (OR 1.07; 95% CI 1.01–1.13; $p = 0.026$) which might be due to more homogenous population and relatively high dairy consumption in Finland [11] . In China, no significant relationship with this type of cancer was observed, putting into consideration that consumption of total dairy there was lower than in the Western countries [12]. On the other hand, a large scale cohort study on the Japanese population showed that milk and yogurt consumption presented a significant positive association with tumor development and a dose–response relationship [13]. Scientists found out that migration from developing to industrialized countries increased prostate cancer risk in immigrants. Such a phenomenon was observed in Chinese, Korean and African groups of people who moved to the United States of America. It was connected to changing lifestyle including higher dairy intake [5]. A 2015 meta-analysis by Aune at al. reinforced aforementioned conclusions about positive association between milk products and neoplasm risk by insinuating that high intakes of total dairy products, cheese, total milk, and calcium (excluding non-dairy and supplemental sources) might increase total prostate cancer risk. Significant inverse effect was observed only in whole-milk consumption, other dairy products showed no such association. The results diverged for types of dairy products and sources of calcium, additionally non-dairy calcium intake showed no significant association with higher prostate cancer risk in that meta-analysis. This teased the possibility that other components of dairy apart from this macroelement might increase the prevalence of male neoplasm [14]. A 2019 systematic review claimed that although the data was not unequivocal, most of the reviews approved milk as a prostate neoplasm risk factor, moreover, there was strong evidence in literature that associated dairy food with this type of cancer [2]. The three recent meta-analyses reported that high milk consumption in adulthood was linked with an increased prostate cancer risk [5,15, 16]. The last one by Zhao et al. analyzed the data from 1989 to 2020. They reported a positive association between prostate tumor risk and high intake of total dairy, milk, butter and cheese. An inverse association was observed regarding whole milk. No correlation between cancer risk and low-fat milk, ice-cream and yogurt was observed [5]. Contrarily, a review focused only on cheese showed no association with total and advanced prostate cancer incidence rate [17].

Pathophysiology

Recent years brought immense amounts of new information about potential mechanisms of this interdependence. Dairy products contain hormones such as estrogens, androgens, progesterone, corticoids, insulin-like growth factor 1 (IGF-1), prolactin as well as prostaglandins [4,18]. Although data about statistically significant positive association between dairy food and IGF-1 level had been nonunanimous, recent studies concluded that there was moderate evidence for a positive correlation between high milk products intake and IGF-1 concentration [19,20]. Research performed on the German population using 24h-dietary recalls showed significant positive association between dairy consumption and circulating IGF-1, whereas no connection to cheese and yogurt was found [20]. Another analysis delivered some evidence that dairy protein elevates the level of circulating IGF-1, which might result in increased prostate tumor risk [21]. The same hypothesis was formed in other collected data [19, 20]. For example, under serum free conditions, prostate gland cancer cells exposed to casein expressed higher concentrations of IGF-1 receptor B and insulin receptor B compared to the control sample [22]. This most important protein of milk has been reported to stimulate proliferation of prostate tumors itself [4]. An article by Kim et al. focused on gene changes caused by casein to PC3 prostate cancer cells. By gene expression profiling they identified several changes in cells exposed to casein under serum-free conditions. Genes related to the growth control, cell survival, and metabolism were promoted by forementioned milk protein [22]. In this research exposition induced an activation of rapamycin complex 1 (mTORC1) which complemented the information delivered in another study [2] indicating mTORC1 and PI3 kinase-AKT as potential mechanisms of prostate carcinogenesis and milk components as activators of these pathways. Casein inhibited autophagic death by activating mTORC1, up-regulation of 1p70S6K, and down-regulation of LC3. Elevated levels of PCNA and E2F1 were also detected showing another pathway of casein-caused proliferation in prostate cancer cells [22]. As the pathomechanisms of inducing tumors are more and more understandable, Watling et al. indicated that reported positive association between milk protein, IGF-1 and tumor risk might not have much impact on disease occurrence, because of other components of dairy food which might have protective properties against oncogenic IGF-1 influence [21]. Articles pointed out that almost every body tissue is affected by estrogens, the result of which can be growth of estrogen-sensitive cells [18,23]. Early data indicated the significant role of estradiol as a growth factor in neoplasms. Additionally, estradiol's metabolites were listed as tumor initiators. Generated semiquinone and quinone were capable of forming carcinogenic stable or depurinating DNA adducts [18]. Nevertheless, dietary hormones and their role in carcinogenesis still needs to be discussed. Several studies indicated that market-available milk had insufficient concentration of biologically-active estrogens, making them incompetent to act harmfully [23] and as previously mentioned [21], the role of other dairy components needs to be thoroughly researched. One of the examples is phosphorus, which was also observed to be positively associated with cancer [11]. High intake of dairy calcium has been described as a potential reason for prostate tumors coincidence for a long time. Proposed mechanism in cancer development was suppression of the conversion of 25(OH) vitamin D to 1,25(OH)2 vitamin D, a well- known anti-carcinogen which counteracts mitogenesis [19]. Another component of milk, lactose, also increased this macroelement absorption [10].

Some data pointed out dairy fat as a potential carcinogen by enhancing testosterone levels which led to activating pro-oncogenes [24]. An alternative version for being a risk factor was triggering the changes in gut microbiome by being a fermented food [24] or elevating c-peptide level [4]. Nevertheless, the difference between intake of fermented and non-fermented dairy was not confirmed by PLCO cohort trial analysis [10]. As fatty acids in dairy food were associated with prostate cancer in older studies, a 2016 meta-analysis reported that evidence on positive relation between them was limited and inconclusive [25], which could be explained by recent findings that each kind of fatty acid had different effects [13]. In case of lactase, the meta-analysis by Travis at al. implied that the lactase variant was not strongly related to prostate cancer risk, but with current state of knowledge it was impossible to deny the correlation either [26]. There was a review that presented dairy exosomes as a potential new pathogens in many diseases. Prostate cancer could be promoted by transfer of components of commercial bovine milk exosomes: oncogenic miRNAs and TGF-β [27]. For example, miR-148a, miR-125b, and miR-21 were reported to be involved in tumor initiation and progression [28]. Refrigeration and pasteurization technology has been preserving exosomes by reducing lactobacteria which plays a crucial role in degrading milk exosomes in bacterial fermentation. Ultra-high temperature (UHT) method was much more effective in prevention from dairy exosomes reaching the human circulatory system and tissues [27]. While looking for answers as to what could be regarded as prostate cancer risk factor Lan et al. focused on adolescent diet and dairy intake in puberty. Age adjusted analysis resulted in suggestive positive association between dairy ,milk, calcium intake and total and advanced prostate cancer (T3-T4, N1,M1 or tumor-caused death) [29], which was in accordance with previous Reykjavik Study and other research [28,30]. Inverse trends were observed for cheese and ice cream. Adding adjustments such as other components of diet of 12-13 years old like red meat attenuated the results [29]. Meta-analysis of adolescent dairy consumption from 2022 did not find statistically significant correlation, but results need to be interpreted with caution, as available data was scarce [16].

Course of disease

Most of the epidemiological studies revolved around occurrence of prostate cancer and milk as a risk factor, whereas connection between already existing early-stage tumors and dairy consumption was not studied as often. Bernichtein et al. performed in-vivo study with two models of genetically modified mice. The first simulated human benign prostatic hyperplasia by overexpression of rat prolactin, the other portrayed precancerous lesions evolving to cancer. It was achieved by knock-in of SV40 large T antigen at the PSP94 locus. Both models were fed whole or skim milk, precisely 1.4 g of milk powder/day/mouse. The experiment was conducted during a specified time frame. The results showed that milk did not induce prostate growth nor did it aggravate prostate tumor histopathology when assessed at the beginning of the disease. Collected data indicated no correlation of dairy diet with expression of cancer markers and tumor invasiveness [31]. Experiments on animals found no connection, but systematic review by Vasconcelos et al. claimed that it was possible to establish a relation between tumor progression and dairy intake [2].

According to another data, men with the highest (Q5) versus lowest (Q1) intake of whole milk had increased risk of cancer progression (Q5 vs. Q1 adjusted HR 2.15 95% CI 1.28–3.60), in addition, it was confirmed that larger dosage of high-fat milk was associated with worse cancer progression (>2.5 servings/day vs. ≤0.5 servings/day, adjusted HR 2.17 95% CI 1.34–3.51) [32].

Meta-analysis by Lu et al. for dairy products as cancer mortality risk was conducted. It consisted of 11 population-based cohort studies involving 778,929 participants. The food was categorized into milk, whole milk, low-fat milk, butter, yogurt and cheese. Only whole milk intake impacted prostate cancer mortality risk significantly with RR of 1.43 (95 % CI 1.13–1.81, p = 0.003). Additionally, the linear dose–response relationship between increased whole milk intake and fatal prostate tumor was observed. Low total dairy intake reduced relative risk of carcinogenesis [33]. In accordance with this data was a research study performed by Steck at al. which concluded 74% higher chances of aggressive prostate cancer among whole-milk drinkers compared to non-whole milk drinkers [34]. Other groups of dairy food were not associated with increased mortality risk [32, 33, 34, 36]. Aune at al. in their meta-analysis described the relation between high dairy consumption and mortality as insignificant [14]. One case-control study in Australia observed significant inverse association between total dairy and milk and aggressive prostate cancer risk [35], but it was an isolated case. This led to the impression that results about fatal cases are inconclusive, which brought up substantial matter of differentiation of dairy products. Previous studies on fatal prostate cancer and milk had ambiguous results and majority of negative correlation conclusions came from research which did not differentiate milk fat levels [36]. Some scientists went a step further and specified tumor stages which presented undermentioned results. Research performed on Swedish population of 525 men with newly-diagnosed prostate cancer showed significant association between increased high-fat milk intake and prostate mortality risk in localized tumors - TNM classification T≤2 and M0 (HR=6.10; 95% CI: 2.14, 17.37; p=0.004). Skim milk was associated with a borderline reduction in deaths caused by prostate neoplasm. In a group with an advanced tumor (TNM classification T ≥T3 and/or M1) no relevant correlation between any type of milk and prostate cancer-specific mortality was observed, only for butter [36].

Research by Lan et al. suggested that other factors apart from dairy such as socioeconomic status, cancer screening and treatment could influence the results of mortality data [29]. Pal et al. confirmed previous results of positive association between aggressive form of tumor and body mass index (BMI) (1.34, 1.02-1.78, p = 0.04) [35]. Multiethnic analysis found significant positive association between high calcium intake and aggressive form of this male gland cancer [37]. Although high calcium (Ca) intake in adulthood was linked with fatal tumors in many studies, some research did not have the same conclusions. The key to this matter seems to be magnesium (Mg), to be specific interdependence between Ca and Mg which was not widely studied and taken into account before. Higher dietary Ca:Mg doses significantly increased risk of aggressive course of the disease. A hypothesized mechanism for that was activation of TRPM7 due to an imbalance in Ca:Mg, which could stimulate prostate cancer cell proliferation [34].

Tat at al. examined post-diagnostic consumption of dairy products in relation to risk of prostate cancer recurrence among people with non-metastatic prostate cancer. 1,334 men were selected from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE™). Participants with high whole-milk intake had an 73% increased risk of recurrence [HR: 1.73; 95% CI: 1.00, 2.98; p=0.04] compared to men who rarely consumed it, particularly obese individuals. Adding saturated fat to the multivariate model changed results to [HR: 1.66; 95% CI: 0.96, 2.87], which implied fat being the part of milk that concurred to prostate cancer recurrence. Other dairy products did not present a statistically significant relation with tumor recurrence [38].

3. Conclusions

Publications over the years about milk and dairy food were unequivocal, nevertheless, data from meta-analyses showed that there is a positive association between total dairy products, milk and prostate cancer risk. Whole milk drinkers had an increased risk of fatal prostate cancer and recurrence compared to non-whole milk drinkers. Results for skim milk were inconclusive. What needs to be taken into account is insufficient control of confounding factors. Most of the studies were based on food frequency questionnaires, many adjustments were included, but with the current state of knowledge it is impossible to distinguish all interactions between lifestyle factors, dairy food and prostate cancer. Differences in PSA screening availability could also influence the results. As of now, there are not strong enough reasons to limit dairy products in diet, but scientists bring awareness to secondary prevention. The Mediterranean diet had significant association in reducing progression of the neoplasm [2], lowering high-fat dairy intake is suggested for men with prostate cancer [39]. Studying dietary patterns showed that patients with diagnosed localized prostate tumor and preferred Mediterranean diet had lower all-cause and cancer specific mortality [40]. In recent years, there has been tremendous progress in understanding the pathomechanisms behind the relationship between dairy and prostate cancer, which is very important as understanding the mechanism behind prostate cancer initiation and progression is crucial for finding new effective therapy, especially for treatment-resistant cases. Apart from calcium, phosphorus and fatty acids, IGF-1 concentration, casein and dairy's exosomes were presented as mediators in the development of prostate tumors. Bovine miRNA , which reaches our system through milk, could be proposed as prognostic prostate cancer biomarkers. All in all, additional studies need to further explore the association between milk products and subtypes of prostate cancer.

Disclosure:

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