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The Role of Dairy Products in Prostate Cancer: A Review

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Abstract: Prostate cancer is an important health problem for all men in the world, in particularly in west countries such as ABD and Europe. Although, it is the most common cancer type in men and second reason for death due to cancer, what the most suitable treatment of prostate cancer is still being discussed. It is well known that eating healthy was a very important factor for production from cancer and also it has been discussing for a long time. Dairy products, that are important parts of a healthy diet, are source of especially dietary calcium, phosphate, vitamin D, fatty acids and IGFs. There are many researches about these components in milk and milk products had effects on various cancer types. In this review, it was examined that the relationship between milk and milk product consumption and prostate cancer and researches that were related to this subject.

Key words: Dairy products, prostate cancer, vitamin d, calcium, fatty acids

INTRODUCTION

Dietary factors clearly have major impact on cancer development as well as other chronic diseases. Milk (or dairy products like butter, cheese and yoghurt) is one of the most important components of human diet particularly in the Western world and increasingly also in Asia. A large number of epidemiological studies have been aimed at assessing the influence of milk intake on cancer development but the data are generally not obvious, in line with the complex mixture of ingredients (Tsuda *et al*., 2000).

The ratio of Prostate Cancer (Pca) is high in North America and North Africa; is medium in Mediterranean countries; and low in Asia Countries such as China and Japan (Clinton *et al*., 1988). Although, it is the most common cancer type in men ant it's the second reason for death due to cancer, what the most suitable treatment of prostate cancer is still been discussing (Soylu, 2008). Prostate cancer remains the most common non-cutaneous malignancy in American men with an estimated lifetime risk of disease of 16.6% for African-Americans and a lifetime risk of death of 3.5 and 4.3%, respectively. The discrepancy between the clinical incidence and mortality rate reveals that not all prostate cancers behave similarly. Most remain latent and never manifest clinically. Indeed, foci of prostate cancer may be found in 30% of men over age 50 years, a percentage that continues to increase with age (Sonn *et al*., 2005).

It is not known which factors include this cancer and which agent leads to latent prostate tumors-whose incidence is very high in men worldwide-progressing to a clinically detectable prostate cancer, the incidence of which, by contrast, shows a high variation in different geographical areas. There are different risk factors, familial antecedents and dietary variables. Among dietary variables, fat consumption was of great interest because animal studies suggested that fat intake, in combination with other dietary variables, could increase tumors growth (Álvarez-León *et al*., 2006).

Results of ecological studies suggest that prostate cancer is associated with a western lifestyle and in particular, diet that includes a high intake of dairy products. The association between dietary factors and prostate cancer has now been investigated in epidemiological studies. The results of these studies are mostly conflicting or negative but some dietary components are consistently associated with prostate cancer-eg, high intakes of alpha-linoleic acid (a polyunsaturated fatty acid in vegetables and dairy products) and calcium (Grönberg, 2003).

Dairy products, in addition to supplying a significant source of dietary calcium, also supplies a significant amount of phosphate (phosphorus as phosphate), essentially equimolar to calcium in dairy products (Newmark and Heaney, 2009). In this review, it had been investigated effects of dairy products and their components on prostate cancer.

Dairy products and cancer: The carcinogenesis effect of milk is related to calcium and vitamin D that milk contains. It is observed that the consumption of milk and dairy products was related to the increasing of prostate cancer risk in some epidemiological studies prospective and case control studies (Unal and Besler, 2008).

Current evidence for the potential use of probiotic fermented milks in human cancer is mostly indirect in animal and *in vitro* studies, due mainly to the difficulty of carrying out such studies in humans. Case-control studies suggested an inverse association between yoghurt consumption and the risk of colon cancer. In

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same way, a large case-control study of long-term intake of fermented milk with *L. rhamnosus Shirota* has been conducted, suggesting that the habitual intake of the strain reduces the risk of bladder cancer in the Japanese population. Many of these beneficial effects appear to be mediated through the modulation of the intestinal microbiota and immune system (Sánchez *et al*., 2009).

A number of studies found that high intake of skim milk but not whole milk, was associated with an increased risk of prostate cancer. There are number of components in milk fat such as sphingolipids, conjugated linoleic acid butyric acid, branched-chain fatty acids and the fat-soluble vitamins which in animal models, have exhibited anticancer reaction. However, it is also probable that men who drink skim milk are more health-conscious and have regular medical examinations that result in detection of prostate cancer. Milk and its products are large contributors of calcium to the diet and this calcium could be a factor the role of dairy products in prostate cancer (Parodi, 2009). Moreover, milk estrogens and IGF systems are related to the prostate cancer (Qin *et al*., 2004; Parodi, 2009).

Calcium intake and prostate cancer: High dietary phosphate content thus may explain the possible dairy product risk factor for prostate cancer rather than the calcium content. This concept adds rationale to those nutrition experts who are attempting to persuade the food industry to reduce phosphate food additives and beverage use of phosphoric acid (Newmark and Heaney, 2009). Evidence from *in vitro* and animal studies suggests that risk may be increased by higher levels of calcium, since these suppress 1, 25-dihydroxy vitamin D3, the most active form of vitamin D3, that inhibits the proliferation of prostate cancer cells and promotes their differentiation. However, relevant studies have yielded inconsistent results, although few studies have considered intake from calcium supplementation that can provide higher doses than dietary intake (Koh *et al*., 2006).

One of the strongest evidence for an association between calcium intake and risk of prostate cancer comes from the Health Professionals Follow-up Study which had a comprehensive dietary assessment of calcium from food as well as multivitamins, calcium supplements and other sources. In this study, men who consumed more than 2,000 mg of calcium daily had a multivariate relative risk of 4.6 (95 percent confidence interval: 1.9, 11.1) for metastatic and fatal prostate cancer compared with men consuming less than 500 mg of calcium daily. This association was dependent of age, body mass index, total energy intake, fat, fructose, phosphorus, vitamin D, vitamin E and lycopene intake. Independent associations were observed for calcium from supplements only and calcium from foods (Giovannucci *et al*., 1998; Chan and Giovannucci, 2001).

Rodriguez *et al*. (2003) examine the association between calcium, dairy intake and prostate cancer incidence in the Cancer Prevention Study II Nutrition Cohort of elderly United States adults. Results supported that very high calcium intake, above the recommended intake for men, may modestly increase risk of prostate cancer.

Vitamin D and prostate cancer: Although, vitamin D deficiency is known mainly for its association with fractures and bone disease, its newly recognized association with risk of several types of cancer is receiving considerable attention. The high prevalence of vitamin D deficiency, combined with the discovery of increased risks of certain types of cancer such as prostate. Residents of sunny areas and those with a history of exposure to high levels of sunlight, had lower risk of prostate cancer (Garland *et al*., 2006).

Schwartz and Hulka (1990) hypothesized that vitamin D deficiency may be related to risk of prostate cancer. They made the observation that black race, northern latitudes and older age all appeared to be positively correlated with greater risk of prostate cancer as well as vitamin D deficiency (Chan and Giovannucci, 2001).

In a study of 19000 men, those with 25 (OH) D levels below 16 ng/mL had a 70% higher incidence rate of prostate cancer than those with levels above 16 ng/mL, incidence of prostate cancer was 3.5 times higher than for those with levels of 16 ng/mL or above and incidence of invasive cancer was 6.3 times higher (Ahonen *et al*., 2000).

Vitamin E and prostate cancer: Vitamin E is used to refer to a group of fat-soluble compounds that include both tocopherols and tocotrienols (Brigelius-Flohe and Traber, 1999). This vitamin is present in the diet in two forms, gamma tocopherol and alpha tocopherol, the most active form (Sonn *et al*., 2005).

Alpha-tocopherol is an important lipid-soluble antioxidant. It performs its functions as antioxidant in what is known by the glutathione peroxidase pathway and it protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction (Wefers and Sics, 1988; Herrera-Barbas, 2001; Traber and Atkinson, 2007). Effects of alpha-tocopherol on prostate cancer incidence and mortality was researched by “alpha-Tocopherol and beta-Carotene Cancer Prevention Study (TCCPS)” (Hartman *et al*., 1999).

There are also studies that show vitamin E didn’t affect the risk of prostate cancer. In United States Health Professional Study (USHPS) that researches the effect of additional vitamin E in 47780 healthy men’s diet for 10 years (1986-1996), no relationship between the additional vitamin E in diet and prostate cancer development could be found (Hartman *et al*., 1998).

IGF system and prostate cancer: The potent mitogenic activity of IGF-I in cell culture made it an obvious candidate risk factor in cancer development but it was not until 1998 that several prospective studies suggested that high circulating levels of IGF-I were associated with an increased risk of developing prostate cancer. A significant amount of data were accumulated that suggested IGF system had played an important role in the prostate. Prostatic stromal cells and epithelial cells in primary culture secrete IGFBPs and stromal cells produce IGF-II and both stromal and epithelial cells express the IGF-I receptor and are responsive to IGF-I with respect to proliferation (LeRoith and Roberts, 2003). Insulin-like growth factor 1 (IGF-1) has mitogenic and antiapoptotic effects on prostate epithelial cells *in vitro*. These results prompted epidemiologic studies to determine the role of IGF-1 in human prostate carcinogenesis (Wolk *et al*., 1998).

Finne *et al*. (2000), in a screening trial, did not find an association between serum IGF-I levels and prostate cancer risk, while Baffa *et al*. (2000) actually found that circulating IGF-I levels were lower in a group of patients undergoing radical prostatectomy as compared to age-matched controls. In prospective studies, however, Harman *et al*. (2000) and Stattin *et al*. (2000) found that IGF-I levels were associated with prostate cancer risk and that this association was especially evident in younger men.

Chan *et al*. (1998) for investigate associations between plasma IGF levels and prostate cancer risk, a nested case-control study within the Physicians' Health Study was conducted on prospectively collected plasma from 152 cases and 152 controls. A strong positive association was observed between IGF-I levels and prostate cancer risk. Men in the highest quartile of IGF-I levels had a relative risk of 4.3 (95 percent confidence interval 1.8 to 10.6) compared with men in the lowest quartile. This association was independent of baseline prostate-specific antigen levels. Identification of plasma IGF-I as a predictor of prostate cancer risk may have implications for risk reduction and treatment.

Dietary fat and prostate cancer: A possible relation of dietary fat intake to cancer incidence has also been hypothesized because the large international variations in rates of cancer of the prostate and endometrium are strongly correlated with apparent per capita consumption. However, these associations are due to correlations with intake of animal fat, not vegetable fat, raising the possibility that fat per se is not the responsible factor. Dietary fat promotes tumours in many animal models but this has been either weak or nonexistent in some studies designed specifically to address the independence of fat and total energy intake (Willett, 2000).

Associations between fat intake and risk of prostate cancer have been seen in many case-control studies but sometimes only in subgroups. In a large case-control study among various ethnic groups within the U.S., consistent associations with prostate cancer risk were seen for saturated fat but not for other types of fat (Willett, 2000). Lipid consumption at high level stimulates proliferation of Pca cells both *in vivo* and *in vitro* (Clinton *et al*., 1988). Although, in general it has been thought that fat consumption increased the risk of prostate cancer, there are evidences that long chain omega-3 and omega-6 fatty acids in fish oil had a protective effect on prostate cancer (Rose and Connolly, 1999).

In Canada, Fleshner *et al*. (2004) reviewed articles published looking at the relationship between prostate cancer and fat intake (total fat intake or fat in specific foods like dairy products). They analyzed seven short studies, including more than 180 000 subjects, only one showed a statistically significant association, once adjusted; the other six found no association.

In a few studies based on survey, it was found that taking of large amount of n-3 polyunsaturated fatty acid alpha-linoleic acid increases (Ramon *et al*., 2000; Leitzmann *et al*., 2004). Although, many epidemiological and biologic studies support lipid consumption at high level is a risk for pca, additional epidemiological studies are also needed to provide it (Aronson *et al*., 2010).

Bovine milk and dairy products are the main dietary sources of the cis 9, trans 11 isomer of conjugated linoleic acid (9c, 11t-CLA). In most cases this isomer is the most abundant CLA isomer in bovine milk. Minor amounts of other geometrical and positional isomers of CLA also occur in milk, with different biological effects (Haug *et al*., 2007). According to the knowledge of conjugated linoleic acid effects in metabolism and anti-proliferative and pro-apoptotic activities on various types of cancer cells it could be assumed that the cis-9, trans-11 isomer of conjugated linoleic acid belonged among candidates for nutritional cancer therapy. Based on studies of the health-promoting activities of lipids, both *in vitro* and *in vivo*, the possibility of using such lipids as active ingredients in prophylactic and therapeutic dosage is considered (Ebringer *et al*., 2008). Although many epidemiological and biologic studying support lipid consumption at high level is a risk for Pca, additional epidemiological studies is needed to provide it (Aronson *et al*., 2010).

Milk estrogens and prostate cancer: Estrogen is a hormone that comprises a group of compounds, including estrone, estradiol and estriol. It is the main sex hormone in women and is essential to the menstrual cycle. Although, estrogen exists in men as well as women, it is found in higher amounts in women, especially those capable of reproducing (Anonymous, 2011). The concentration of naturally occurring

estrogens in food largely depends on the type of animal product and the food producing species and its gender, age and physiological condition (Malekinejad *et al*., 2006). Bovine milk contains estrogens which some authors believe could be an aetiological factor for prostate cancer. The predominant estrogens in milk are estradiol and estrone. The processing of milk does not appear to destroy estrogens but because to hormones are lipophilic they tend to concentrate in the fat phase of dairy products (Parodi, 2009).

The prostate gland is an androgen-dependent organ, in that growth and maintenance of its functional and structural integrity require the constant support of physiological supply of circulating testosterone which is synthesized by the Leyding cells of the testis and is the major circulating androgen in males. Aging which is considered as an established risk factor for prostate cancer, is often associated with gradual reductions of gonadotropin-stimulated testicular steroid production and lesser declines in hypothalamic-pituitary gonadotropic activity. In general, the serum level of testosterone gradually decreases while estradiol and estrone increase as a function of increasing age. Thus, an estrogen-dominant milieu, developing after middle age, precedes the incidence of prostate cancer (Qin *et al*., 2004).

Conclusion: Epidemiological studies suggested that milk consumption is probably as one of the risk factors for prostate cancer. So that studies usually focus on the fat and calcium in milk but reached no definitive conclusion. Despite the declaration that calcium in milk can avoid osteoporosis, some studies doubted that calcium in milk might increase prostate cancer of drinkers. Fat was suggested as a risk factor for prostate cancer more than any other milk component because, in part at least, whole milk was the second-leading source of fat in the typical diet of developed countries. In Actual functional food development studies, some fat substitutes are used instead of milk fat; thus some diseases that are caused by consumption of milk fat are tried to be prevented. Although there is no definitive reason to rule out the possibility that fat in milk is a risk factor, the evidence that milk was apparently stronger than that of other animal fat sources suggests some other risk factor (s) in milk and dairy products are related to prostate cancer. And also, according to the measurements of estrogen levels in milk by different studies, it was indicated that estrogen in milk was a possible risk to cause prostate cancer. Estrogen levels in prostate fluid are also significantly correlated with the prostate cancer. Moreover, it is thought that vitamin D in milk decreased the risk of prostate cancer. In this content, even if many researches was done about milk and milk products had positive and negative effects on prostate cancer, more studies should be done.

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