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Review

Milk and Cancer: Is There any Relation?

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ABSTRACT

It has been shown that the consumption of milk, which is an important part of our diet, increases the serum levels of insulin-like growth factor (IGF) in the blood. IGF is a mitogenic hormone known to play a role in cell growth, differentiation, and metabolism. Therefore, it is thought that it could potentially promote tumor development and growth. Cancer is the uncontrolled proliferation of cells with impaired growth characteristics and is a fatal disease. Studies have suggested that as a result of these connections, milk may trigger cancer formation due to its positive effects on growth hormones. In this review, studies examining the relationship between milk and IGF, IGF and cancer, milk, IGF and cancer are compiled.

Keywords: Cancer, insulin-like growth factor, milk.

Milk and dairy products are a nutrient that has positive effects on maintaining postnatal growth in mammals, induces species-specific growth, and is consumed by children and adults after weaning age.[1-3] Milk proteins consist of approximately 80% casein and 20% whey. Casein in cow's milk; Contains alpha-s1, alpha-s2, beta and kappa-casein. Whey consists of a large number of globular proteins, including beta-lactoglobulin, lactoferrin, alpha-lactalbumin, immunoglobulins, glycomacropeptide, serum albumin, enzymes and growth factors.[4]

Whey and casein are classified as high-quality proteins based on human amino acid requirements, digestibility, and bioavailability. As a result of evaluations made by various methods, the digestibility score of milk proteins is higher than other protein sources.[5] Whey protein contains a higher percentage of branched-chain amino acids (leucine, valine, and isoleucine) compared to casein. Among other essential amino acids, casein contains a higher proportion of methionine, histidine, valine and phenylalanine than whey protein. Also casein; contains high levels of many amino acids, including arginine, proline, glutamic acid, tyrosine, and serine.[6]

INSULIN-LIKE GROWTH FACTOR (IGF)

Insulin-like growth factor is a natural growth hormone that plays a role in growth and development. The IGF family consists of insulin and insulin-like factors called IGF-1 and IGF-2. These factors regulate cellular functions by interacting with specific cell surface receptors and activating various intracellular signaling pathways.[7] IGF-1 is a peptide hormone similar to insulin as a result of stimulation by growth hormone, most of it is produced by the liver and may have certain local effects. IGF-1 plays a role in proliferation, differentiation and glucose regulation by activation of signaling pathways. IGF-2 has a high degree of structural homology with IGF-1 and insulin. It has key roles in fetal development and plays an important role in development, epigenetic regulation, and growth-related situations.[8] There are two known IGF receptors - type 1 IGF receptor (IGF-1R) and IGF-II receptor (IGF-2R). Six IGF binding proteins have been identified (IGFBP-1-6). IGFBPs (insulin-like growth factor-binding protein) function as transport proteins, extend the half-life of IGFs, regulate their clearance, directly modulate their effects and provide a tissue-specific localization.[9]

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It is also accepted that many IGFBPs have actions independent of IGF.[10]

CANCER

Cancer is the clonal spread of cells with impaired growth characteristics. Somatic cancer is the most common and most complicated genetic disease.[11] The basis of cancer formation is the accumulation of mutations that affect biological events such as cell survival and growth control. Mutations of tumor suppressor genes and proto-oncogenes cause malignant phenotype formation through different mechanisms. In the development process of cancer, tumor cells acquire phenotypic properties, and these changes cause the unlimited and rapid order of tumor cells to proliferate and spread to surrounding tissues. In addition, these cells can survive independently of the specific microenvironment and metastasize (leaving the organ where the cancer originated and spreading to other organs).[12] Oncogenic mutations targeting signal transduction pathways and signal proteins are frequently encountered.[13] Changes in signal transmission may be the reason for cell proliferation and loss of control of living functions. Oncogenic signal transduction plays an active role in tumor development and metastasis process.[14]

Protein kinases provide protein activation during signal transduction. They are divided into two main groups as membrane-located ones and cytoplasmic tyrosine kinases. These proteins are also classified as tyrosine and serine/threonine kinases according to their catalytic properties (the type of amino acid that is phosphorylated).[15,16] Proteins located on the membrane are called receptor tyrosine kinases (RTK). There are 58 transmembrane proteins in the RTK superfamily. These receptors include ephrin receptors, insulin receptor, and growth factor receptors.[16]

RTKs contain a region responsible for activation (tyrosine kinase region) in their cytoplasmic part. RTK's inactive and active conformations are in equilibrium in cells at rest. These receptors become active after binding with growth factors and transmit signals by interacting with target proteins in the cytoplasm.[17] IGF-IR is a cell membrane receptor with tyrosine kinase activity. By activating IGF-IR, the intracellular tyrosine phosphorylation chain is induced, which leads to the activation of transcription factors necessary for cell proliferation and transformation. In addition, by stimulating angiogenesis factors (Epidermal growth factor=EGF, Transforming growth factor alpha=TGF-α), it can regulate the formation of new vessels and initiate tumor growth.[18-20] Studies have shown that IGF-1R is overexpressed in many malignant tumors, including breast cancer, lung cancer, prostate cancer, gastrointestinal cancer, glioma.[21-25] Additionally, clinical studies show that IGF-1R has potent antiapoptotic and transforming activities, and increased IGF-1R activity is associated with treatment resistance, tumor metastasis, poor disease prognosis, and shortened survival.[26-28] Insulin-like growth factor 1 receptor may therefore be a potentially emerging and promising marker in cancer diagnosis and treatment.[29] Insulin-like growth factor 1 receptor is also closely related to breast cancer gene 1 (BRCA1). In fact, wild-type BRCA1 expression caused a significant decrease in IGF- 1R promoter (DNA fragment that initiates transcription of genes) activity and endogenous IGF-1R levels in breast cancer cell lines, while mutant BRCA1 expression did not affect IGF-1R levels.[30] IGF-1R targeted imaging can be a good method for tumor diagnosis and monitoring treatment efficacy.[31]

MILK AND INSULIN-LIKE GROWTH FACTOR

Studies have shown that a diet rich in milk increases serum levels of insulin-like growth factor (IGF-1).[32,33] It also contains cow's milk, active IGF-1 and IGF-2. Milk has been observed to maintain high IGF-1 levels even after processing.[34] Studies have shown that increased milk consumption is directly proportional to circulating IGF-1 levels in adults and children.[35-38] Milk and dairy products increase IGF-1 levels more than meat and other animal protein sources. Moreover, it has been shown that the bioavailability of IGF-1 increases by increasing the IGF-1/IGFBP-3 ratio with milk consumption.[39] Milk consumption causes postprandial hyperinsulinemia (increase in the amount of insulin in the blood) and permanently increases IGF-1 serum levels. While insulin/IGF-1 signal regulates fetal and linear growth in the thymus, it can also cause cancer.[10]

The effect of whey and casein fractions of milk on fasting IGF-1 and insulin concentrations was studied. While serum IGF-1 increased by 15% in casein group, no change was observed in fasting insulin. In the whey group, fasting insulin increased by 21% with no change in IGF-1. It has been reported that the insulin response to a whey meal is higher than to a dairy meal. This differential response suggests that the insulinotropic component of milk is predominantly found in whey, and casein has a stronger IGF-1 stimulating effect than whey. A diet consisting of milk and hyperglycemic foods can have strengthening

effects on serum insulin and IGF-1 levels.[34] Milk may increase IGF concentration due to the branched amino acids found in casein and other milk-derived proteins.[40] An important factor for hepatic (liver-related) IGF-1 synthesis is the proteins found in milk.[41,42]

INSULIN-LIKE GROWTH FACTOR AND CANCER

Studies have shown that the IGF system may play a role in tumor formation.[7] An increase in neoplastic cell proliferation was observed with the increase in IGF-1 concentration.[43] Increased IGF-2 production may also cause suspicious cancer development and progression in many cases.[7] *In vivo* studies show that carcinogenesis and cancer progression may be affected by germline variation of genes encoding signal molecules in the Growth hormone (GH)-IGF-1 axis, and these mutations may often be associated with genetic manipulations.[44] When a cell is at risk, IGF bioactivity in the cellular microenvironment affects cell survival and transforms into malignant cell lineage or apoptosis in early carcinogenesis. Balancing apoptotic cell death and survival of damaged cells may be susceptible to survival in an environment with high IGF levels, and this can lead to the emergence of malignant cells. The course of millions of such DNA damaged cells is determined every hour, and the effect of higher IGF-1 levels on the probability of survival may lead to the level in circulation being associated with cancer risk. The effect of the IGF-1 level on cancer risk is somewhat related to early carcinogenesis. Higher IGF-1 levels make it easier for early cancers to reach the stage where they can be detected clinically. Such lesions are common in adults and the diagnosis of cancer reflects the likelihood of these lesions progressing to a detectable and clinically significant size. The clinical detection process of cancers is affected by the IGF-1 level.[45] Insulin-like growth factor binding protein-3 (IGFBP-3) has an antiproliferative effect that inhibits the mitogenic effect of IGF-I by stimulating apoptosis.[46] In many recent epidemiological studies, it has been reported that high IGF-I and low IGFBP-3 levels in serum or an increase in IGF-I/IGFBP-3 ratio are associated with an increased risk for many cancers, such as changing the order of the breast, colon, lung, prostate.[47] It has been found that serum IGF-I levels increase and IGFBP-3 levels decrease in many tumor types.[48,49] Physiologically, IGF-I is responsible for the effect of growth hormone. It has a strong effect on cell proliferation and differentiation and is a potent inhibitor of apoptosis. IGFBP-3 is a protein with an antiproliferative effect that inhibits the mitogenic effect of IGFI by stimulating apoptosis.[46,50]

It was concluded that IGF-I serum levels were significantly increased and IGFBP-3 levels were significantly decreased in patients with advanced prostate cancer compared to patients with benign prostatic hyperplasia.[51-53] IGFs are known to be potent mitogens for lung cancer cells. However, there is insufficient evidence regarding its effects on lung cancer development. Studies have shown that high IGF-I and low IGFBP-3 levels may be associated with a high risk of lung cancer.[54]

In a study involving 56 patients with gastric cancer, it was reported that the expression of IGF-1/IGF-1R and gastrin/cholecystokinin B receptor (CCK-BR) increased, and this may have a role in the development of gastric cancer by causing the proliferation of the gastric mucosa epithelium. It was found that serum gastrin and IGF-1 levels increased in patients with esophagus and stomach cancer and this increase was significant for gastrin. It was concluded that this increase in gastrin level may play an important role in the development of esophageal and stomach cancers.[55]

As a result of some studies, a positive relationship was found between the circulating IGF-1 concentration and breast cancer in premenopausal women. However, it was concluded that this situation was not valid in postmenopausal women.[56] In another study, no difference was found between serum IGF-1 levels between postmenopausal breast cancer patients and post-menopausal control group, and no statistically significant difference was observed in the comparison of IGF-1 levels of premenopausal and postmenopausal patient groups.[57]

MILK, INSULIN-LIKE GROWTH FACTOR AND CANCER

IGF-1 is a mitogenic hormone known to play a role in cell growth, differentiation, and metabolism, so it is thought to potentially promote tumor development and growth in the breast and prostate.[58,59] However, not all results are consistent with each other. Studies have shown that there is a relationship between milk consumption, serum IGF-I and prostate cancer.[60] Studies have shown that higher milk consumption in colon cancer patients increases serum IGF-I concentrations by approximately 11%.[61]

Milk increases IGF-1 activation and the signaling mechanisms of milk are applied to ensure the long-term increase in serum IGF-1 levels and the regulation of rapid post-meal insulin secretion. Several mechanisms have been suggested by which milk can support prostate cancer. When studies examining the relationship between IGF and prostate cancer are examined, the insulin-like signaling pathway may be a possible factor for prostate cancer initiation and progression.[62,63] However, due to the possibility of pleiotropy, it has not been determined that any individual IGF protein has a specific association.[64]

It should be recognized that in most common solid tumors, IGF itself is not directly caused, but secondary to another molecular event that affects the expression of ligands or receptors. Increased regulation of IGF-1R, often seen in common solid tumors, is usually secondary to the loss of negative regulatory effect of tumor suppressor genes, including changed the order of BRCA1, TP53, WT1 and vHL.[65] Overexpression or activation of IGF axis components promotes signaling through effectors, including AKTs and ERKs, that cause resistance to cancer therapies, including radiotherapy, chemotherapy, endocrine derangement therapy, and targeted agents. It is recognized that tumor growth, treatment resistance, and can be promoted by IGFs secreted by cellular components of the tumor stroma.[66,67]

In studies, a function of IGF-1R with IGF has been defined. This function can translocate to the receptor nucleus after clathrin-dependent endocytosis and can function as a transcription factor by binding to the regulatory regions of DNA. The findings reported that IGF-1R is detectable in a variety of invasive malignancies, including prostate, kidney and breast cancers in preinvasive lesions and is associated with an advanced tumor stage in prostate cancer and an unfavorable prognosis in kidney cancer. Promoters may contribute to cell survival and motility, chemodirence, and the expression of these genes that change the order of angiogenesis.[68,69]

In addition to increased tumor formation and treatment resistance, IGFs may also cause the risk of developing cancer. An example of this can be shown with almost complete protection from cancer in patients with Laron syndrome (type of dwarfism) who have very low serum IGF-1 levels due to the GH receptor mutation.[70-72] In addition to being regulated by GH, circulating levels of IGF-1 are known to be affected by dietary factors, including dairy products and total protein intake. It is known that subjects in the general population with serum IGF-1 levels at the upper end of the normal range have an increased risk of developing various types of cancer, including altered breast, prostate, and colorectal cancer.[73]

RESULT

Milk contains high amounts of IGF-1 and the reason why it causes cancer can be related to IGF, which is in its structure. Because IGF plays a role in cell growth, differentiation, and metabolism, it is thought that it could potentially promote the development and growth of breast, prostate, and other cancers. In addition, not all studies are consistent with each other. For example, while studies are showing that it may cause breast cancer, it has also been concluded that serum IGF levels do not cause a significant change in breast cancer. On the other hand, as mentioned above, it has been reported that patients with Laron syndrome who have low growth hormone have complete protection from cancer, from which it can be concluded that they have less cancer because they have a small number of growth factors. In other words, if we combine the information that milk contains IGF and some of the factors that cause cancer are IGFs, high milk consumption or an increase in milk consumption may cause cancer. More studies are needed to address the issue better.

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