Dairy products and breast cancer: the IGF-I, estrogen, and bGH hypothesis

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Abstract — Research on the role of dietary factors in breast cancer causation has focused predominantly on fat intake. While some studies have examined associations between breast cancer rates and consumption of whole milk, there has been less attention given to dairy products in general. Dairy products contain both hormones and growth factors, in addition to fat and various chemical contaminants, that have been implicated in the proliferation of human breast cancer cells. This literature review evaluates the epidemiological and mechanistic evidence linking dairy consumption with breast cancer risk.

Epidemiological evidence

Epidemiological studies have indicated a positive correlation between dairy product consumption and breast cancer risk (1-12). Two studies have specifically examined breast cancer mortality and frequency of consumption of various milk products, concluding that cancer risk was associated with milk intake (1,2). Stocks found low death rates for breast cancer where dairy product consumption was low and intake of other fats was high.

Other studies found a dose-dependent increase in breast cancer risk among women who consumed milk (especially whole milk) and/or cheese (3-7). Further studies reported a relative risk (RR) coefficient that was more statistically significant than that for meat (8-10). When La Vecchia adjusted the RR coefficients for age at first birth and economic variables, the risk factors for milk and cheese were the only dietary variables to remain significantly positive (8). Maruchi et al examined the incidence of breast cancer in Japan, and found a significant increase in both the consumption of dairy products and occurrence of breast cancer in urban areas ($P < 0.001$), where the average intake of the other fatty foods, including meat, was at or below average (9). Talamini et al also found the relative risk factors for breast cancer to increase with the amount of dairy products consumed (1.0–3.4, $P < 0.001$); however, the trend was not as evident in values for meat consumption (10).

Several studies examined the relative risks of consuming whole versus low-fat milk (11–13). Toniolo (1989) and Ewertz (1990) concluded that breast cancer risk was significantly related to increasing consumption or whole milk, as well as frequent intake of low-fat or skim milk (11–12). In Ewertz’s study, the RRs decreased when adjusted for total fat intake, with the exception of the RR for low-fat milk. In a study of Seventh-Day Adventists, Phillips found a positive correlation between dairy products other than...
milk, and breast cancer (14). Not all studies have shown these associations; four articles noted an inconclusive or negative risk of breast cancer from dairy product consumption (13,15–17). Some studies, however, suggest the possibility of another factor relating dairy products to breast cancer, aside from its dietary fat content.

**Insulin-like growth factor I and breast cancer**

Dairy products may affect breast cancer risk through the absorption of peptides called insulin-like growth factors I and II (IGF-I and -II, also known as somatomedin C and A respectively). Both IGF-I and -II are potent mitogens present in normal, untreated human and bovine milk. Dairy studies found the concentrations of IGF-I in cow’s milk to be 6–162 ng/mL, depending on whether the milk is obtained during the prepartum or postpartum period. The US Food and Drugs Administration (FDA) reported that IGF-I levels are approximately 30 ng/mL (53). Those of IGF-II are approximately 350 ng/mL (18–21). The relative percentages of free and protein-bound IGF-I vary considerably. IGF-I has been the focus of most studies because, unlike IGF-II, its concentration is affected by bovine growth hormone (bGH) administration to dairy cows.

Many studies indicate that IGF-I is a potent stimulus for breast cancer cell proliferation in vitro, possessing either an autocrine or paracrine role in breast cancer (22–26).

**Characteristics of insulin-like growth factor I**

Although IGF-I is a normal body component, it may be associated with malignant disease when present in excess (27). Free IGF-I levels decline with age, consistent with their role in growth (28). Tissue levels range from 950 ng/L at 20–30 years of age to 410 ng/L at > 60 years (28). IGF-I levels are higher in teenage girls than boys, with the difference extending into adulthood. They are elevated in pregnant women (29). Although IGF-I is essential for growth, its levels do not correlate exactly with growth rates, which suggests, among other possibilities, that IGF-I may be of external origin. Both Perdue and Underwood et al suggest that IGF-I levels may be affected by nutritional status, but they do not refer to specific foods (29,30).

Human and bovine IGF-I are identical (31,32). IGF-I in milk is present in its unbound form; in human blood, IGF-I forms a complex with binding proteins. Free IGF-I can act directly on target tissues, but it must dissociate from its binding proteins to exert biological activity (33). This occurs in the presence of heparin, which frees 70–80% of IGF-I (34). IGF-I has growth-promoting effects in response to concentrations as low as 1 ng/mL (33). Milk contains approximately 30 ng/mL.

**Mechanism of tumor proliferation**

IGF-I does not act as a circulating mediator of growth hormone (GH), but rather as a growth factor exerting local tissue effects (35,36). It has been hypothesized that IGF-I contributes to breast cancer cell proliferation through actions on IGF-I receptors (IGF-IRs) and six IGF-I binding proteins (IGF-BPs) (37–39). In vitro studies reveal that breast cancer cells respond to nanomolar IGF-I concentrations, multiplying as much as 4–5 fold (25). Nearly all breast cancer cell lines and breast cancer cells from fresh tumor biopsies have receptors for IGF-I, and binding to both benign and metastatic human breast tumors is increased compared to normal mammary tissue binding (27, 40–42). Highly malignant human breast cancers are know to produce and secrete IGF-I (43). Median IGF-I concentrations in primary breast cancers were found to be significantly higher than in normal breast tissue (41).

IGF-I also causes changes in the cell cycle (44) and oncogenes such as c-fos (45,46). Nanomolar concentrations of IGF-I alter the relative number of breast cancer cells in each phase of the cell cycle (44). Such alterations in the cell cycle may cause the unregulated growth of cancer. Five-nM IGF-I concentrations also resulted in a 10-fold increase in c-fos messenger ribonucleic acid (mRNA) levels, leading to gene activation (46). Evidence suggests that oncogenes may encode IGF-IRs, whose over-expression is thought to be a key factor in the transformation from normal mammary tissue growth to breast cancer (45,47). In fact, one criterion for effectiveness of cancer treatments is their ability to successfully lower IGF-I levels or block IGF-IR binding (22,48–50).

Other hormones and growth factors may interact with IGF-I in encouraging tumor growth. IGF-I’s mitogenic activity may be due to its ability to make transformed cells more responsive to signals from other growth factors (51). A synergism of IGF-I and other growth factors causes a 2–4 fold increase in the number of chromaffin cells (52).

**Insulin-like growth factor I absorption**

For IGF-I in milk to increase breast cancer risk, it must be absorbed intact through the gastrointestinal mucosa or exert effects from within the gut. Research on growth-factor digestion in human adults is limited.
During digestion, proteins are typically degraded into individual amino acids. Some proteins or peptides, however, are absorbed intact. Most studies have focused on intact digestion, showing that some absorption results in the appearance of antibodies to certain proteins in the bloodstream (54). The absorption of intact proteins has also been demonstrated in adults (57,58).

Absorption of IGF-I in humans has not been studied. However, experiments have characterized the absorption of epidermal growth factor (EGF). Both IGF-I and EGF have similar molecular weights (approx. 6000–7000 Da), three disulfide bridges, and form a large complex with binding proteins (27,33, 59). An in vitro study revealed that human jejunal juice does not destroy EGF when a milk protein, casein, is also present, suggesting that milk proteins can inhibit luminal digestion of growth factors by blocking the active sites of pancreatic proteases (60). Infant studies indicate that EGF is absorbed intact from the human GI tract (61,62). It is not unlikely that IGF-I in milk could be similarly protected and absorbed.

Ross et al found that people who ingested large quantities of milk had antibody titers to bovine milk xanthine oxidase (BMXO) (63), suggesting that BMXO can be absorbed intact from the gut in digestion-resistant liposomes created by milk homogenization. Frequent milk drinkers do, in fact, absorb BMXO into the intestinal mucosa, despite its high molecular weight (290 000 Da) (63). It may be that IGF-I is absorbed in a biologically active form through a similar mechanism.

Regrettably, studies on IGF-I absorption have been conducted only in the suckling rat. It is difficult to extrapolate information from rat studies, due to species variability in gastrointestinal (GI) tracts (64–70). The FDA Human Food Safety Evaluation reported that bovine milk contains approximately 30 ng/mL of IGF-I, so that two 8-oz glasses of milk a day would contain 200 ng IGF-I/kg/day for a 70-kg human (53). However, both Olanrewaju et al (65) and the FDA concluded that IGF-I was biologically inactive when ingested orally because it did not cause a major effect on rat body weight. Neither study assessed long-term effects of IGF-I because they assumed it could not be absorbed, a conclusion which is not supported by research.

IGF-I is not destroyed during the pasteurization of milk. After being heated for 175°F for 45 s (longer than the United States Department of Agriculture (USDA) pasteurization protocol), IGF-I concentration was not reduced (71). Pasteurized supermarket milk was found to contain 8.2 ng/mL of IGF-I. IGF-I, however, was found to be destroyed during the preparation of baby formulas (71).

**Estrogens and breast cancer**

Dairy products may increase breast cancer risk through a second mechanism, involving estrogens working in synergism with IGF-I. High plasma levels of estrogens have been linked with breast cancer incidence (72–77). IGF-I has been called an ‘estromedin’ because it has been shown to mediate the effects of estrogen (78,79). Estrogens increase the level of IGF-I in human breast tissue (80,81). IGF-I, in turn, may be a more potent mitogen than estradiol in breast cancer cells (82). Huff et al examined 17-β-estradiol, reporting that it induced IGF-I secretion by human breast cancer cells in vitro without affecting IGF-I mRNA (83). Furthermore, IGF-I stimulates estrone sulphatase activity in a dose-dependent manner (84). Additionally, the number of IGF-IR has been positively correlated with the number of estradiol receptors, which suggests a synergistic mechanism (85–87).

Estrogens are found in milk, in both free and protein-bound form (88–90). The 17-β-Estradiol concentration in whole milk ranges from 4–14 pg/mL, with 65% of it reported as biologically active and associated with the fat component. In skim milk, 84–85% of 17-β-estradiol is protein-bound (91). Bound estrogens are found in human breast milk (90%) as well, which suggests that women are able to transform them into usable form (92). Woldorf et al stated that milk estrogen concentrations are too low to exert an important biological effect, but this conclusion results from research predating the in vitro studies on IGF-I relating it to estrogens (90). Although estrogens in milk may or may not exert a direct effect, they may stimulate expression of IGF-I, resulting in indirect, long-term tumor growth.

Free estrogens have been found in commercial, pasteurized bovine milk, and are diminished, but still present, in skim milk as well (93). The correlation between the estrogen levels and milk fat may offer a partial explanation for why breast cancer has been correlated with high-fat diets, including dairy products, in epidemiological studies (94).

**Industry-related milk additives**

**Milk carcinogens**

Milk may function as a transporting medium for carcinogens. Some have hypothesized that milk contaminants were implicated in doubling the Israeli breast cancer mortality rate before 1976 (compared to other countries with the same average consumption of dietary fat). Three carcinogens found in Israeli milk (a-BHC, g-BHC, and DDT) possess characteristics...
similar to estrogens (95). Westin asserts that public disapproval of these contaminants resulted in governmental action in 1978, which drastically reduced their presence in milk. Subsequently, there was a dramatic decline in Israeli breast cancer deaths from 1976 to 1986 (96).

**Bovine growth hormone**

The use of bGH by the dairy industry presents new implications relating dairy products to breast cancer risk. Recombinant bovine growth hormone (bGH) increases IGF-I plasma concentrations in cows by 2-4 fold and IGF-I milk levels accordingly (97–101). In 1990, the FDA’s Center for Veterinary Medicine approved the sale of bGH-treated milk (53). The FDA finding that recombinant bGH poses no health concerns was based on the following assumptions: (1) bGh concentrations in milk are low, approximately 1-4 ng/mL, and do not significantly change with recombinant bGH-treated cow’s milk; (2) bGH is not orally active in humans; and (3) bGH activity is destroyed during the milk pasteurization process (53). Each of these remains questionable at best.

Based upon composition studies, the FDA concluded that recombinant bGH made from *Escherichia coli* was ‘essentially chemically the same’, as natural bGH. Recombinant forms of bGH do, however, differ by 1–9 amino acids (53,102). In most cases, the N-terminal alanine is replaced by methionine (met-bGH). Such a small change in amino acid sequence can have profound effects (102). Kronfeld claims that the FDA did not properly address issues of immunogenicity in met-bGH. Dairy industry experiments indicate that the additional, terminal methionyl residue to GH makes it more immunogenic than human GH (103,104).

Furthermore, a recent, independent study on recombinant bGH determined that it contained an unusual amino acid, e-N-acetyllysine, instead of the usual lysine (105). Although rat and monkey studies indicate no major differences in biological effects between biosynthetic and natural forms of GH, the usual lysine (105). Although rat and monkey studies indicate no major differences in biological effects between biosynthetic and natural forms of GH, the extent that they can be extrapolated to long-term effects in humans is questionable (53,106–108).

The FDA Human Food Safety Evaluation based its claim that bGH was biologically inactive in humans on studies from 1950 to 1965 that led to the 'species specificity concept', that animal growth hormone preparations are ineffective in humans (53,109). BGH’s and human growth hormone’s (hGH’s) molecular weights are very different (bGH-45 000; hGH-21 500) (110). These studies, however, were conducted when there was less knowledge about hormonal mechanisms, including second messengers like IGF-I.

Short-term studies found bGH to have no carcinogenic effect in Rhesus monkeys, but the relevance of these studies is uncertain at best (109,110). Moreover, Knobil and Kaplan’s measures of biological activity were limited to short-term effects, such as nitrogen retention and insulin sensitivity (109–110). They hypothesized that bGH could possess an ‘active core’ that might elicit effects in humans when cleaved by enzymes.

Accordingly, Forsham et al discovered that chymotrypsin digests of bGH caused nitrogen retention in humans, without any diabetogenic effects (111). This study indicates that, indeed, a biologically active core might be found during digestion. Therefore, the species specificity question, pertaining to carcinogenic effects, has not been properly addressed.

Pertaining to the question of whether bGH is destroyed upon pasteurization, the FDA cites a study by Groenewegen stating that 85–90% of bGH is, in fact, destroyed. However, the standard protocol for pasteurization of US Grade A milk is 63°C for 30 min, 72°C for 15 s, or 89°C for 1 s (112). Groenewegen, however, treated milk at 69–71°C for 25–30 min (113). Therefore, less immunoreactive bGH might have been destroyed, if the USDA protocol had been used.

Furthermore, Groenewegen’s study reporting that 85–90% of bGH was destroyed upon pasteurization refers to the heat treatment of control milk with bGH directly added to it, not milk from bGH-treated cows which the public consumes (113). Neither control milk nor milk from bGH-treated cows showed statistically significant reduction in immunoreactive bGH concentrations upon pasteurization. Instead, 80.95% of the bGH in milk from bGH-treated cows remained after heat treatment (113).

Gong et al reported an increase in IGF-I levels in bovine ovarian follicles following bGH treatment, raising the possibility that increases in blood IGF-I could affect other tissue (114). Baumrucker et al reported that IGF-I stimulated a 10-fold increase in [3H] thymidine in bovine mammary tissue, indicating that it increased DNA synthesis there (115). BGH increases IGF-I levels in the blood, mammary tissue, and milk of cows.

Bovine GH treatment increases IGF-I levels in bovine milk in a dose-dependent manner, but studies disagree whether this increase is statistically (116–120). The range of IGF-I concentrations in milk from untreated cows is < 1–30.5 ng/mL, depending on the number of days pre- or postpartum. Levels of IGF-I in human milk were 17.6 ng/mL during the first day postpartum, which declined to 6–8 ng/mL over the next eight days, and then increased during the next six weeks post-partum (19,121).
bGH has been found to increase the fat content and IGF-I binding proteins (IGF-BPs) in bovine milk, which is of concern because international studies show that the risk for breast cancer increases with dietary fat intake, even after other factors have been controlled (122–124). Another study indicated that the fat content in milk is increased because bGH causes the formation of more long-chain fatty acids in milk, relative to medium- and short-chain ones (129). IGF-BP-3 also enhances IGF-I stimulation of breast cancer cell proliferation (125). bGH alters IGF-BP serum levels in cows 3.3 times, and increases the fat concentration from 3.5–29% (126–128).

The FDA’s assumption that bGH and IGF-I are inactive when administered orally is based on unpublished studies conducted by the FDA with the dairy industry, in which hypophysectomized and normal rats were given recombinant bGH and IGF-I orally (53). They found no significant weight gains, although there was a significant mean body weight gain after treatment with recombinant bGH and IGF-I by subcutaneous injection (53). The oral studies, however, were conducted for 14 days or 90 days, which is not sufficient time to detect IGF-I stimulated tumor growth. These short-term animal experiments did not investigate cancer risk, nor are these results necessarily applicable to humans. If orally ingested IGF-I were to play a role in proliferation of breast tumors, it would have to be absorbed through the intestinal wall, taken into the bloodstream, circulated to breast tissues, and cleaved from its binding protein complex, and/or also exert effects from within the gut. These may be long-term effects. If orally administered IGF-I did not produce weight gain in rats, this does not guarantee its safety for lifelong human ingestion.

An experiment involving transgenic mice with 20–30 fold increases in IGF-II levels indicated the development of a wide range of tumors after 18 months and suggested the possibility of a long latency period in the mouse growth factor mechanism (130). Rat and human IGF-I are similar, but not identical, and they may play different physiological roles in each respective organism (30). Studies on the physiological role of IGF-I have determined that ‘the explanation for the absence of acute effects does not appear to be applicable to long-term effects on tissue concerned with growth’ (33).

Conclusion

Epidemiological evidence indicates a correlation between breast cancer incidence and dairy product consumption. A substantial body of medical literature provides possible mechanisms by which milk may promote breast cancer: (1) IGF-I and estrogens are present in all milk in micromolar to nanomolar concentrations; (2) IGF-I is not destroyed during milk pasteurization; (3) IGF-I has been shown to stimulate or initiate growth of human breast cancer cells; (4) IGF-I acts synergistically with estrogens, which increase its effects even at nanomolar concentrations; (5) bGH increases IGF-I levels in milk; (6) IGF-I and bGH can possibly be absorbed intact from the GI tract; (7) IGF-I can travel through the bloodstream and be cleaved to exert local mitogenic tissue effects.

Although more human studies need to be done, the existing evidence indicates possible cancer risks associated with the consumption of dairy products. Bovine Gh has not been considered to be of health concern because subsequent increase in bovine milk IGF-I levels are within the ‘normal range’ based on untreated cows and human breast milk (53). However, it is possible that the ‘normal range’ could be carcinogenic when milk is ingested regularly over a lifetime. Hormones and growth factors in milk, such as bGH and IGF-I, are consumed in nature by the fast-growing infant; it may be that regular milk ingestion after the age of weaning produces enough IGF-I in mammary tissue to cause the cell cycle to supersede its boundaries of control, increasing the risk of cancer.

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