Title
The Cancer Cow: A study of the risks associated with milk from rbGH treated cows

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Introduction

In 1990 the FDA approved large-scale commercial use of recombinant bovine growth hormone (rbGH) in dairy cows to increase their level of milk production. However, before and after this event, there have been numerous public health concerns raised over the safety of milk from rbGH treated cows. In fact, the safety of this milk is so questionable, it is banned in both Canada and the entire European Union. The EU published report raises concerns that primarily regard an increased risk of colon, breast, and prostate cancer associated with compounds found in rbGH milk (22).

Milk from rbGH treated cows is relatively prevalent in the United States. The most common commercial form of rbGH is called Posilac and is sold primarily by a company called Monsanto. Although Posilac has only been on the market for eight years (since 1994), it is already used by many American dairy farmers. According to Monsanto, 13,000 farmers are currently using Posilac. It is legal and available in all 50 states. Monsanto estimates that 1/3 of the 9 million dairy cows in the United States are in herds treated with rbST. Furthermore, Monsanto confirms the steady growth of the product in terms of sales, total number of cows receiving the product and percentage of cows within herds receiving the product (1).

When, in 1990, the FDA approved the sale of milk from rbGH treated cows, it evaluated the following: the absorption of the protein in adults and neonates, the effects of growth hormone, its effects on other growth hormones and the potential for biological and oral activity in humans (8). The FDA concluded that bGH concentrations in milk are low, that bGH is not orally active in humans and that bGH activity is destroyed during the pasteurization process (23). While the correctness of even these conclusions is questionable (23, 3) the FDA completely failed to do tests that properly examine the cancer risks of this milk (23, 7). Furthermore, many of the studies on which the FDA based its decision are out of date. This paper will examine some of the conclusions of the FDA as well as explore the public health concerns about rbGH derived milk.

Does rbGH enter the milk?

One of the reasons the FDA justified its approval of rbGH for dairy cows is because the rbGH does not seem to enter the milk (23). The use of this recombinant hormone in lactating cows does not cause an increase in the concentration of bGH in their milk (4). There is, however, a significant increase in the concentration of insulin-like growth factor-1 (IGF-1) in the milk of rbGH treated cows. According to one study, only ten days after the treatment with rbGH, the average concentration of IGF-1 increased significantly (from 1to 5 ng/ml to 6-20 ng/ml) (5). Other studies show an average IGF-1 concentration increase of 6-fold (8), and Monsanto reported a 10-fold increase (6).

IGF-1is a hormone that is primarily produced by the liver but it is also produced at the local level by other tissues. It can exert its effects via the autocrine, paracrine, or endocrine pathways. It mediates somatic growth and can induce metabolic effects: it regulates transport processes, cell growth, replication and differentiation (7). IGF-1, like

growth hormone, is naturally bound by IGF binding proteins (IGFBP) to control the amount of free IGF in circulation and to increase the hormone's half life. The IGF-1 of cows is identical to that of humans (7).

The IGF-1 that is found in the milk of rbGH treated cows is usually bound to IGFBP; however, a "significant proportion (19%) is found in the free unbound form," which is also the bioactive form (6). Furthermore, the pasteurization process increases the levels of unbound IGF-1 in the milk by 70% (7). It is thought that this might occur because the pasteurization may interfere with the tertiary structure of the binding protein (8).

Can IGF-1 be absorbed when administered P.O.?

According to the FDA, it cannot be absorbed intact when administered orally. This conclusion is based on studies mainly conducted by the same pharmaceutical companies that sell rbGH (Monsanto and Elanco) (8). All of these studies were conducted on rats (both newborn rats and adult rats) and all of the studies were conducted for a relatively short period of time (between 2-4 weeks) (7). The Journal of Nutrition also published a study on the bioactivity of milk from bST-Treated Cows. The study was conducted on adult hypophysectomized rats and lasted for 14 days. The study concluded that the milk was not bioactive because it did not cause enlargement of the rats' livers, thymuses and epiphyseal plates of their tibias (3). This study, like those conducted by Monsanto and Elanco, only examined a very narrow set of effects that IGF-1 may produce and, most importantly, did not investigate the cancer risk of this milk when evaluating its bioactivity. This would require a longer treatment time and a different set of criteria for measuring the milk's bioactivity. It would seem that very little research has been done examining this issue (7).

In general, it is assumed that most proteins will have little to no activity when administered orally. This is because they are expected to be degraded in the gastrointestinal tract and to enter the blood as free amino acids. However, some proteins are absorbed intact and have oral activity such as gonadotropin-releasing hormone (8). It would seem that IGF-1, when in milk, may also be one of these proteins. In a study that investigated a rat's ability to absorb human IGF-1 intact by directly measuring the amount of protein in the GI lumen, the mucosal cells and plasma at a set time after oral administration, IGF-1 was found to cross the GI tract intact (9). The study found that IGF-1 is largely degraded in the intestinal contents when administered alone. However, when administered with casein, the intestinal degradation was inhibited (9). Casein is a protein found in all milk. It makes up 40% the protein in human milk and 80% of the protein in cows' milk (10). The study concludes that: "immunoreactive and bioactive rhIGF-1 could appear in the systemic circulation after p.o. administration" and that "coadministration with the protease inhibitor casein enhanced its bioavailability significantly" (9).

Do increased levels of circulating IGF cause cancer?

IGF is a potent mitogen as well as an anti-apoptotic agent (11). Its receptor is a tyrosine kinase and it functions via several signaling pathways including, but not limited to the Ras/Raf/MAP kinase signaling pathway (15). It would seem that IGF-1 itself may not cause cancer but rather exacerbates other cancer risks. A small increase in cell cycle rate can lead to, over a long period of time, billions of additional cell divisions and this can provide more chances to accumulate and proliferate somatic mutations. Furthermore, because IGF-1 has anti-apoptotic properties, it may give even more opportunities for somatic mutations to develop. Some studies indicate that IGF-1 may increase cancer risk by stimulating neovascularization and angiogenesis (16). Various studies implicate elevated IGF-1 levels in colon, prostate, breast, lung, skin and bladder cancers (11-21).

Colon Cancer

Because colon carcinogenesis relies upon a number of mutations in proto-oncogenes or tumor-suppressor genes, the accelerated cell proliferation which IGF stimulates may increase the rate at which the mutations collect (16). Acromegaly, because it is often associated with increased circulating levels of IGFs provides an opportunity to study the relationship between cancer and IGF-1. Numerous studies of acromegalics indicate that there is, consistently, an elevated risk of colon cancer amongst this population (10-15 fold higher risk) in comparison to the general population (15, 18). Furthermore, a relatively small case control study (n=91) revealed that individuals with IGF-1 levels in the upper two tertiles of the distributions had an elevated odds ratio when compared to individuals in the lower tertile (OR=5.2) (14). The authors of this study assert that high levels of circulating IGF-1 may be associated with colorectal cancer (14). In vitro studies demonstrate similar findings (17, 18). Jenkins et al. summarize that "epidemiological data have clearly demonstrated that circulating IFG-1 and IGFBP-3 levels can predict the risk of colorectal cancer" (18).

Prostate Cancer

Human prostate epithelial cells (which are believed to be the precursors of prostate adenocarcinoma) express high levels of IGF receptors (16). In vitro studies reveal that these cells are very sensitive to the growth stimulating effects of IGF-1 (16). There are a number of studies describing an association between various types of cancer and high plasma levels of IGF-1. For example, in a prospective case-control study of 14, 916 men, IGF-1 was significantly associated with prostate cancer risk presenting a 2.4 relative risk (12). The authors conclude that: "administration of GH or IGF-1 over long periods may increase the risk of prostate cancer" (12).

Breast Cancer

IGF-1 stimulates the proliferation of both normal and cancerous breast epithelial cells (15). In general, case control studies find around a 10% increase in serum levels of IGF-1 in patients with breast cancer. A case control study involving 1017 women showed that the relative risks of elevated IGF-1 concentration for premenopausal women under and over the age of 50 were 7.28 and 2.88 respectively (13). The authors assert that high

levels of IGFs as well as low levels of IGFBPs may increase the risk of cancer (13). A study of 220 acromegalics reveals a significantly increased incidence of malignant breast tumors (3.39-fold increased rate) in comparison to the general population (16). In a study designed to explore the effect GH and IGF administration may have when administered to older adults, aged rhesus monkeys were treated with GH, IGF-1, GH+IGF-1 or saline for seven weeks. The results revealed a 2-fold increase in mammary glandular size and epithelial proliferation index in the treated monkeys(19) revealing that increasing the concentration of IGF-1 in circulation actually causes tumorigenesis. Finally, it has been shown that IGF-1 can freely diffuse from external medium to breast cancer tissue in in vitro studies (2) In mice, monkeys, acromegalics, as well as in vitro, breast epithelial cells are extremely sensitive to the mitogenic and apoptotic effects of IGF-1 (13, 15, 16, 19).

Bladder Cancer

IGF-1 has also been implicated in bladder cancer. IGF-1 is lowered during dietary restriction. Dietary restriction significantly slows the progression of cancer in rodents (20). Dunn et al. designed an experiment that sought to capture events that modulate tumor progression from preneoplasia to malignant cancers. They used mice with induced bladder preneoplasias. The group found that when rodents on dietary restriction are supplemented with IGF-1, their rate of cancer returns to that of rodents not on dietary restriction (20). The authors determined that "IGF-1 increased the transitional cell carcinoma staging based on the criteria of tumor invasion; this is important because tumor invasion carries a poor prognosis in humans" (20). Similarly, another study found that persistent activation of the IGF receptor with IGF-1 leads to spontaneous tumor promotion in the basal epithelial cells of mice (21).

In many cases there has been evidence of a significant correlation between circulating elevated IGF-1 levels and increased cancer risk or rate. In vitro and animal studies have shown that IGF causes increased tumor formation and staging (11, 13, 15, 16, 18, 19, 20, 21) however, there has been no causality relationship defined in in vivo human models. In most cases IGF-1 is believed to exert its effects by increasing the rate at which progress through the cell cycle and by limiting apoptosis. Furthermore, IGF-1 may also protect cancer cells from chemotherapy-induced apoptosis (16, 13). It seems that more and more researchers are looking to IGF-1 and its receptor as targets for cancer therapy. It also seems that increased IGF-1 levels present a substantial risk for developing cancer.

Conclusion

While there are no studies exploring, directly, if milk from rbGH treated cows is dangerous to humans, there is a great deal of evidence that would suggest this milk presents a serious risk to a consumer's health. Nevertheless, the following issues should be explored to gain a more complete understanding of this risk: 1) the actual amount of IGF-1 that is absorbed in the GI tract from rbGH milk as well as the amount of IGF-1 absorbed while bound to IGFBP; 2) The effects of lifetime exposures to increased IGF-1 in milk; 3) The role IGF-1 has in tumorigenesis and carcinogenesis; 4)The threshold amount of serum IGF-1 required to effect cancer development.

Despite these unanswered questions, there still seems to be ample reason for caution with regard to milk from rbGH treated cows. The evidence presented in this paper describing the risks of rbGH milk is fostered the fact that this milk is banned in Canada and the European Union as well as by the poor track record of the FDA for putting public health as its top priority. A 1986 Congressional report stated: "FDA has consistently disregarded its responsibility…repeatedly put what it perceives are the interests of the veterinarians and the livestock industry ahead of its legal obligation to protect consumers,…jeopardizing the health and safety of consumers of meat, milk and poultry" (24). Furthermore, it would seem that the FDA may have some conflicts of interests, specifically because at the time the FDA approved the commercial sale of rbGH milk (1993), the deputy commissioner of the FDA (Michael Taylor) was the former chief counsel of the International Food Biotechnology Council and Monsanto! (8). In light of these findings, the safety of the United States' milk supply seems quite questionable and consumers should be very weary of milk derived from non-organic sources.

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