

Hormones and Contaminants in Food

The hormonal activity of veterinary medications and additives used in food production has raised concern about the potential effect on breast cancer. Many animals are intentionally exposed to growth hormones to maximize meat, egg or dairy output. In some cases, hormone residues end up in the food itself. In other cases, as with cow's milk, hormone additives can raise the levels of endogenous hormones in the finished food product.

While most work has focused on hormones, other signaling molecules and growth factors that work through receptor based mechanisms may also play an important role. In addition, changes in production methods have also influenced endogenous hormone levels. The potential effects of both exogenous hormones and changing levels of endogenous hormones are considered in this chapter, which focuses on the potential cancer-promoting and endocrine-disrupting compounds used in animal food production and their potential for affecting breast cancer risk. Extensive and ongoing research has been and is being devoted to the role of diet in breast cancer risk, particularly on dietary fat, therefore this discussion will be limited to the use of hormones in food production, rather than the diet composition or other more frequently addressed topics.

Other exposure issues associated with diet are addressed elsewhere in this document. Animal fats often contain measurable amounts of probable or known human carcinogens, such as hexachlorobenzene, polycyclic aromatic

hydrocarbons (see chapter I.B.1), dioxins, furans, and PCBs (see chapter I.B.2). Pesticide use in animal feed may also be a concern and is addressed in section I.B.3. Nonylphenols, an endocrine disruptor discussed in chapter I.B.4, are also found in food. Production and storage practices may also increase hormonal activity in food by introducing compounds such as phthalates. In the past, cow's milk and maple syrup were often collected in plastic tubing, allowing plasticizers to leach into the food products. The potential effects of phthalates on breast cancer are addressed in I.B.10. Antibiotics are routinely and extensively used in poultry and pork production; chapter I.D discusses the relationship between antibiotics and breast cancer.

Milk and Dairy Products

On average, U.S. dairy cows produce six times more milk than they did a century ago.¹ Most of this increase is attributable to selective breeding. The vast majority of dairy cows are now conceived through artificial insemination and are sired by just a few individual bulls. Because milk production is regulated hormonally, some researchers speculate that the breeding for higher milk production has selected for endocrine variants, and this in turn, may have altered hormonal microconstituents in milk.¹ Evidence for an overall increase in the hormonal activity of cows' milk does not currently exist. However, lack of high-quality milk banks means there is an absence of data to enable researchers to understand whether and how hormonal profiles of dairy milk may have changed over time.

Cows cannot give milk until they have given birth. The gestation period of a cow is about nine

months long, and dairy farmers attempt to impregnate adults about every 13 months. Cows are typically milked early in their pregnancies and then allowed to dry up during late pregnancy. Some researchers speculate that simultaneous pregnancy and lactation is more common now than in years past and that the contemporary practice of milking cows into late pregnancy has boosted estrogen levels in the milk,² however, there has been little research into whether contemporary milk supplies have a higher proportion of milk from pregnant cows than in previous years. It is nonetheless an important question because dairy cow pregnancy status and stage affect estrogen and progesterone levels in milk.² A major estrogen in milk of particular concern is estrone sulfate. When ingested, this compound is highly absorbed in the gut (high oral bioactivity).....) and has a long plasma half-life. It can be readily converted to estrone and estradiol in the body. One study found that almost 47% of estrone intake in a standard human diet came from dairy products.^{2,3} Milk and dairy products have been estimated to account for approximately 60–80% of the estrogens and progesterone consumed in the average U.S. diet overall.⁴

One notable change in dairy production occurred in 1993 when the FDA approved the use of recombinant bovine growth hormone (rBGH), also known as recombinant bovine somatotropin (rBST).⁵ The use of rBGH is not approved in Canada or the European Union. While rBST is still used to maximize milk production in dairy cattle, less than 30% of U.S. dairy cattle are now treated and that number is decreasing.⁵

The human health concern about rBGH in milk production is its potential for increasing levels in milk of another compound made by the cow itself, insulin-like growth factor I (IGF-I). In response to concerns about rBGH, the FDA contended that it is not recognized as a hormone in the human body and that, because it is a protein hormone, it is broken down during human digestion. Industry and governmental bodies have found that milk from rBGH supplemented cows does not differ from that of untreated cows in the composition of macronutrients, such as lactose, total solids, and relative percentages of, for example, casein and lactalbumin.⁶ However, there is little data on the effect of rBGH on levels of hormonally active agents. Monsanto, the manufacturer of rBGH, has reported the milk from rBGH-treated cows does have significantly higher levels of IGF-1,⁷ and these findings have been reported by others (for example, Gulay et al.⁸). Casein, however, can protect IGF-1 from digestion. A 1990 paper by FDA staff reported that pasteurization of rBST milk could increase IGF-1 further and that the undigested protein could cross the intestinal wall in humans.⁹

IGF-1 in cow's milk is identical to IGF-1 in humans where it is used to regulate the growth of cells. It has also been demonstrated to promote tumor growth on a cellular level, including mitogenic, anti-apoptotic, pro-angiogenic and cell migration and is linked to chemically and genetically-induced mammary tumors in vivo.¹⁰ IGF-1 and estrogen interact and share regulatory functions. IGF-1 receptors and estrogen receptor sites in the brain appear to affect one another (cross-talk). IGF-1 appears to be a key part of the mechanism for estradiol signaling and is required

for the priming actions of estradiol on the hypothalamus pituitary gland axis and in this way is involved in pubertal timing.¹¹⁻¹⁴

Animal studies show that dairy consumption has estrogenic effects. A study of rats found that ingestion of commercially available cow's milk (i.e. with normal levels of estrogen) for 7 days had a weak but biologically significant hormonal effect in both young ovariectomized rats and sexually immature rats. This study used uterotrophic assay to test for estrogenicity, incorporating both metabolic effects and pharmacokinetics.¹⁵ Another study found that commercially available low-fat milk promoted the development of DMBA-induced mammary tumors in rats, and only to a slightly lower degree than those fed 0.1 µg/ml estrone sulfate.¹⁶ The authors hypothesized that the high estrogen content in the milk may be responsible for the promotional effects, acting in concert with other hormones such as IGF-I.

Drawing firm conclusions about the role of dairy hormones in breast cancer causation from human studies is made difficult because of at least four factors. First, rBGH was introduced in the dairy industry only within the last two decades; therefore, not enough time has passed to detect an effect. Second, not all dairy farmers use rBGH, and the milk from rBGH-treated cows is not evenly distributed within the national milk supply. Third, many studies of milk consumption and cancer risk combine human data from many nations, including those where rBGH is not used and where the milk practices regarding pregnant cows may be very different. Fourth, dairy consumption by itself, regardless of artificial

hormones used in the production of the milk, may have a relationship to cancer risk. Dairy consumption does appear to elevate IGF-1 levels in humans.¹ IGF-1 levels vary considerably within and between individuals. While levels can be influenced by meat and dairy in the diet, it is not known how much rBGH-treatment may contribute to IGF-1 increases.

The association between milk consumption and breast cancer has been inconsistent in case-control and cohort studies, particularly when they did not control for menopausal status.¹⁷⁻¹⁹ One meta-analysis observed a small increase in breast cancer risk with high milk consumption,²⁰ while a pooled analysis of cohort studies found no significant association.²¹ An analysis of the Nurses' Health Study data found that among premenopausal women, higher intake of lowfat dairy foods was associated with reduced risk of breast cancer.²² They also found that the lower risk was associated with specific components of dairy foods—calcium and vitamin D, but independent associations were difficult to distinguish. Milk in the U.S. is usually fortified with vitamin D, a prosteroid hormone thought to prevent cancer and associated with lower of developing premenopausal breast cancer.²³ However diet, including consumption of dairy products, provides a relatively small part of vitamin D dosage. For a more in-depth discussion of vitamin D, please see Section I, Chapter I.

The association between milk consumption and circulating IGF-1 levels is clearer. In an analysis of samples from more than 1000 women participating in the Nurses' Health Study, the most consistent positive association with plasma levels of IGF-1 was greater milk intake.²⁴ This

association held when adjusting for other factors and in an analysis of the biologically active fraction of IGF-1. Likewise, a 2007 IARC study found a modest association between circulating IGF-1 levels and intake of milk and cheese among European women.²⁵

The association between circulating IGF-1 levels and breast cancer is not consistent and is currently under revision. The data have become less clear just during the past few years as results from large-scale cohorts have been published. One meta-analysis found that higher concentrations of IGF-1 were positively associated with increased risk of breast cancer in pre-menopausal but not post-menopausal women [pooled odds ratio = 1.93 (CI 1.38–2.69)]. The IGF-I binding protein IGFBP-3, was also associated with breast cancer [pooled odds ratio = 1.96 (CI 1.28–2.99)].¹⁰ The authors suggested that IGF and its binding protein could have both potentiating and attenuating associations. They also took exception with conclusions of no association between IGF-1 and breast cancer from analyses of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort²⁶ and the Nurses Health Study II.²⁷

Beef

The European Union has forbidden the use of exogenous hormones as promoters of animal growth since 1989.²⁸ By contrast, six hormones are approved for use in beef cattle in the United States. One is estradiol. Another is zeranol, a non-steroidal hormone with estrogenic activity.²⁹ Also used by the beef industry are two androgens—testosterone and trenbolone acetate, and two hormones with progestogenic activity—

progesterone and melengestrol acetate.³⁰ Many animals are dosed with more than one hormones. Synovex C, for example, is a calf implant that contains 100 mg of progesterone and 10 mg of estradiol. It is used to increase the rate of weight gain in suckling beef cattle.³¹ Zeranol, trenbolone acetate (TA), and melengestrol acetate (MGA) are not metabolized as quickly as estradiol, progesterone and testosterone.³² More than 90% of US livestock are currently injected with these hormones to increase production of veal and beef.³³

The FDA has reported that “concentrations of the hormones in edible tissues remain within the normal physiological range that has been established for untreated animals of the same age and sex.”³² These estimates assume that veterinary products are used as directed, which may not always be the case. Additionally, steroid hormones (in contrast to protein hormones) are not digested in the human gut and may pass into the bloodstream, making even low doses of concern, particularly during critical stages of development.

Additionally, federal risk assessments for safe threshold levels for estrogens in meat are based on overestimates of children’s own endogenous production of estrogen, which are now known to be many times lower than presumed by previous models.²⁸ This means that estrogenic chemicals in food contribute a higher proportion of sex hormone levels in prepubertal girls than was presumed when federal risk assessments established legal limits for estrogen levels in meat. Moreover, the three synthetic hormones given beef cattle—trenbolone acetate, zeranol and melengestrol acetate—were found to cross the

placental barrier of pregnant rabbits that were treated. Fetuses had detectable levels of both parent compounds and their metabolites.³⁴

The form of estradiol used in beef production (17 β) is a cancer promoter and has shown genotoxic activity in certain conditions.³⁵ In addition to hormonal action, it is suspected of acting as a chemical carcinogen by binding to cellular macromolecules. Some evidence suggests that certain catechol metabolites induce free-radical damage of DNA in cell and laboratory animal test systems.³⁰

It also is biologically plausible that estrogens in meat could contribute to the falling age of menarche in U.S. girls; early menarche is a known risk factor for breast cancer. Estradiol is known to accelerate hypothalamic maturation, which controls pubertal timing.³⁶ In addition, known exposures to estrogens in personal care products and ingested pharmaceuticals have been documented to induce precocious breast development in young girls.^{28, 36}

There are also reasons to be concerned about the synthetic estrogen zeranol, which is also used in beef production. The estrogen receptor-positive MCF-7 human breast cancer cell line showed estrogen-dependent growth *in vitro*, as well as estrogen-dependent tumorigenicity *in vivo* in the presence of zeranol.^{29, 37} Zeranol has induced estrogenic responses in primary cultured breast cells and breast cancer cell lines. Meat and serum from zeranol treated cattle were mitogenic (heat-stable) for cultured breast cells, and both normal and cancerous human breast cells exhibited estrogenic responses to zeranol.¹⁶

Human epidemiological studies sometimes have shown an association between meat consumption and breast cancer incidence. However, many analyses blended data from nations that do and do not use hormone supplements. Analysis of dietary data from 40 countries found meat was the most closely correlated with breast cancer incidence ($r = 0.827$), followed by milk (0.817) and cheese (0.751).² A step-wise regression again found the highest correlation with meat, while breast cancer mortality was most closely associated with cheese. An Italian study found that, after parity, only dairy consumption had a significant positive correlation with breast cancer mortality.³⁸

Increased breast cancer in humans and increased mammary gland tumors in animals has been associated with the form of estradiol used in beef production (17 β).³⁹ Recent findings from a large prospective cohort study found a link between increased breast cancer incidence and red meat consumption in premenopausal women. They found a strong positive relationship (test for trend, $P = 0.001$) between the amount of red meat younger women reported consuming and rates of estrogen receptor positive breast cancer in the 12 years of follow-up.⁴⁰ Meat consumption was reported at three times during this prospective study, limiting potential recall bias and error. Previous negative findings were based on studies of older women, did not account for menopausal status and/or did not account for cancer hormone receptor status.

Poultry

Little information is available about nithiazide, a veterinary medicine used in poultry production. It may persist in the tissues and eggs of treated

poultry and when administered in the diet, it increased the incidence of fibroadenomas and cystadenomas of the mammary gland in female rats.³⁹ It was also found to be positive for mutagenicity.⁴¹

In addition to nithiazide, roxarsone, an organic arsenic derivative, is routinely used in poultry feed in order to kill parasites in broiler chickens and to promote growth.⁴² A percentage of roxarsone converts to inorganic arsenic within the chicken, and also is rapidly transformed into inorganic arsenic when poultry litter is applied to fields. From here, it may easily move to groundwater. There are, thus, two important routes of human exposure for arsenic used the poultry industry: consumption of chicken and drinking water.

Data published in 2004 by Lasky and her colleagues at the USDA calculated that some heavy consumers of chicken—who include children, senior citizens, and African Americans--may be ingesting more arsenic than the WHO/FAO tolerable daily intake (2 micrograms/kg/day inorganic arsenic).⁴³ Moreover, consumption in the United States is on the rise, having increased by 2.5 fold between 1966 and 2000.⁴² Arsenic may also be ingested with groundwater, fish and some brands of rice, adding to total exposure.

Arsenic is a known human carcinogen.⁴⁴ It is also an endocrine disruptor. Arsenic alters the ability of glucocorticoid receptors, progesterone receptors, and mineralocorticoid receptors to respond to their normal hormonal signals. It does so by affecting the regulation of gene expression. The dose-response curve is non-monotonic: at very low doses, arsenic enhances gene expression.

At higher doses, it inhibits these receptors.⁴⁵ These results suggest that arsenic may have very different carcinogenic influences at lower and higher doses. Arsenic also disrupts estrogen receptors both in vivo and in MCF-7 cell cultures. Specifically, arsenic significantly inhibited E2-mediated gene activation of an ER-regulated reporter gene and the native ER-regulated GREB1 gene in human breast cancer cells. Arsenic is also discussed in I.B.8. Metals.

Discussion & Conclusions

The relationship between diet and cancer is very complex, involving not only potential exposure to risk factors for breast cancer, but also protective effects of nutrients. It is difficult to distinguish between carcinogens produced by cooking meat and those in animal fat, or between endogenous and exogenous hormones in meat and milk. Given this conflicting evidence, some researchers call for further work to identify the relationship between specific components of milk and the development of breast cancer.¹⁶ The use of equipment and containers with hormonally active compounds, such as plastics with the potential to leach phthalates, is an additional factor that may confound research on the role of food and should be considered in future studies.

Studies cited here offer evidence of a positive association between IGF-1 levels in humans with milk consumption; however, more information is needed about the effect of IGF-1 levels in milk on the levels in humans. It is also important to evaluate differences in human response to treated and untreated milk, as well as responses to milk from dairy cow by pregnancy status and stage. While governments in Canada and the EU have

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banned the use of rBST, consumers concerns about human health are driving change in the U.S. Following a few other large producers (Tillamook, some Safeway and Kroger plants), California Dairies Co., which supplies about 10% of U.S. milk, is eliminating rBST in the milk it handles by mid-2007.⁴⁶ Kroger will finish eliminating rBST from milk it processes and sells by early 2008.⁴⁷

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