Dairy and Cancer
Is there a link?

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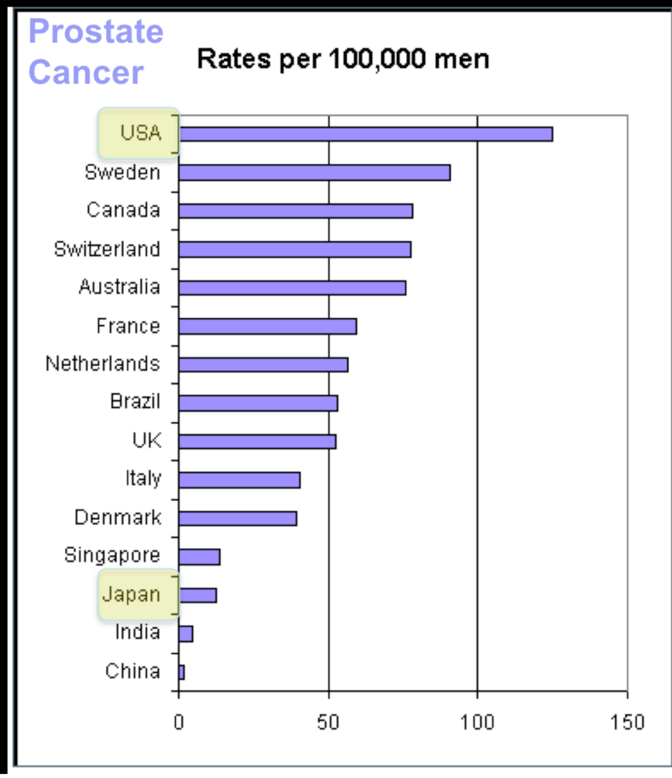
Environmental factors promote cancer progression



The environment can affect cancer rates in two ways. It can expose us to agents that cause genetic mutations that initiate cancer and/or it can expose us to agents that cause already initiated cancers to progress.

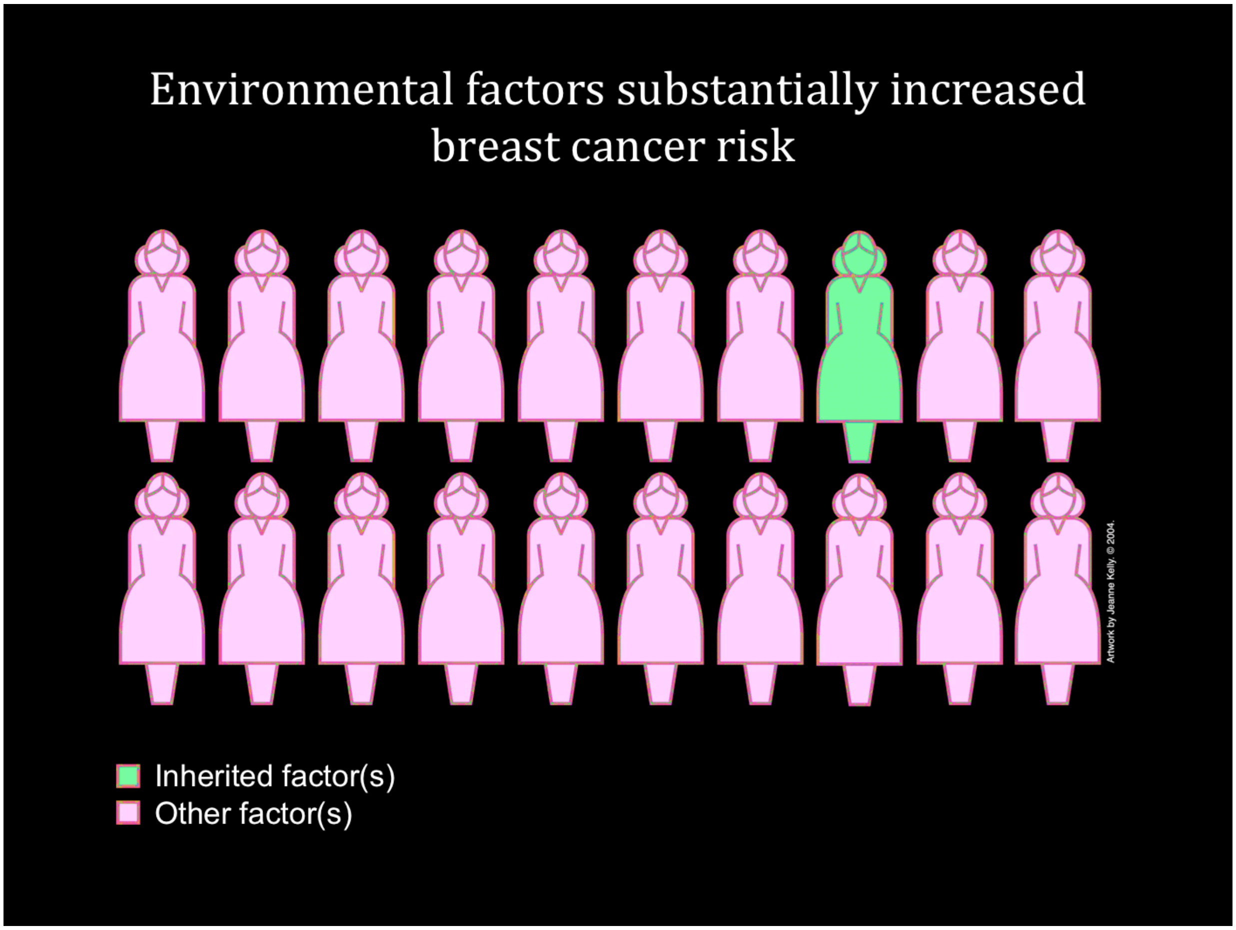
The incidence of clinical (diagnosed) prostate cancer is ten times higher in the U.S. than Japan.[1] Yet autopsy studies on men who died of causes other than prostate cancer show that the prevalence of undiagnosed prostate cancer is the same in both countries.[2] If the environmental effect was related to the initiation of prostate cancer, then we would expect autopsy studies to show a higher frequency of undiagnosed cancer among Japanese men who migrated to the U.S. in comparison to those who remained in Japan, but this is not the case. Instead, there is an increase in clinical cancers observed in these migrants.[3] This indicates that the effect of environmental exposures on prostate cancer is a promotional effect that favors cancer progression among U.S. men.[4]

[1]Watanabe M, Nakayama T, Shiraishi T et al. Comparative studies of prostate cancer in Japan versus the United States. A review. Urologic Oncology 2000; 5(6)**:** 274–283.

[2]Yatani R, Chigusa I, Akazaki K et al. Geographic pathology of latent prostatic carcinoma. International Journal of Cancer 1982; 29(6): 611–616.

[3]Shiraishi T, Watanabe M, Matsuura H et al. The frequency of latent prostatic carcinoma in young males: the Japanese experience. In Vivo (Athens, Greece) 1994; 8(3)**:** 445–447.

[4]Holly J, Perks C. Cancer as an endocrine problem. Best Pract Res Clin Endocrinol Metab 2008;22(4): 539-550.



Only 1 in 20 breast cancers are thought to be due to inheritance of certain forms of the breast cancer susceptibility genes, BRCA1 and BRCA2.[1] In a study of 1,000 Ashkenazi Jewish women in the U.S. with these inherited mutations, the risk of developing breast cancer by age 50 tripled in women born after 1940, compared to women born before 1940.[2] Similarly, in women in Iceland with BRCA2 mutations the risk of developing breast cancer by age 70 quadrupled between 1920 and 2002 and the risk among the general population also quadrupled over the same time period. This means that changes in environmental exposures affected women with and without these inherited factors relatively equally and that these environmental changes during the 20th century substantially increased breast cancer risk.[3]

[1]NCI Website: http://cancer.gov/cancertopics/understandingcancer

[2]King MC, Marks JH & Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003; 302(5645): 643–646.

[3]Tryggvadottir L, Sigvaldason H, Olafsdottir GH et al. Population-based study of changing breast cancer risk in Icelandic BRCA2 mutation carriers, 1920–2000. J Natl Cancer Inst 2006;98(2): 116–122.

What's the single best dietary change you can make?

35%

Breast and prostate cancers are called hormone-dependent cancers because they do not progress in the absence of the hormones that promote their growth. In 1981 Sir Richard Doll, the preeminent 20th century epidemiologist who was among the first to show that smoking causes lung cancer, estimated that 35% of all cancer deaths were due to diet.[1] Although too little research attention is focused on this, food is the major route of hormonal exposure in humans.[2]

I was diagnosed with breast cancer 13 years ago. At the end of treatment I was informed that, statistically, my daughter's risk had doubled simply by having a mother diagnosed at a young age and in the absence of any known genetic predisposition. Many researchers believe that the source of this "family history" risk factor lies in the genes. That is where much of the research funding is currently invested. But hunting for genetic variations that increase cancer risk has yielded minimal returns to date. I think it's just as plausible that the source for my daughter's increased risk lies with our common diet and lifestyle factors. So I decided to find out what I could do to protect her from the same fate. It took me 12 years, but I found what I was looking for.

There are many things we can do to lead healthier lives, including maintaining a healthy weight and moderating alcohol consumption. But, the most important dietary change we can make to protect ourselves from breast or prostate cancers or their recurrence is to eliminate the single greatest environmental exposure to the hormones that fuel their growth. I can sum up my 12 years of research in two words: AVOID DAIRY.

[1]Doll R & Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981; 66(6): 1191–1308.

[2]Courant F, et al. Exposure assessment of prepubertal children to steroid endocrine disruptors. 2. Determination of steroid hormones in milk, egg, and meat samples. J Agric Food Chem 2008; 56: 3176-3184

The hormonal cocktail - that is cow's milk - was designed by nature to grow a calf from 60 to 600 pounds in 9 months, and it works great for the calf, but not for us. Despite what the ads say, milk and products made from milk do not do our bodies good. Most of what we know about milk comes from the dairy industry. What I learned about milk, I learned from the peer-reviewed scientific literature.

Here's what I learned;

- The steroid, estrogen and the protein, insulin-like growth factor-1 (IGF-1) are critical hormones that promote the growth and progression of breast and prostate tumors.
- IGF-1 is the most prevalent and potent growth stimulator known. Unlike other growth factors, IGF-1 is unique in that it also prevents the natural and programmed death of both normal and abnormal cells. The IGF-1 in milk is identical to the IGF-1 in humans. Of the 16 estrogen metabolites measured in humans, 11 are present in milk, including the estrogen metabolite that has the potential to cause DNA mutations.
- Estrogen and IGF-1 act synergistically. This means that their combined effect on growth stimulation is not additive, as in 1+1=2, but exponential; like the difference on the Richter scale between the earthquakes that happened here in 1906 (8.0) and 1989 (6.9).
- Milk is the **only** environmental substance that simultaneously exposes us to both estrogen and IGF-1 and increases our blood levels of these hormones.
- Industry production and processing changes during the 20th century increased the concentrations of these hormones in milk.
- Year-round, lifelong milk consumption is a phenomenon that began in the 20th century and preceded rising breast and prostate cancer rates.

I've organized this presentation into 3 parts.

I'll begin with a review of the **scientific evidence** that links dairy consumption to breast and prostate cancer risk.

Then I'll move to **milk production and processing**, where I'll talk about 4 production changes that increased hormone concentrations in milk and why processing of reduced fat milk substantially increases its hormone concentrations relative to whole milk.

Finally I'll review **dairy consumption** over the course of the 20^{th} century and compare changes in consumption with breast cancer incidence.

Milk is the only substance that increases IGF-1 and estrogen levels in the consumer

First I want to take you through an excellent and very important study of low fat milk and mammary tumors in rats. What do mammary tumors in rats have to do with prostate tumors in men? Research shows that prostate cancer incidence in 21 countries is most closely correlated with breast, endometrial and ovarian cancers, all estrogen-responsive cancers.[1] Research also shows that worldwide - breast, prostate, endometrial and ovarian cancer incidence is highly correlated with milk and cheese consumption.[2,3] This rat mammary tumor study reveals the mechanism by which milk promotes tumor progression.

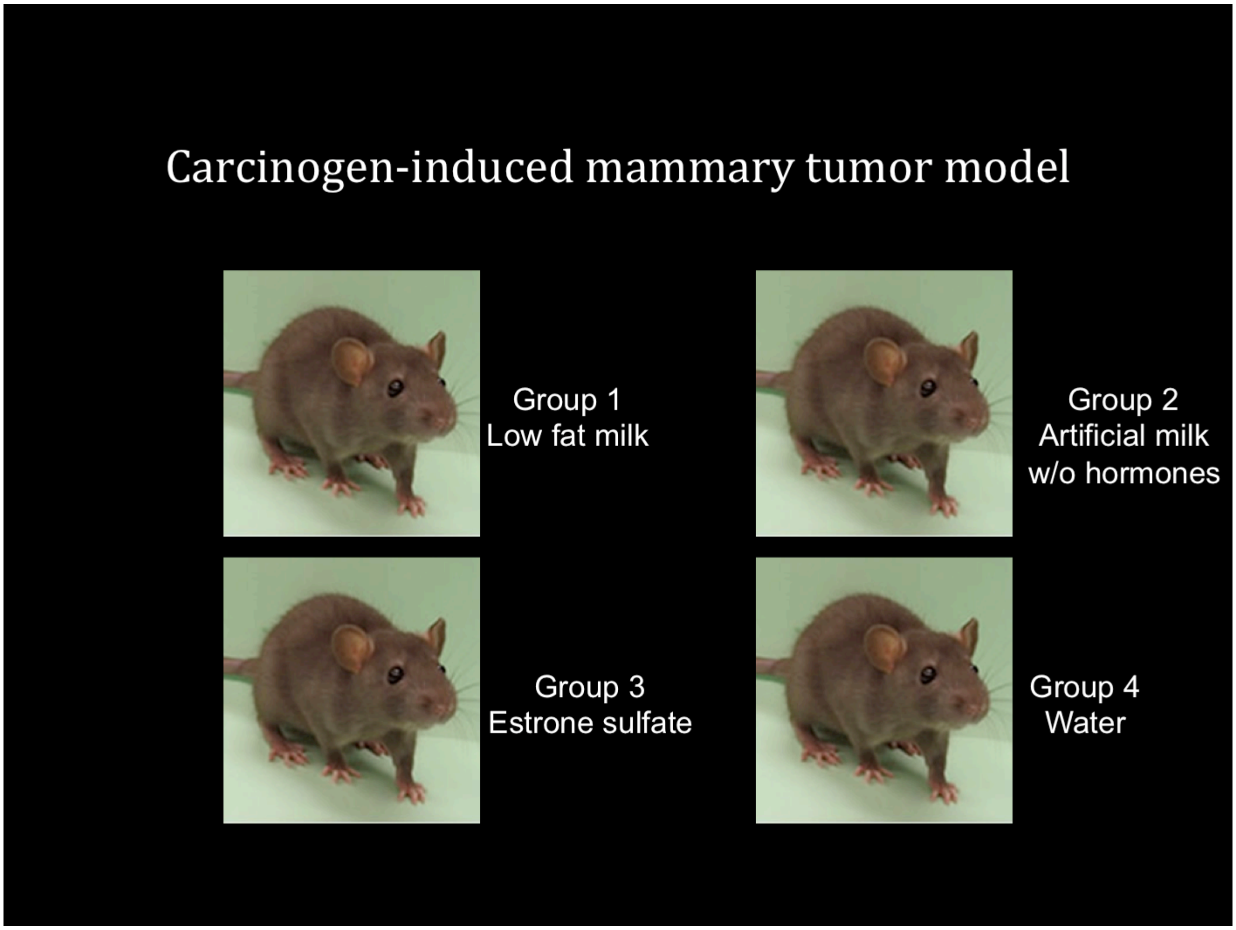
Next we'll look at the relationship between estrogen levels in women and men and their respective breast and prostate cancer risk. Then we'll do the same for IGF-1. We have to look at each of these hormones separately because that's how the studies were conducted. To my knowledge no studies have yet examined the combined effect on cancer risk of higher blood levels of both estrogen and IGF-1.

Finally, we'll look at the relationship between diet and IGF-1 levels and diet and breast and prostate cancer risk.

[1]Coffey, D. Similarities of Prostate and Breast Cancer: Evolution, Diet and Estrogens. Urology 2001; (suppl 4A):31-38

[2]Ganmaa D, Li XM,Wang J et al. Incidence and mortality of testicular and prostatic cancers in relation to world dietary practices. Int J Cancer 2002; 98: 262–67.

[3]Ganmaa D, Sato A. The possible role of female sex hormones in milk from pregnant cows in the development of breast, ovarian and corpus uteri cancers. Medical Hypotheses 2005;65:1028037.

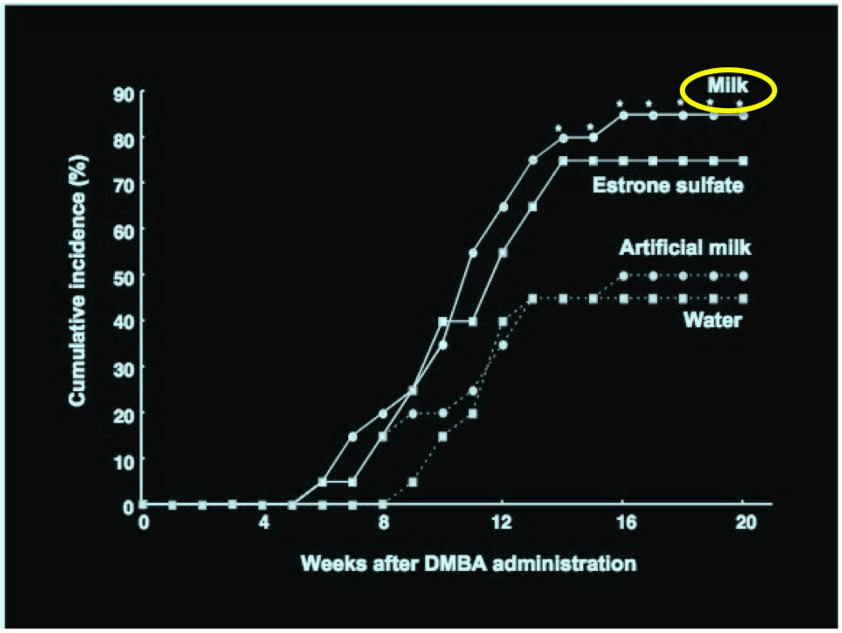


Cancer was initiated in these rats by giving them a dose of the carcinogen, dimethylbenzanthracene and then the rats were divided into 4 groups. The 1st group got low fat milk with their chow. The 2nd group got artificial milk matched in nutrient content to the low fat milk, but containing no hormones. The 3rd group got a huge dose of estrone sulfate dissolved in their water (100 ng/ml, 265 times the amount of conjugated estrones measured in the low fat milk) and the 4th group got plain water with their chow. The rats were watched closely for the development of tumors and autopsied after 20 weeks.[1]

Estrone sulfate is a conjugated form of estrogen, meaning it is attached to another substance, in this case a sulfate molecule, which inactivates it. It is the most prevalent form of estrogen in milk and in the human bloodstream where it serves as a reservoir for uptake by estrogen responsive tissue like the breast, prostate endometrium and ovary. Both normal and malignant cells in these tissues express specific proteins (organic anion transporter polypeptides[2,3]) that actively transport estrone sulfate from the bloodstream into these cells. These cells also express an enzyme that removes the sulfate and another enzyme that readily converts the estrone into the most potent estrogen, estradiol.[4,5,6,7]

[1]Qin LQ, Xu JY, Wang PY, Ganmaa D, et al. Int J Cancer 2004; 110:491-496.
[2]Pressler H, Sissung TM, Venzon D, Price DK, Figg WD. PLoS ONE 2011; 6(5): e20372
[3]Maeda T, Irokawa M, Arakawa H, et al. J Steroid Biochem Mol Biol 2010;122(4):180-85.
[4]Santner S, Feil P, Santen R. J. Clin. Endocrinol. Metab 1984;59:29–33.
[5]Nakamura Y, Suzuki T, Fukuda T, et al. Prostate 2006; 66: 1005–1012.
[6]Tanaka K, Kubushiro Y, Iwamori Y, et al. Cancer Sci 2003;94:871-76
[7]Kirilovas D, Schedvins K, Naessén T, et al. Gynecol Endocrinol 2007; 23:25–28.

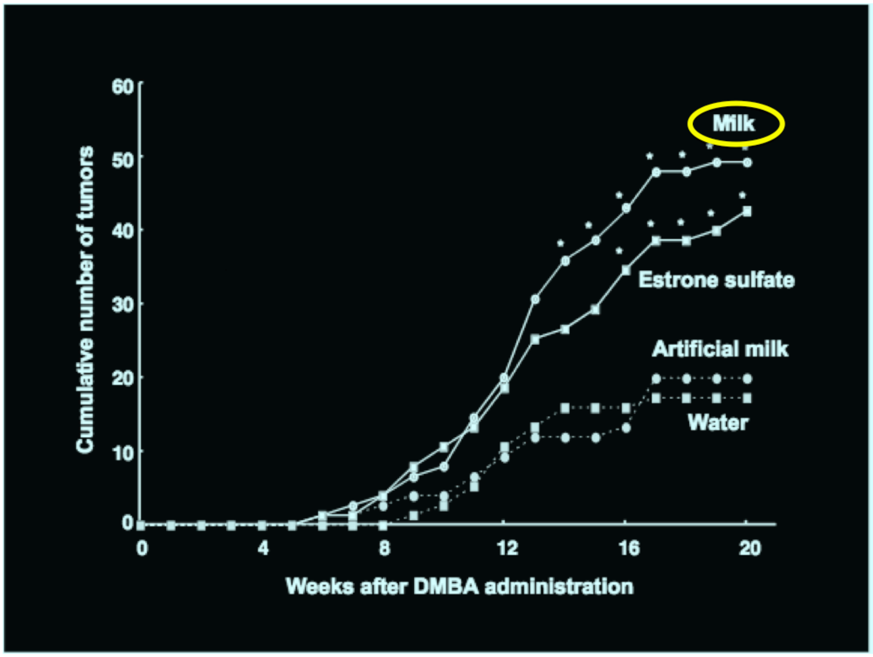
Rats fed low fat milk had the highest incidence of tumors



This graph shows the percentage of rats in each group that developed tumors and as you can see, a much greater percentage of rats in the low fat milk group than the artificial milk group developed tumors. It's important to note that there was no difference in calories or body weight between the rats fed low fat milk and the rats fed the artificial milk.

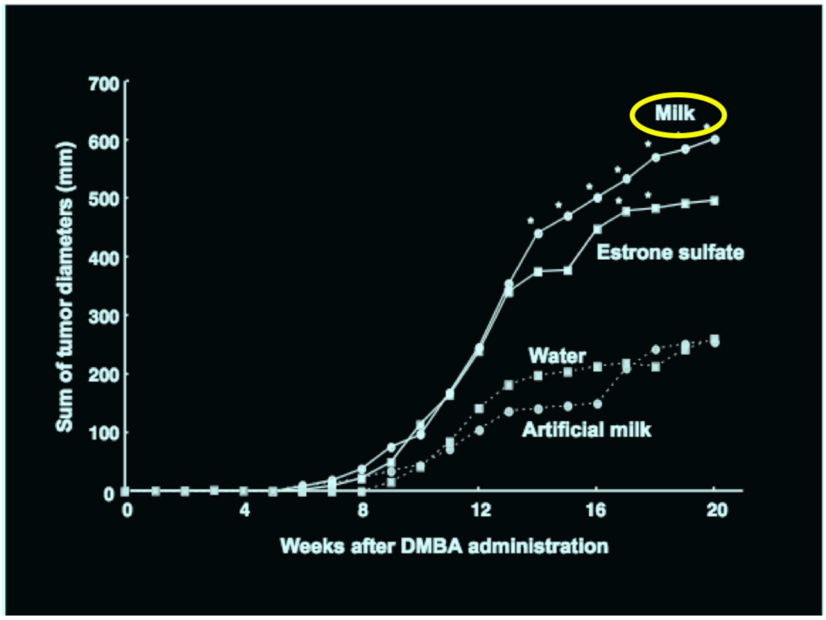
And as you can also see there was a strong promotional effect in the group fed estrone sulfate.

Rats fed low fat milk had the highest number of tumors



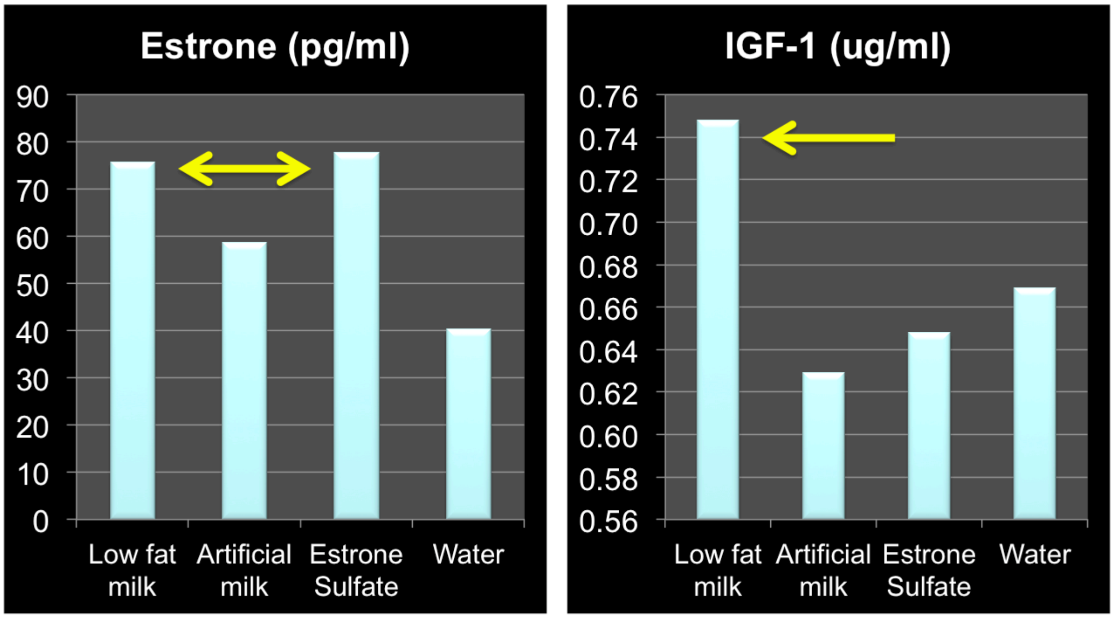
The number of tumors was also greater in the low fat milk group than the artificial milk group.

Rats fed low fat milk had the largest tumors



And lastly, the size of the tumors was far greater in the low fat milk group than in the artificial milk group and as with the previous slides you can see that the estrone sulfate had a strong promotional effect.

Low fat milk increases blood estrone and IGF-1



In the chart on the left you can see that the estrone levels in the blood of the rats fed low fat milk were about the same as the rats fed that whopping dose of estrone sulfate (100ng/ml) dissolved in water. In the chart on the right you can see that the IGF-1 levels in the blood of rats fed low fat milk were higher than the other groups. Both differences were statistically significant. The authors of this study conclude that it is the combined effect of estrogen acting in concert with IGF-1 and possibly other milk hormones, that is responsible for the effect on tumor development in the rats fed low fat milk, because only the low fat milk increased both the IGF-1 and the estrone levels. This study has been replicated by other groups. All types of milk, whole, reduced fat and skim promote the growth of carcinogen-induced mammary tumors in rats.[1,2]

Now let's turn to the epidemiology studies on breast and prostate cancer risk in humans.

[1]Qin L, Xu J, Tezuka H, et al. Consumption of commercial whole and non-fat milk increases the incidence of 7, 12-dimethylbenz(a)anthracene-induced mammary tumors in rats. Cancer Detect Prev 2007;31: 339-343.

[2]Ma D, Katoh R, Zhou H, Wang P. Promoting effects of milk on the develoment of 7,12-dimethylben(a)anthracene-induced mammary tumors in rats. Acta Histochem Cytochem 2007; 40:61-67

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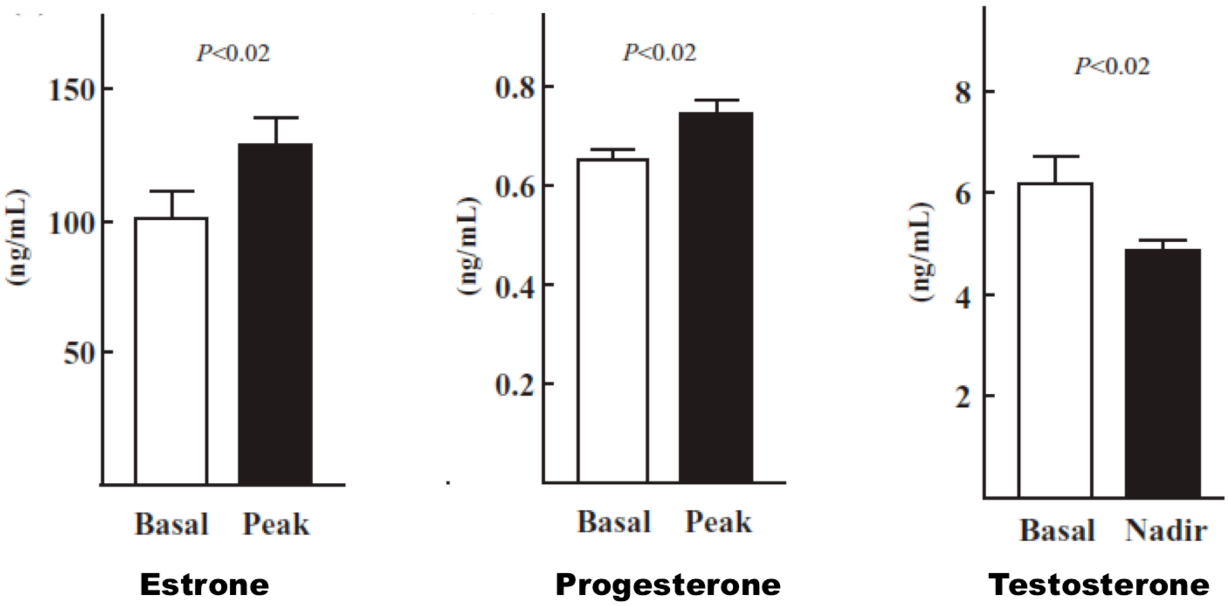
The largest and best study to date on the link between blood levels of steroid hormones and breast cancer risk in postmenopausal women was published in 2002 and involved the collaboration of numerous research teams throughout the world (Endogenous Hormones and Breast Cancer Collaborative Group) who combined their data to be able to have a large enough number of breast cancer cases and controls to evaluate not only whether or not there was a link between these hormones and breast cancer risk but the magnitude of the risk. They looked at 5 estrogens and 4 androgens. In women who had the highest blood levels in comparison to women who had the lowest blood levels, breast cancer risk doubled for each of the hormones studied, including estrone, the estrogen most prevalent in milk.[1]

What about men? A similar group (Endogenous Hormones and Prostate Cancer Collaborative Group) published a study in men in 2008 that found no relationship between prostate cancer risk and blood levels of 6 different androgens, including testosterone, and the estrogen, estradiol. Unfortunately, estrone was not examined.[2] However, it is known that African American men, who are at much higher risk of prostate cancer, have higher estrone levels.[3] It has also been shown that higher estrone sulfate levels are indicative of faster tumor growth in men with prostate cancer.[4] Finally, last year, the first study to examine the relationship between estrone, estradiol and testosterone and prostate cancer risk, reported that only blood estrone levels were linked to prostate cancer risk. Compared to men with the lowest level, those with the 2nd, 3rd and 4th higher levels combined had quadruple the risk of developing prostate cancer.[5] These results await replication in larger studies.

[1]Key T, Appleby P, Barnes I, Reeves G, et al. J Natl Cancer Inst 2002;94:606-16.
[2]Roddam AW, Allen NE, Appleby P, Key TJ. J Natl Cancer Inst 2008;100(3):170-83.
[3]Bosland MC. J Natl Cancer Inst Monogr 2000;27:39-66.
[4]Giton, F, Taille A, Allory Y, et al. J Steroid Biochem Mol Biol 2008;109:158–167.
[5]Daniels NA, Nielson CM, Hoffman AR, Bauer, DC. Urology 2010;76(3):1034-40.

Whole milk increases blood estrone and progesterone and decreases testosterone in men



The next question is, does milk increase estrone levels in men and women?

Although dairy represents 60-80% of total dietary estrogen exposure,[1] the effect of milk on circulating estrogen concentrations in consumers has not yet been well studied. Last year, a study in 765 postmenopausal women showed that dairy consumption was statistically significantly linked to higher total and unconjugated estradiol blood levels, but the observed increase in estrone sulfate levels was not statistically significant.[2] However hormone replacement therapy studies indicate that conjugated estrogens, when taken orally, are more readily absorbed into the bloodstream and markedly increase circulating levels of estrone sulfate.[3]

Shown here are the results of a very small study published last year involving just 7 men, which needs to be replicated with much larger numbers. Nevertheless it is the only intervention study I know of where blood levels of hormones were measured before and directly after consuming store bought milk, in this case 4 to 5, eight-ounce glasses of whole milk.[3] As you can see the blood estrone levels went up and the progesterone levels went up. While the testosterone levels went down after consuming the milk.

[1]Hartmann S, Lacorn M, Steinhart H. Natural occurrence of steroid hormones in food. Food Chem 1998;62: 7-20.

[2]Brinkman MT, Baglietto L, Krishnan K, et al. Consumption of animal products, their nutrient components and postmenopausal circulating steroid hormone concentrations. Euro J Clin Nutri2010; 64:176–183.

[3]Slater CC, Hodis HN, Mack WJ, Shoupe D, Paulson RJ, Stanczyk FZ. Markedly elevated levels of estrone sulfate after long-term oral, but not transdermal, administration of estradiol in postmenopausal women. Menopause. 2001;8:200-203.

[4]Maruyama K, Oshima T, Ohyama K. Exposure to exogenous estrogen through intake of commercial milk produced from pregnant cows. Pediatr Intl 2010;52:33-8.

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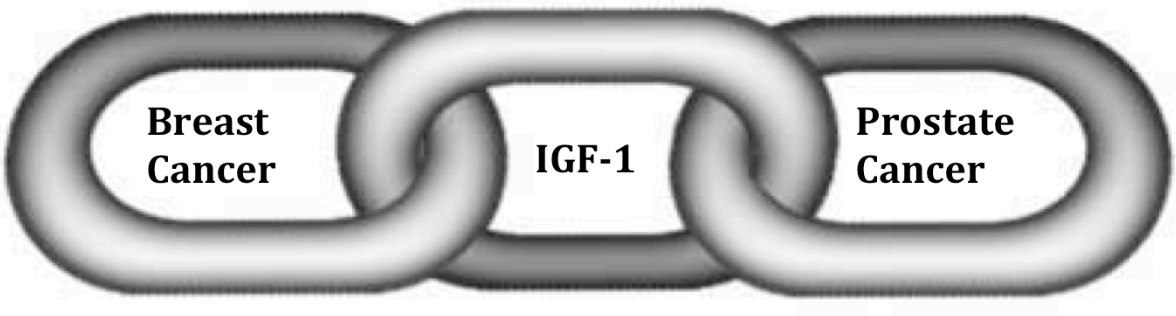

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These same collaborative groups (Endogenous Hormones and Breast/Prostate Cancer Collaborative Group) also studied the link between breast and prostate cancer risk and IGF-1 levels. Last year they reported that higher blood IGF-1 levels in both pre and post-menopausal women are highly significantly linked to a 38% increase in estrogen-receptor positive breast cancer risk, which is the most common type.[1] And the same relationship holds for men and prostate cancer risk; a 38% increase in risk for men with the highest levels of IGF-1 relative to those with the lowest.[2] Although the magnitude of the increased breast and prostate cancer risks is modest, it is of the same order of magnitude as these well-known heart disease risk factors, diastolic blood pressure and total cholesterol.[3] The true relative risks are likely to be larger because IGF-1 measured in a single blood sample per individual is subject to substantial random error, which dilutes the true association. As we will see on the next slide, the effect of diet on IGF-1 also appears to be of moderate magnitude, but may be of great importance, if present over many years.[4]

[1]Key T, Appleby P, Reeves G, et al. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol 2010; 11:530-542.

[2]Roddam AW, Allen NE, Appleby P et al. Insulin-like growth factors, their binding proteins, and prostate cancer risk: Analysis of individual patient data from 12 prospective studies. Ann Intern Med 2008; 149: 461–471.

[3]Rowlands M, Gunnell D, Harris R, et al. Circulating insulin-like growth factor peptides and prostate cancer risk: A systematic review and meta-analysis. Int J Cancer 2009: 124, 2416–2429

[4]Key, T. Diet, insulin-like growth factor-1 and cancer risk. Proc Nutr Soc 2011; 3:1-4. [Epub ahead of print].

Dairy protein is the link between diet and IGF-1 levels

- ☑ Protein intake
  - ~~Plant protein~~
  - Animal protein
    - ~~Meat and meat products~~
    - ~~Fish and shellfish~~
    - ~~Eggs and egg products~~
    - Dairy protein
- ☒ Total fat
  - Saturated fat
  - Monounsaturated fat
  - Polyunsaturated fat
- ☒ Carbohydrates
  - Starch
  - Sugars
- ☒ Fiber
- ☒ Calcium

Now we turn to the science on diet and IGF-1 levels. A very large and well-respected European group published this study in 2009 involving nearly 5,000 men and women in 9 different countries (Denmark France, Germany, Greece, Italy, Netherlands, Norway, Spain and the UK). They found no relationship between dietary fat, carbohydrates, fiber or calcium and blood IGF-1 levels, but protein intake was related. When they dug further, there was no relationship between plant proteins and IGF-1 and among animal proteins there was no relationship between meat and meat products, fish or shellfish, eggs or egg products. Only dairy protein was associated with blood levels of IGF-1 in both men and women.[1]

This same European group also examined the relationship between animal food intake and prostate cancer risk. They found no association with meat, fish or eggs. When they looked at individual dairy products they found inconsistent relationships. But when they looked at the totality of dairy protein intake they found that dairy protein was associated with a 22% increased risk of prostate cancer. Dairy calcium, but not other sources of calcium, was also linked to increased risk. They attributed this to the fact that dairy protein and calcium are themselves high correlated. And since calcium from other sources is not related to risk, they conclude that it is the dairy protein that is relevant to prostate cancer risk.[2]

[1]Crowe F, Key T, Allen NE et al. The Association between Diet and Serum Concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 in the European Prospective Investigation into Cancer and Nutrition Cancer Epidemiol Biomarkers Prev 2009; 18: 1333-1340

[2]Allen, NE, Key T, Appleby P, Travis R, et al. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2008; 98: 1574 – 1581

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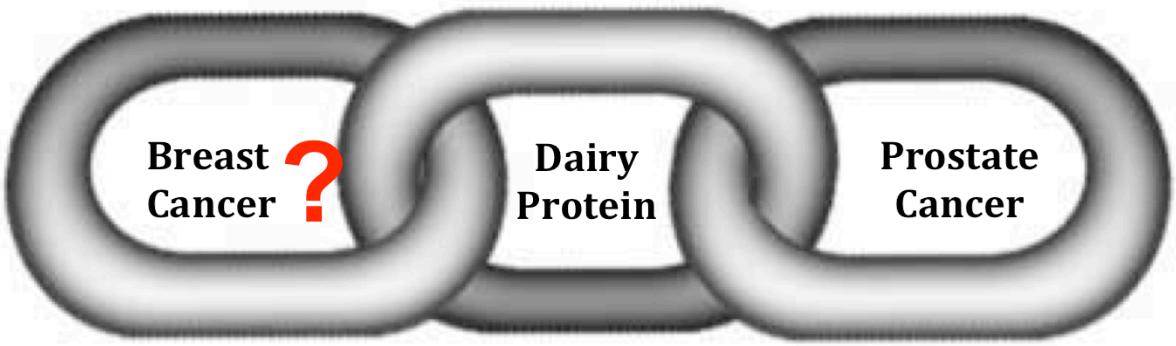

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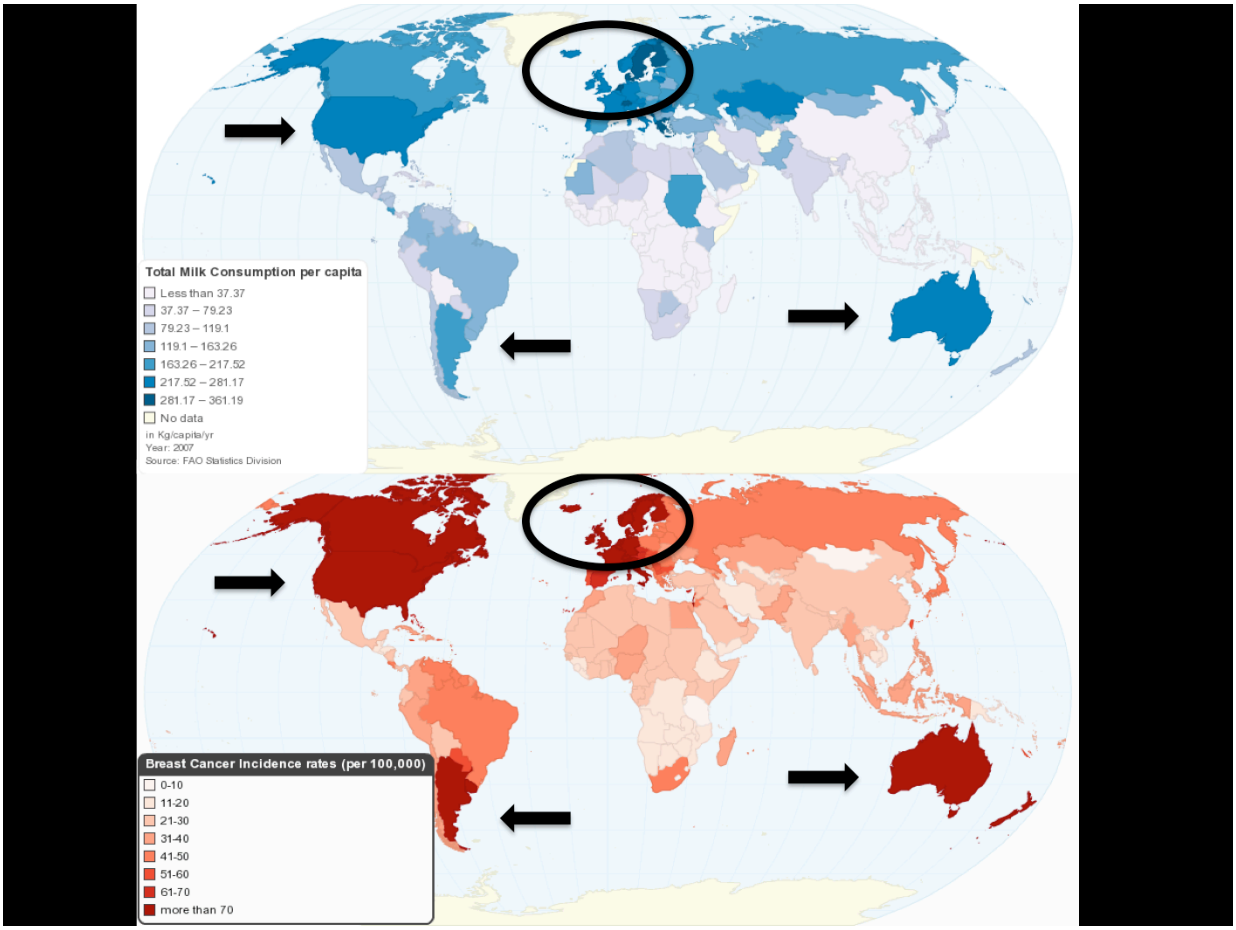
Currently the evidence for an association between dairy intake and breast cancer risk is inconsistent. However, in comparison to prostate cancer risk, the assessment of dairy exposure relative to breast cancer risk is complicated by both the timing of exposure and the fact that women's diets are more difficult to assess. In the presence of a dietician or trained interviewer, women are less likely to report caloric intake that is inconsistent with their body build and weight. However, with hundreds of thousands of participants in these large epidemiologic studies, physical interviews are not possible. Instead, participants report the frequency and amount of their food consumption through periodic questionnaires that are exchanged by mail. This gives women the freedom to under report their food intake. They are more likely to do so if they think they are overweight or obese. Foods associated with weight gain, many of which contain dairy, also tend to be under reported by women.[1] Nevertheless, when we look at dairy consumption and breast cancer incidence around the world we see a clear pattern.

[1]Olafsdottir AS, Thorsdottir I, Gunnarsdottir I, et al Comparison of women's diet assessed by FFQs and 24-hour recalls with and without underreporters: associations with biomarkers. Ann Nutr Metab 2006; 50:450-460



The top map shows worldwide total milk consumption (excluding butter) per capita.[1] The bottom map shows worldwide breast cancer incidence rates.[2] The darker the shade the higher the dairy consumption and cancer rates. Archaeological evidence suggests that dairying began in Northern Europe. Descendants of these early Northern Europeans brought dairying to the United States and Canada, Australia and New Zealand, Argentina and Uruguay. And these are the areas today with the most industrialized production and consumption of cow milk and the highest rates of breast cancer. Prostate cancer incidence is very similar.

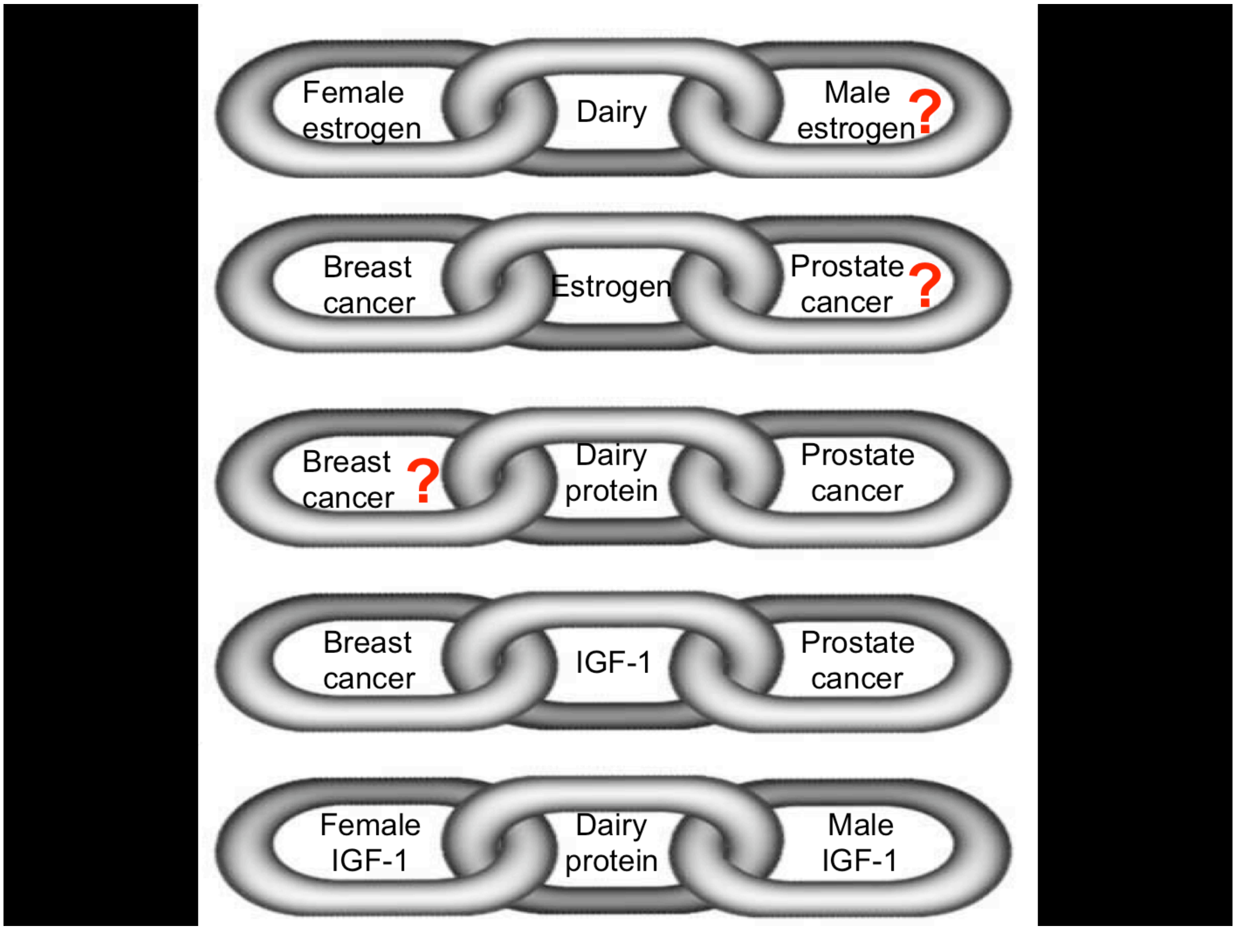
Comparisons between countries with large differences in diet show clear associations between dairy consumption and hormone-dependent cancers.[3,4] However, it has proved quite difficult to replicate these associations within individual countries largely because of the relatively small variations in diet within most countries, which is not much greater than the errors in the techniques currently available for measuring diet.

[1]ChartsBin statistics collector team 2011, *Current Worldwide Total Milk Consumption per capita*, ChartsBin.com, viewed 10th July, 2011

[2]ChartsBin statistics collector team 2010, *Current Worldwide Breast Cancer Incidence Rate*, ChartsBin.com, viewed 10th July, 2011

[3]Ganmaa D, Li XM,Wang J et al. Incidence and mortality of testicular and prostatic cancers in relation to world dietary practices. Int J Cancer 2002; 98: 262–67.

[4]Ganmaa D, Sato A. The possible role of female sex hormones in milk from pregnant cows in the development of breast, ovarian and corpus uteri cancers. Medical Hypotheses 2005;65:1028-37.



To recap, the rat mammary tumor study shows that the mechanism by which commercial milk causes tumor progression in rats is by increasing blood levels of estrone and IGF-1. In humans, there is very strong epidemiologic evidence that higher IGF-1 levels are linked to increased breast and prostate cancer risk and that dairy intake is linked to higher IGF-1 levels in both men and women. There is also strong evidence that dairy protein intake is directly linked to increased prostate cancer risk, but the evidence for breast cancer is inconsistent. However, in population studies comparing countries with large dietary differences, the evidence is highly suggestive of increased breast cancer risk.

There is very strong evidence that higher estrone levels increase breast cancer risk, but only one study to date has shown a link between higher estrone levels in men and increased prostate cancer risk. So this finding awaits replication in larger studies. Finally, the relationship between dairy intake and estrogen levels has not been well studied. Currently there is only one small pilot study that showed a statistically significant increase in blood estrone levels in men who consumed whole milk. But we do know that the conjugated estrones in hormone replacement therapy when taken orally markedly increase blood levels of estrone in women and this is the most prevalent type of estrogen in milk.

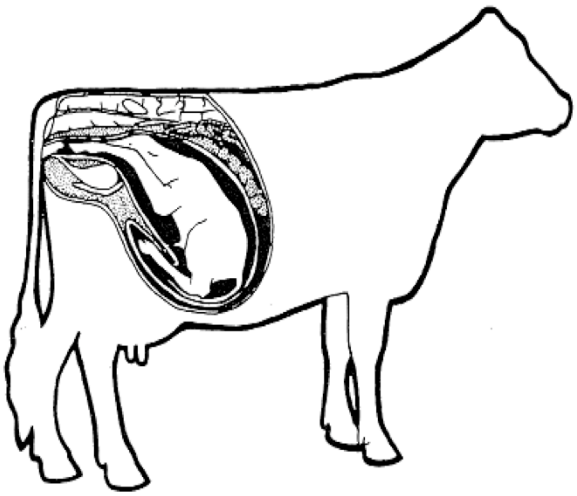
Now let's turn to the milk production and processing changes during the 20th century.

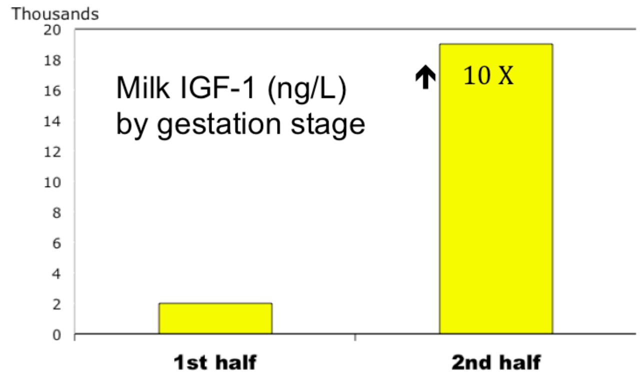
Dairy industry production and processing changes increased hormones in milk

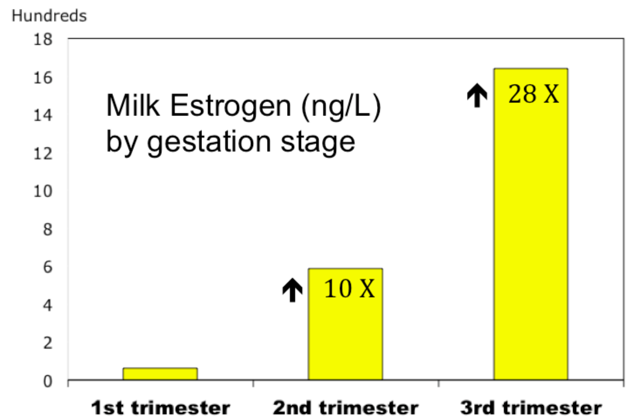
There were 4 production changes that led to rising hormone concentrations. The 1st was the transition from a seasonal to an industrial model of milk production that began in the 1st half of the century and took the entire century to complete and this led to rising estrogen and IGF-1 concentrations in commercial milk.

And in the 2nd half of the century genetic selection, recombinant bovine somatotropin or rbST injections, and mastitis, a bacterial infection of the cow's udder, further increased commercial milk IGF-1 levels.

Finally, the way in which raw milk is processed to meet government mandated standards for 1%, 2%, and nonfat milk results in higher estrogen and IGF-1 concentrations in these reduced-fat milks in comparison to whole milk.







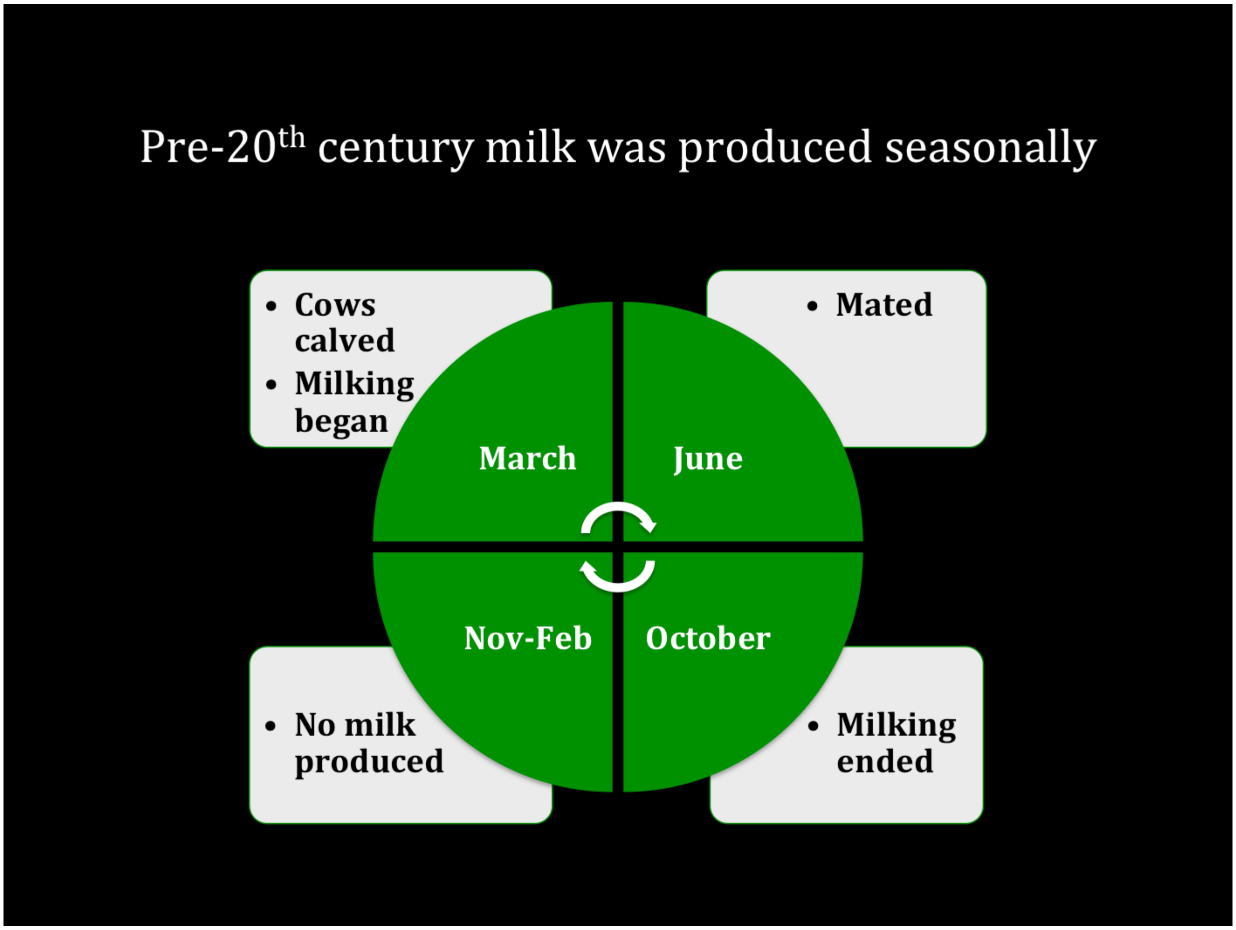
First, we need to understand that most milk comes from pregnant cows. Why? Because cows must give birth before they can give milk and about 3 months after calving they are re-impregnated so that they will give milk again the following year. Milk that comes from pregnant cows contains higher hormone concentrations and these concentrations in milk increase as pregnancy progresses.

Cows in the 2nd half of gestation have 10 times more IGF-1 in their milk than cows in the 1st half of pregnancy.[1]

In comparison to cows in the 1st trimester, cows in the 2nd trimester have 10 times more estrogen in their milk and cows in the 3rd trimester have 28 times more estrogen in their milk.[2]

[1]Sejrsen K, Pedersen L, Vestergaard M, Purup S. Biological activity of bovine milk; contribution of IGF-I and IGF binding proteins. Livest Prod Sci 2001;70:79–85.

[2]Malekinejad H, Scherpenisse P, Bergwerff AA. Naturally occurring estrogens in processed milk and raw milk (from gestated cows). J Agric Food Chem 2006; 54:9785-9791.



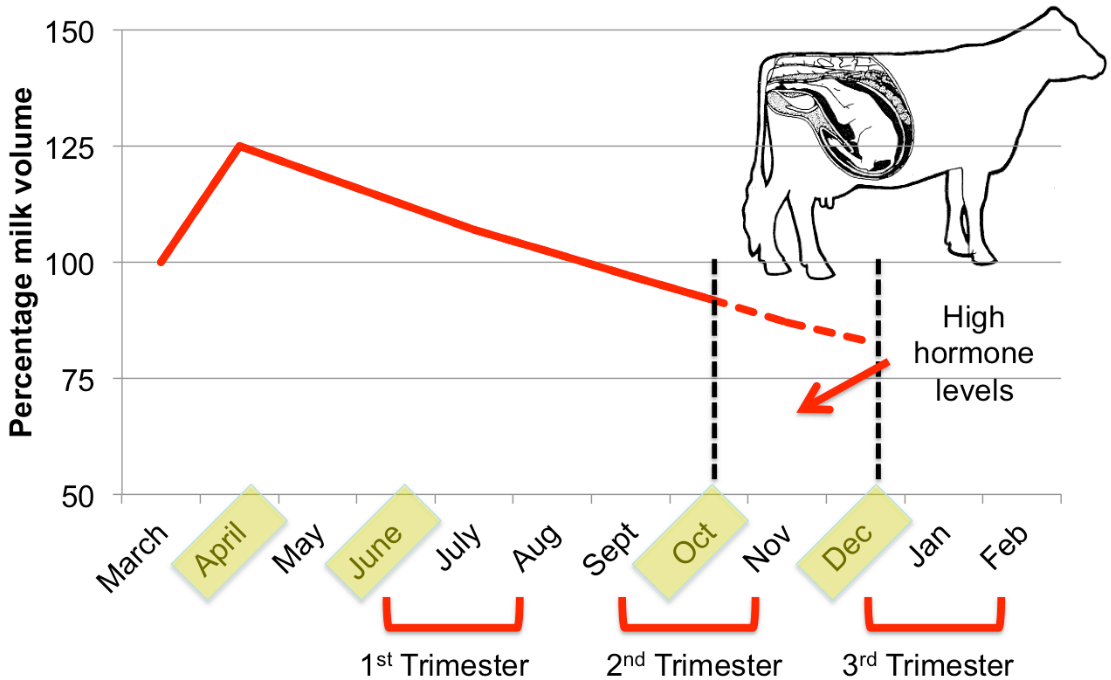
Prior to the advent of industrial production all cows were naturally synchronized to the same fertility cycle.

Farmers let their cows out to pasture in the summer months where usually a neighbor's bull would take care of impregnating the entire herd in short order.

The cows would give birth the following spring when grass was plentiful to support the high-energy demands of lactation.

And they were re-impregnated in June, 3 months after calving, to assure that they would give milk again the following spring. Milk was collected for about 8 months, during which the cows were pregnant for 5. By mid-October milking was stopped and from November through February of the following year no milk was produced, until the cows gave birth again in March.

Seasonal milk production led to acute hormone concentrations in milk

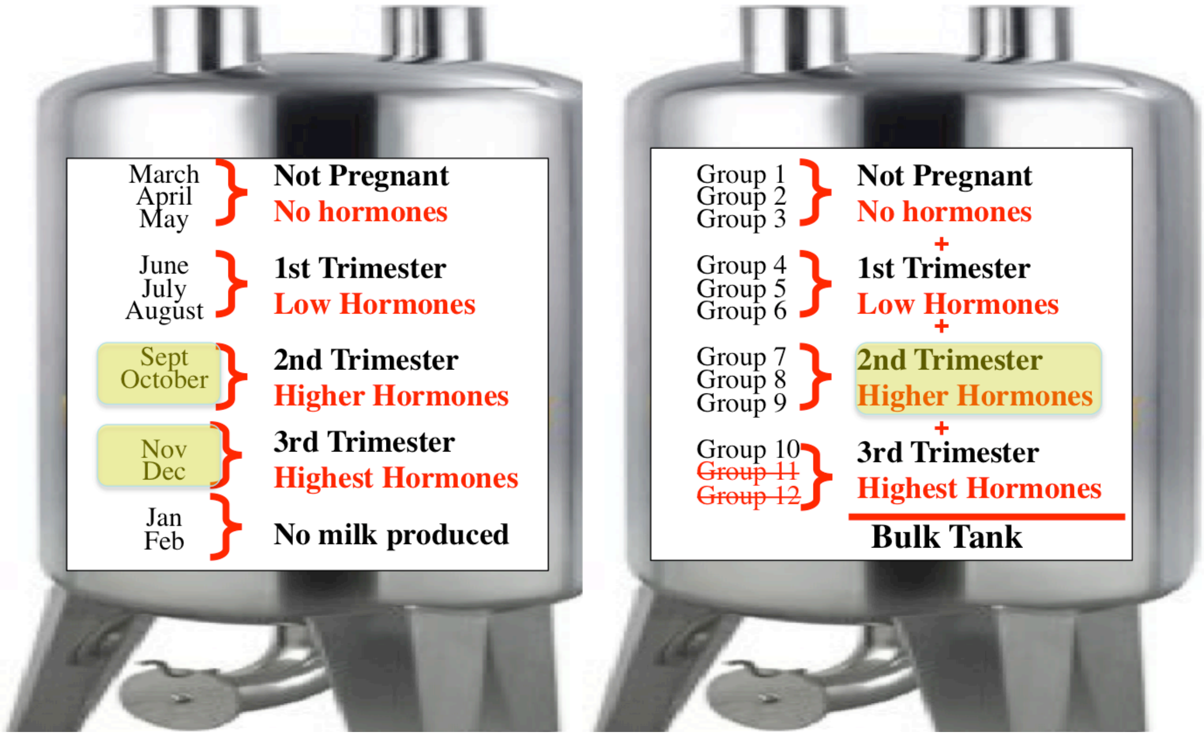


On a graph, seasonal milk production looks like this line, which represents the average volume of milk per cow produced over the course of the year 1850. Since all cows were synchronized to the same fertility cycle, it is representative of the nation's monthly milk supply throughout the year. Then as now, cows' milk production peaks in the second month after giving birth at about 125% of the volume produced in the 1st month and declines by 5% each month thereafter. Cows were re-impregnated in June and milked until October, which just happened to coincide with the mid-point of pregnancy. From an industry perspective, it's difficult to expand when there's no product to sell for 4 months out of the year. So by 1910 the milking period was extended by two months.[1] And unbeknownst to anyone at that time, the milk produced between October and December contained very high hormone concentrations, because all of the cows were now beyond the mid-point of pregnancy when milk hormone levels are highest. So milk hormone concentrations under the seasonal production model can be characterized as acute, meaning high levels, but for a short period of time. However, the diminishing supply of milk produced each month was still problematic for the industry. To grow further, equal monthly milk production volumes were needed, which requires equal numbers of cows to come into peak production every month. This meant that producers had to stagger the pregnancies of their herds. In the 2nd half of the century when artificial insemination became more practical, progress toward equal monthly milk production accelerated.

[1]Bateman F. Improvement in American dairy farming, 1850-1910: a quantitative analysis. J Econ Hist 1968; 28:255

Seasonal Production
Milk hormone concentrations varied by calendar month

Industrial Production
Milk hormone concentrations are high and constant



Under the seasonal production model, when all cows were synchronized to the same fertility cycle, we would find that milk collected in March, April and May had negligible hormone concentrations and low hormone concentrations in June, July and August, commensurate with the 1st trimester of gestation. Only in Sept and Oct would we find high hormone concentrations as gestation progressed during the 2nd trimester, before milking ended. After 1910, when the milking period was extended into late gestation, we would find very high hormone concentrations in the milk collected during November and December. However, it wasn't until after WWI that we started to become a nation of fluid milk consumers. Prior to that most milk was sold to creameries to make butter, which contains only the milk fat. The conjugated estrogens and the IGF-1 are not contained in the milk fat.

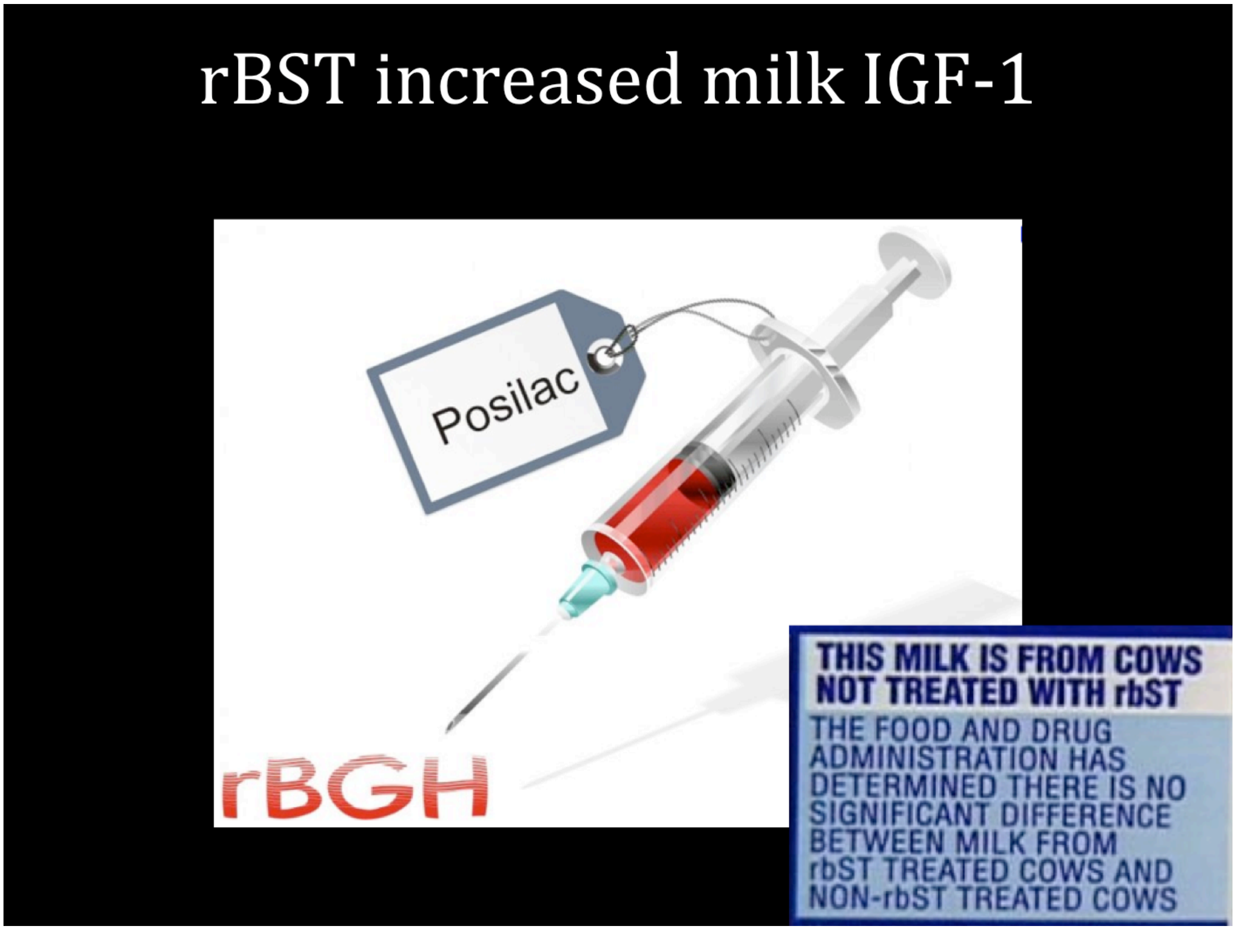
Under the industrial model, following the extension of the milking period into late pregnancy and the pooling of the milk from thousands of regional cows all equally dispersed across different gestation stages, the hormone concentration in modern commercial milk – every day of the year – is now equal to the blended average of the minimal hormones in the milk from not-pregnant cows plus the low levels in the milk from 1st trimester cows plus the higher concentrations in the milk from 2nd trimester cows and the highest levels in the milk from 3rd trimester cows. This blended average rose throughout the century as progress was made toward the industry goal of equal monthly milk production volumes and eventually plateaued when this goal was achieved. Therefore the transition to an industrial model of milk production resulted in chronically high hormone concentrations in modern commercial milk, that most closely match levels found in the milk from cows in the 2nd trimester of pregnancy. Now let's look at the other three production changes that further increased the IGF-1 levels in milk, beginning with genetic selection.

[1]Malekinejad H, Scherpenisse P, Bergwerff AA. Naturally occurring estrogens in processed milk and raw milk (from gestated cows) J Agric Food Chem 2006; 54:9785-9791.

Genetic selection increased milk IGF-1

Cows are now artificially inseminated with the semen from bulls like the one shown here, whose daughters produce the most milk and this is what is meant by genetic selection. The University of Minnesota has maintained 2 separate dairy herds since the start of genetic selection in 1964. One has been genetically selected just like the vast majority of US dairy cows and the other, the static control herd, has been maintained in the exact same way minus genetic selection. Dairy scientists have published numerous studies comparing different aspects of these two herds. From these we now know that the genetically selected cows have higher growth hormone levels.[1,2,3,4] We also know from the science that growth hormone stimulates production of IGF-1 in the mammary gland. [5,6] And that this delays the natural programmed death of the milk-producing cells, which results in higher milk volumes during the later months of lactation.[7,8,9] The science also tells us that as a consequence of higher mammary gland IGF-1 production, more IGF-1 gets passed into the milk. [10,11,12] Unfortunately, we don't know how much greater these IGF-1 concentrations are in modern milk from selected cows because we don't have a source for comparison, except for the static control herd maintained by the University of Minnesota, which has refused to provide these milk samples to interested researchers.

[1]Bonczek R. J Dairy Sci 1988;71(9):2470-79.
[2]Akers RM. J Dairy Sci 2000;83:1151-58.
[3]Knight CH. J Dairy Res 2004;71:141-53.
[4]Weber WJ. J Dairy Sci 2007;90:3314-25.
[4]5uan Wl. Endocrinol 1995;136:1296-1302.
[5]6lath-Gabler A. J Endocrinol 2001;168:39-48.
[7]Prosser CG. Dairy Res 1989;56:17-26.
[8]Hadsell D. J Endocrinol 1993;137:223-30.
[9]Daxenberger A. Analyst 1998;123:2429-35.
[10]Hadsell D. Endocrinol 1996;137:321-30.
[11]Neuenschwander S. J Clin Invest 1996;97:2225-32.
[12]Accorsi PA. J Dairy Sci 2002;85:507-13.



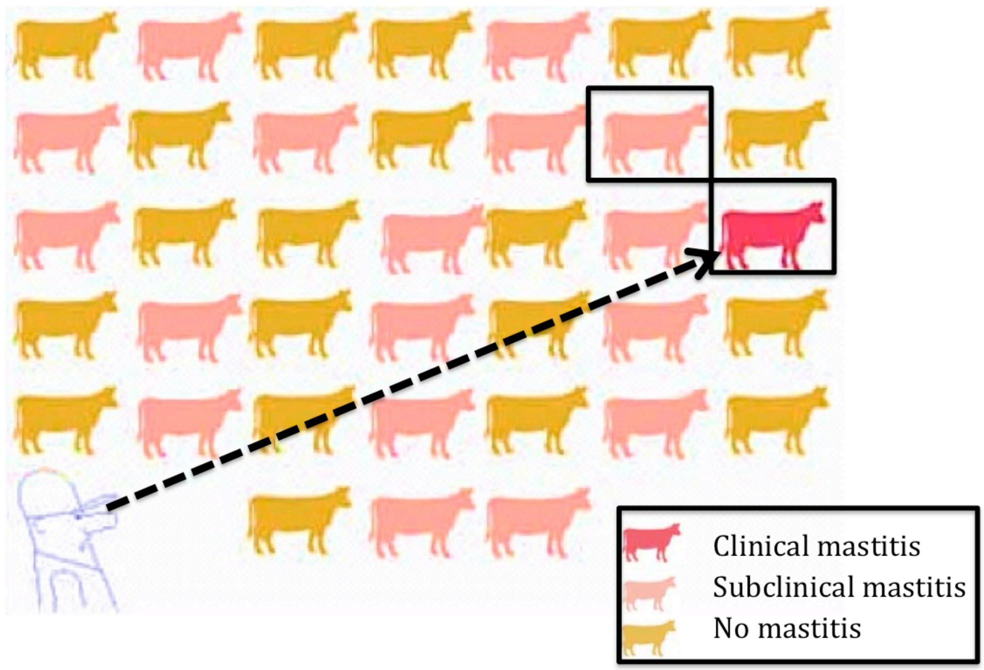
Recombinant bovine somatotropin or rBST, also known as recombinant bovine growth hormone, was the 1st genetically modified organism to enter the food supply. It was developed and marketed by Monsanto and approved by the FDA for use in dairy cows in 1993. It increases milk yields about 10% by the same mechanism that higher growth hormone levels in genetically selected cows increase milk yields, and for that reason it also increases the IGF-1 levels in the milk of treated cows. Each 14-day injection cycle was found to increase the milk IGF-1 concentration by 59%.[1]

Consumers objected to the use of rbST. Some processors responded by excluding milk from treated cows and wanted to label their milk accordingly. The industry and the FDA blocked this and the battle played out in the courts. Finally the FDA allowed the label shown here as long as it included the proviso that the milk was no different than the milk from cows that had been treated with rbST.

However, just last year the United States Court of Appeals for the 6th Circuit held that the milk from treated cows was different for 3 reasons, 1st, it contains higher IGF-1 concentrations, 2nd, when cows are injected there is a period during their lactation when their milk has lower nutritional value and 3rd, there are more somatic cells in the milk from rbST treated cows. Somatic cells, or white blood cells in the milk are caused by mastitis, which we'll talk about next.

[1]Daxenberger A ,Sauerwein H, Breier B. Increased milk levels of insulin-like growth factor 1 (IGF-1) for the identification of bovine somatotropin (bST) treated cows. Analyst 1998; 123: 2429-35.

Genetic selection and rbST increased the prevalence of mastitis, which further increased milk IGF-1 levels



Genetic selection and rbST use each increased the prevalence of mastitis. Mastitis is a bacterial infection in the cow's udder where milk is stored. The udder consists of 4 quarters and an infection usually begins in one quarter and spreads unless treated with antibiotics. IGF-1 levels in the milk from infected quarters are double those of non-infected quarters, whether the cows have obvious or symptomatic mastitis or undetected, early and non-symptomatic mastitis.[1]

I make this distinction because the milk from cows with obvious mastitis must be discarded while they are being treated with antibiotics, but the milk from cows with undetected mastitis enters the milk supply and increases the IGF-1 concentration in commercial milk.

To briefly summarize, the transition to an industrial model of production led to chronic and rising estrogen and IGF-1 concentrations in milk throughout the century and in the 2nd half of the century genetic selection and rbST use each led to further increases in IGF-1 and together increased the prevalence of mastitis and the milk from cows with undetected mastitis enters the milk supply and contains higher IGF-1 levels.

Now let's look at how reduced-fat milk is made.

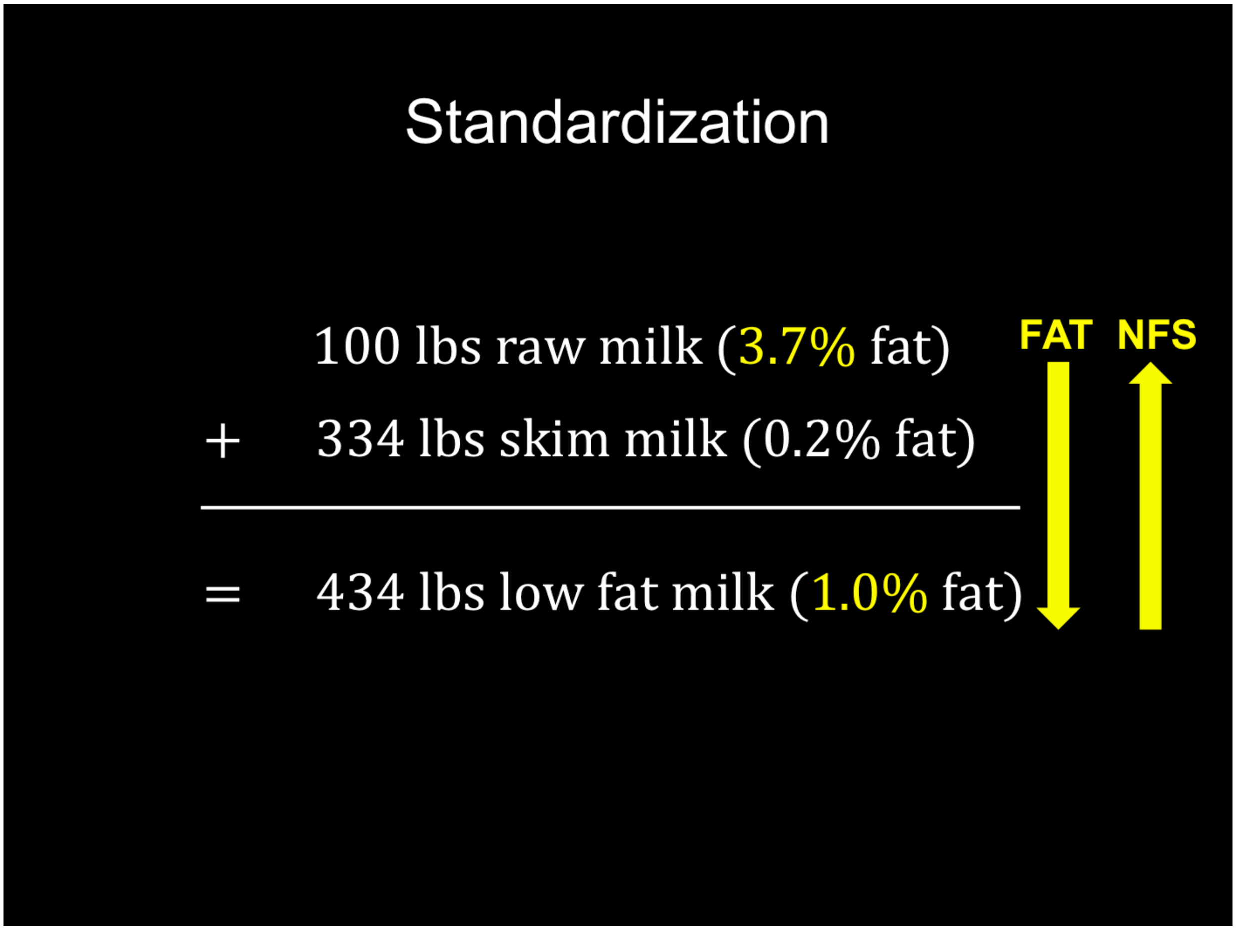
[1]Liebe A, Schams D. J Dairy Res 1998;65:93-100.

Commercial milk composition is regulated on the basis of fat and non-fat solids (NFS) content

The government and the industry consider milk to have 3 main components. By volume, milk is mostly water, together with some fat and everything else that's in milk is included under nonfat solids. The nonfat solids consist of the milk sugar lactose, the proteins casein and whey and more than 500 other proteins like IGF-1, that are in the parts per billion range, and minerals, such as calcium, potassium, sodium and several others in trace amounts. The conjugated estrogens in milk are also contained in the nonfat solids component.

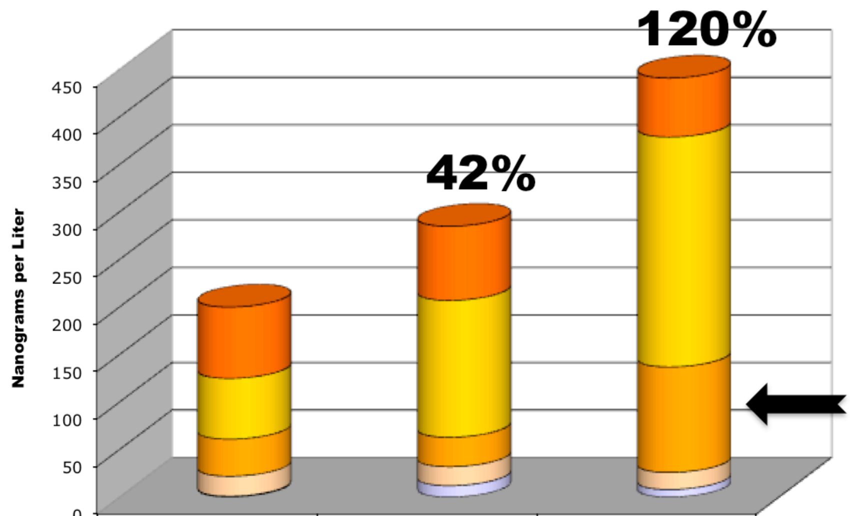
When raw milk comes into the processing plant it is: Clarified, Separated, Standardized, Pasteurized, Homogenized and Vitamin D fortified. Separation involves running a portion of the raw milk through a machine called a separator, which separates the milk into cream and skim. 10 pounds of raw milk yields about 1 pound of cream and 9 pounds of skim.

Standardization involves adding that separated skim back to the raw milk to reduce the fat percentage in the raw milk to that mandated by the government's standards of identity for whole and reduced fat milk.



You may be thinking, as I originally did, that to make low fat milk, for example, processors simply remove some of the fat from the raw milk. But this is not how it's done. Instead the processor adds 334 pounds of the separated skim back to every 100 pounds of raw milk to dilute the fat percentage down from 3.7% in the raw milk to the required 1% in the low fat milk. So low fat milk is 77% skim and skim has the highest hormone concentrations as we'll see on the next slide, because as the percentage fat goes down in milk, the percentage nonfat solids, which contains the conjugated estrogens and IGF-1, goes up. Therefore reduced fat milk will have higher hormone concentrations relative to whole milk.

Reduced fat milk has more estrogen



	Whole	2%	Skim
Estrone	75	78	62
2-Hydroxy Estrone	64	144	242
4-Hydroxy Estrone	39	31	111
Estradiol	21	20	18
2-Hydroxy Estradiol	1	12	8

The National Cancer Institute's Proteomics Lab developed a procedure to measure 16 different estrogen metabolites in human blood samples, and recently measured the same estrogen metabolites in store bought whole and reduced fat milk. The results were published in 2009. They found 11 of these 16 human estrogens in cow milk. Here I'm just showing the most harmful conjugated estrogens because these are the ones that when taken orally through milk consumption are more readily absorbed into our bloodstream.

In the table beneath the graph I have listed the names of the estrogens on the left, and across the top, the type of milk that was analyzed. Each of the colors in the columns signifies a different type of conjugated estrogen. The top 3, which are the most prevalent, are the conjugated estrones and the bottom 2 are conjugated forms of estradiol.

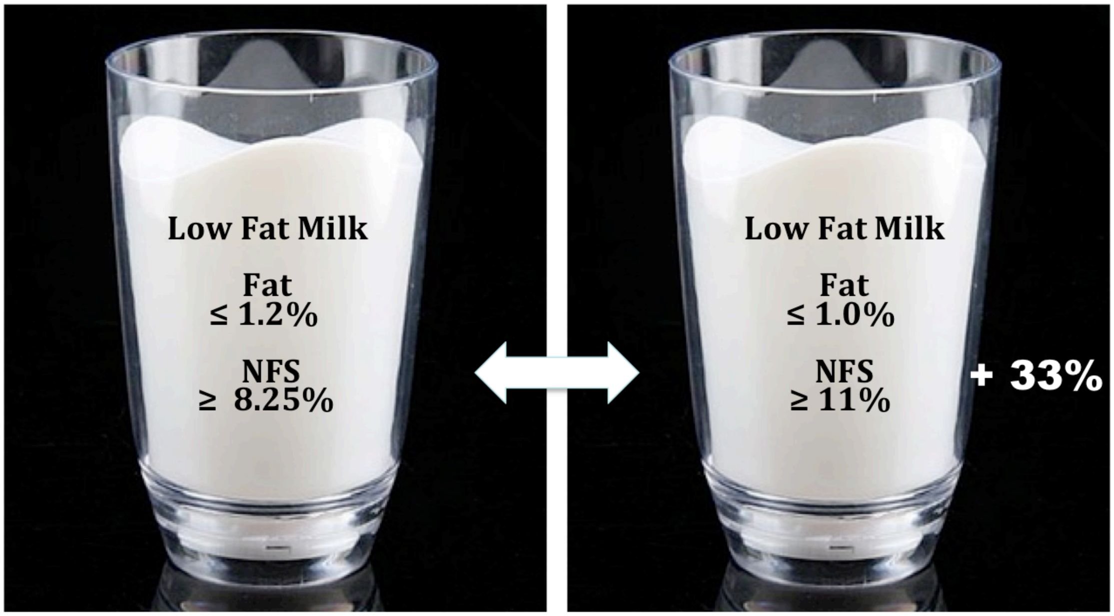
As you can see by the height of the columns alone, 2% reduced fat milk contains substantially more conjugated estrogens than whole milk, 42% more and skim milk contains the highest conjugated estrogen concentration, 120% more. The area of the columns that the arrow is pointing to is 4-hydroxy estrone. This estrogen metabolite has the potential to cause DNA mutations.[2]

[1]Farlow DW, Xu X, Veenstra TD. Quantitative measurement of endogenous estrogen metabolites, risk factors for development of breast cancer, in commercial milk products by LC-MS/MS. J Chromtogr- Biomed. 2009;877(13): 1327-1334.

[2]Cavalieri E, Rogan E. Catechol quinones of estrogens in the initiation of breast, prostate, and other human cancers: keynote lecture. Ann NY acad Sci 2006;1089:286-301.

Standards of Identity

Federal **California**

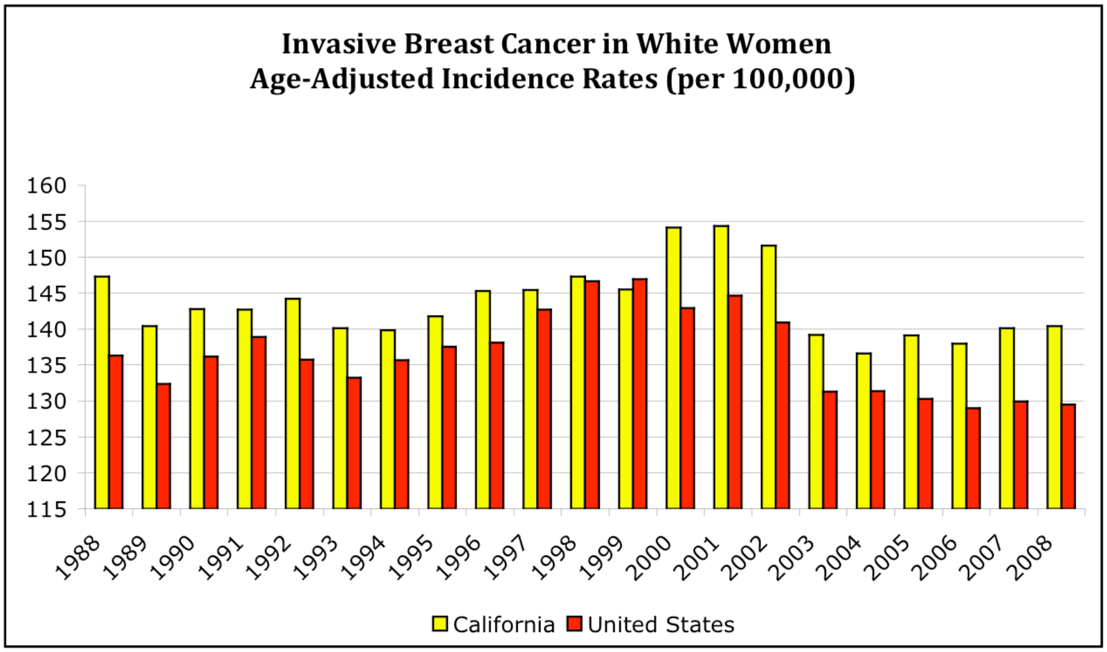


The standards of identity for fluid milk refer to the percentage fat and nonfat solids that must be present in the milk that is sold in interstate commerce and is regulated by the federal government. In 1962 California established different standards of identity and is the only state to have done so. If we compare the federal and California standards for low fat milk, shown here, we see that there is little difference in the required fat content, but a large difference in the required nonfat solids content, and this is true for every type of milk sold in California; whole, reduced fat, low fat and skim all contain more nonfat solids.

To meet the California standard, processors add an additional 9 pounds of condensed skim (containing 33% nonfat solids) to increase the percentage nonfat solids in the low fat milk up to 11%. The addition of 9 pounds of condensed skim may not seem like much, but this is skim that has been highly concentrated by a factor of four. Therefore California low fat milk can contain up to 33% more nonfat solids if we compare it to milk that meets the minimum federal standards. And reduced fat milk can contain up to 21% more nonfat solids than in the rest of the country.

And why do I bring this to your attention? Because, the conjugated estrogens and the IGF-1 in milk are in the nonfat solids component. Therefore in California, low fat milk can have up to 33%, reduced-fat (2%) milk up to 21%, and skim up to 9% higher estrogen and IGF-1 concentrations than in the rest of the country.

Are higher hormone concentrations in California milk contributing to higher breast cancer incidence?



These columns compare the age-adjusted breast cancer incidence rates among white women in California (shown in yellow) against the US national incidence rates (shown in red) in the twenty year period between 1988 and 2008. As you can see breast cancer incidence in California white women exceeds the rate among US white women as a whole.[1, 2] The same is true for ovarian cancer incidence, but I did not find this to be the case for prostate cancer incidence.

In 1997 Harvard epidemiologists reported that among the 120,000 female nurses across the nation enrolled in the Nurses Health Study, postmenopausal women residing in California had a relative risk of developing breast cancer between 1976 and 1990 that was 24% higher than women residing elsewhere. They also reported that women residing in California were more likely to delay childbearing, had slightly fewer children, were more likely to use oral contraception and hormone replacement therapy, to use mammographic screening, and to consume alcohol. After adjusting for age and these established risk factors, the relative risk for breast cancer among California women still exceeded the rest of the nation by 18%. This increased risk was apparent in both the northern and southern halves of the state.[3] This raises an important research question, which has yet to be addressed. Are the increased hormone concentrations in the milk sold in California contributing to higher breast and other cancer rates in California residents?

[1]Howlader N, Noone AM, Krapcho M et al. (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD http://seer.cancer.gov

[2]California Cancer Registry, http://www.ccrcal.org/pdf/AnnualReport/1988-2008_BREAST.pdf

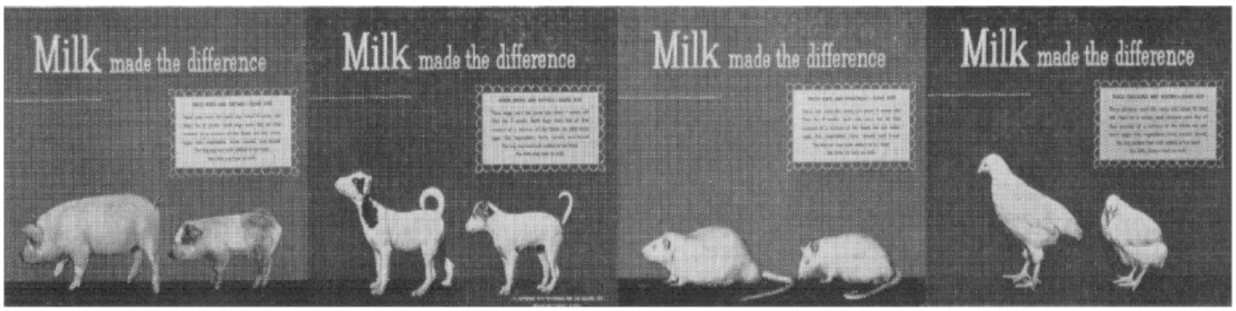
[3]Laden F, Spiegelman D, Neas LM et al. Geographic variation in breast cancer incidence rates in a cohort of U. S. women. J Natl Cancer Inst 1997;89:1373-78.

Now let's take a look at how much dairy – as a nation – we've been consuming in the past 100 years. First we'll look at beverage milk, and then we'll compare combined cheese and milk consumption patterns with breast cancer incidence during the 20th century.

NATIONAL DAIRY COUNCIL

ELMER VERNER McCOLLUM

"Powerful interests
managed to use conclusions
from McCollum's photographs of fat and scrawny mice
to have milk, previously regarded as essential for infants,
… come to be seen as an essential drink for all."

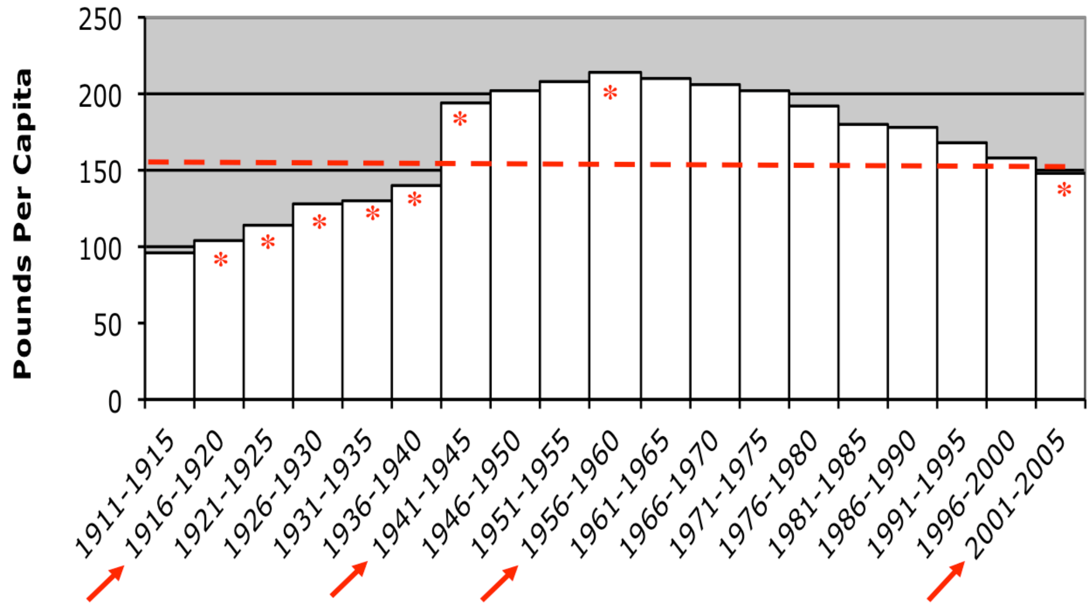


I'd like to begin by reading this quote from the historian, Harvey Levenstein that I came across while researching how we became a nation of milk drinkers.[1] Levenstein is talking about this guy, Elmer Verner McCollum. He was an early 20th century nutrition researcher at Johns Hopkins who came to believe from his experiments feeding cow milk to other animals who then grew bigger, faster, that humans too would benefit from cow milk consumption. In 1918 he published a book called the Newer Knowledge of Nutrition and it became quite popular. In that same year he gave an address before dairymen in Chicago in which he strongly advocated for increased milk consumption as a way to improve the health and vitality of both children and adults.

The National Dairy Council had just been formed a few years before with the express purpose of increasing milk demand because all of the major cities were beginning to mandate pasteurization, which required costly new equipment. And the production capacity for canned milk had been ramped up at the onset of WW I because canned milk was exported as field rations to British and American troops. There was an anticipated need to fill excess capacity when the war ended. So the National Dairy Council latched onto McCollum and his fat and scrawny mice, to create the first of what would be hundreds of marketing campaigns in the years to come. This campaign was called, "Milk made the difference" and hundreds of thousands of brochures were printed and distributed to schools, doctor's offices, and hospitals to promote milk. The caption reads: these animals are sisters; at 4 weeks they were the same size. Then for 6 weeks the bigger animal was given milk with her food and the little animal had none.[2] Thus began America's passion for milk and growth.

[1]Levenstein, Harvey. Revolution at the Table: the Transformation of the American Diet. Oxford University Press NY 1988:154.
[2]Anderson, ZE J Dairy Sci 1960; 43: 1672

Beverage milk sales doubled during the 1st half of the 20th century



These columns represent the average beverage milk sales over each five- year period beginning with 1911 and ending with 2005. The red arrow at the bottom indicates the start of the National Dairy Council's efforts, which were quite successful. Over the next 25 years sales rose by 44 pounds per capita.

But nothing could have helped the industry along more than the effect of WWII. In the next five years alone, milk sales jumped another 54 pounds per capita due to the rationing of meat during the war years.

Milk sales continued to grow over the next 15 years and peaked around 1960 when competition from fruit juice, soda pop, bottled water and other factors began to have an impact. From that point on there's been a slow and steady decline.

But sales in 2005 were still above the pre-WWII years and about 60 pounds per capita above where we started the century.

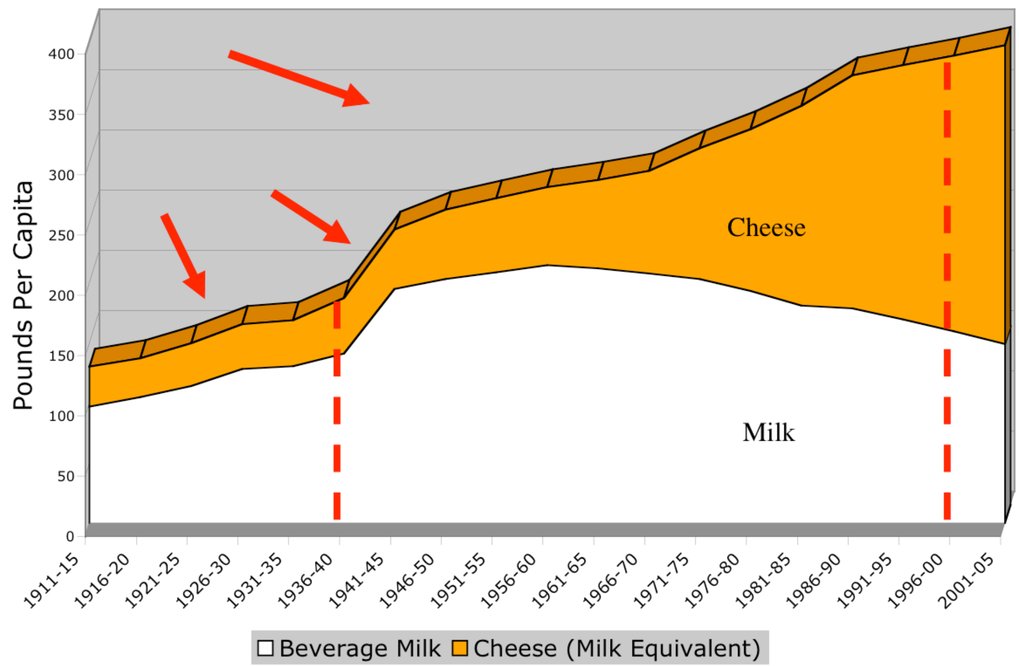
Source: USDA -Economic Research Service data

Reduced fat milk has more hormones

Along with declining sales, our exposure to the hormones in milk would likewise have declined if it weren't for the fact that reduced fat milk became increasingly more popular beginning in the late 60's early 70's. In fact, by the end of the century we were consuming 2.5 times more reduced fat milk than whole, which as I've shown you, contains substantially higher estrogen and IGF-1 concentrations.

Source: USDA -Economic Research Service data

Milk plus cheese consumption more than doubled in the 20th century



But we don't just consume milk, we also consume other dairy products.

It takes 10 pounds of milk to make 1 pound of cheese. So cheese is a 10 to 1 concentrate of the fat and proteins in milk.

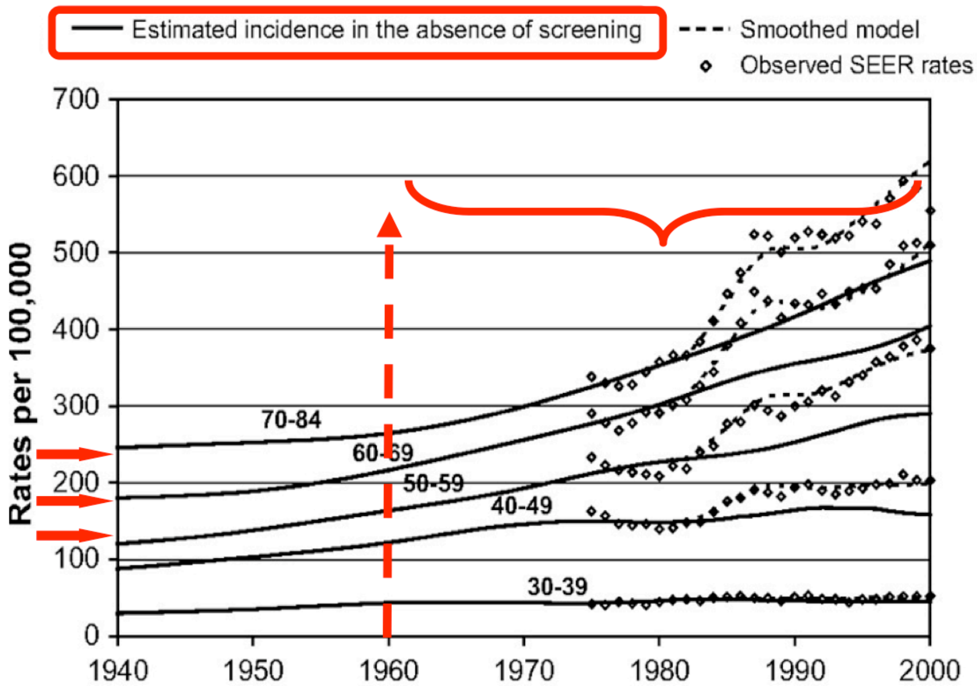
Here I've combined milk and cheese (on a milk equivalent basis), to show you the clearly positive trend in their combined consumption. As you can see based on cheese and milk alone, our dairy consumption more than doubled over the course of the century.

In the next slide I'm going to show you breast cancer incidence rates between 1940, when the state of Connecticut first began to keep track of breast cancer diagnoses, and the end of the century. The reason I'm not showing prostate cancer incidence trends is because we didn't start keeping track of those rates until several decades later.

I want you to remember 2 things: that the combined consumption of milk and cheese was steadily increasing before 1940 and that there was a huge jump in consumption between 1941 and 1945.

Source: USDA -Economic Research Service data

Dairy consumption preceded the rise in breast cancer rates



This graph is a little busy so bear with me as I walk you through it. We're only concerned with the solid black lines that have been adjusted to exclude the effect of screening by mammography beginning in the 1970's. And only the top three lines because these represent breast cancer incidence rates in postmenopausal women in whom the vast majority of breast cancers occur.[1]

In women aged 70 to 84 the rate doubled by the end of the century. And in the next 2 younger age groups, women aged 60 to 69, and 50 to 59 the rates **more** than doubled over the same time period. So during the 20th century, even when we exclude the effect of screening which increased the rate of diagnoses, breast cancer incidence in post-menopausal women doubled, along with their dairy consumption.

Now I want to draw your attention to the difference in the slope of the curves before and after 1960. In 70 to 84 year old women the curve was essentially flat before 1960 and then the rates accelerated quite rapidly. Whereas in the younger women, the acceleration appears to begin about 5 or so years earlier. Remember that milk and cheese consumption was steadily rising before 1940 and that there was a huge, 54 pound per person, jump between 1941 and 1945. Well, 15 years later, about the amount of time it takes breast tumors to grow to a detectable size, breast cancer incidence took off. This was around 1960. Generally, breast tumors grow more aggressively in younger women, and this may explain the earlier acceleration in breast cancer rates among women in the 2 younger age groups.

I believe that the increasing hormone concentrations in commercial milk due to the production changes I've mentioned and our increasing consumption of reduced fat milk fueled the continuing rise in incidence after 1960.

[1]Holford, T et al. J Natl Cancer Inst Monogr 2006;36:19-25

Milk and milk products feed cancer growth

In conclusion,

- ◆ Estrogen and IGF-1 are critical hormones that act synergistically to promote the growth and progression of breast and prostate tumors.
- ◆ Milk is the **only** environmental substance that simultaneously exposes us to both of these hormones.
- ◆ Industry production and processing changes during the 20th century increased the concentrations of these hormones in milk.
- ◆ Year-round, lifelong milk consumption is a phenomenon that began in the 20th century and preceded rising breast and prostate cancer rates.

Is there a link between dairy and cancer?

My answer, based on 12 years of study of the published, peer-reviewed scientific literature, is an unequivocal YES.

Thank you for your attention