Journal of Dairy Research

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Oestrogens in milk and breast cancer: a cause for concern…or not?

Malcolm Peaker

13 Upper Crofts, Ayr KA7 4QX, UK

Abstract

In this short Research Reflection I address and refute the suggestion that oestrogens consumed in milk might contribute in a significant way to endogenous levels and thereby have a physiological action, possibly resulting in adverse consequences including increased breast cancer risk. Quantitative analysis based on published data shows that, even in worst case scenarios, oestrogen consumption in milk is considerably less than regulatory bodies regard as entirely safe.

Research Reflection

Cite this article: Peaker M (2020). Oestrogens in milk and breast cancer: a cause for concern…or not? *Journal of Dairy Research* **87**, 266–269. https://doi.org/10.1017/S0022029920000370

Received: 20 March 2020
Accepted: 7 April 2020

Keywords:
Breast cancer risk; milk consumption; steroids

Author for correspondence:
Malcolm Peaker,
Email: malcolm.peaker@icloud.com

Oestrogens in milk

Certain topics emerge time and time again both in the scientific literature and in the news media long after seemingly definitive conclusions had been reached. Because of their news value, especially to those outlets feeding public anxiety on health, such stories can assume an importance out of all proportion to the validity or novelty of each new claim. In this age of uninformed opinion those reports can be further amplified on social media and taken up by activists for various causes as well as by conspiracy theorists throughout the world.

Ever since oestrogens were detected in cows' milk in the 1970s there has been concern that they could affect consumers of milk and dairy products, especially given the known effects of oestrogens in promoting mammary tumour growth and on male fertility. Even though any material effects of drinking milk on the oestrogen economy of the female body appeared to have been allayed by a considerable amount of evidence such that governmental food-safety bodies have found no cause to intervene, the interest in 2020 came as a result of another epidemiological study on diet and the incidence of breast cancer.

The study in question was on 52 795 women aged 30 and older (mean 57) recruited from members of the Seventh Day Adventist Church in North America between 2002 and 2007 (Fraser *et al.*, 2020). Adherents of this creed place an emphasis on diet and health. This is how the authors of the paper describe their cohort:

> *…Nearly 40% are strict (no meats, eggs, dairy) or lacto-ovo-vegetarians (eggs and dairy allowed) who often consume soy as a protein source and obtain most dietary calcium (79.6%) from non-dairy sources. Half of the cohort averages nearly 68 g of soy foods eaten daily, compared with 2 g/day in men and about 3 g/d in women living in 10 European countries. About 8% of the [study] population consume no dairy and the lacto-ovo-vegetarians are low-dairy (mean, 60% of US levels), but about 50% consume as much as other Americans.*

The aim of the study was to separate any effects of soy (possibly protective) from any effects of dairy (possibly promotive) on the incidence of breast cancer. The diet of each participant was estimated by a Food Frequency Questionnaire at the start of the study. During the follow-up period 1057 new cases of breast cancer were detected (i.e. in 2% of subjects); 906 post-menopausal and 121 pre-menopausal, after an average of 7.9 years of follow-up.

While no clear association emerged from the statistical analysis between the intake of soya products, a positive association was obtained between the intake of calories from dairy products generally and of dairy milk with breast cancer. Similar sized associations were found in pre- and post-menopausal women. Cheese and yoghurt produced no positive associations while there was no difference between full-fat and fat-reduced milks.

The positive association between milk intake and breast cancer was present at what would seem to be low levels of milk consumption, with an initial steep and then a less-steep rise in risk from a point equivalent to about 150 ml whole milk per day. Overall, over the range of the 90th to 10th percentiles of intake the hazard ratios were 1.22 for dairy calories and 1.50 for dairy milk.

The authors, from the Adventists' Loma Linda University concluded:

> *In conclusion, we observe a potentially important positive association between dairy (especially milk) consumption and risk of breast cancer. Comparing medians of extreme dairy milk intake quintiles, risk at the higher intake was greater by 50% (uncalibrated analyses) and more than doubled in calibrated analyses.*

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> *There was an especially strong rise in risk up to 2/3 of an 8 ounce cup of milk* [157 ml] *(about 100 kcals of full-fat milk) per day, possibly less easy to demonstrate in other populations where fewer subjects consume dairy in this relatively low intake range. Hence, data from this US Adventist, but otherwise diverse, population, suggest that either dairy milk or some closely-related unidentified factor(s) increases the risk of breast cancer.*

The Fraser *et al.* (2020) paper contains a section entitled Key Messages, presumably aimed at drawing attention to the views the authors wish to have promulgated. The final bullet point reads:

> *This evidence that a frequently consumed product, dairy milk, is associated with increased risk of a common cancer is noteworthy, as plausible causal hypotheses have already been raised by others on biological grounds.*

Before examining whether that claim of 'plausible causal hypotheses' can be justified, it is worth reporting, in these days of science by press release or social media attention, some of the comments attributed to the first author (Anon, 2020*a* and 2020*b*):

> *…the observational study gives 'fairly strong evidence that either dairy milk or some other factor closely related to drinking dairy milk is a cause of breast cancer in women'. 'Consuming as little as 1/4 to 1/3 cup of dairy milk per day was associated with an increased risk of breast cancer of 30%' Fraser said. 'By drinking up to one cup per day, the associated risk went up to 50%, and for those drinking two to three cups per day, the risk increased further to 70% to 80%'.*

The present author is entirely unqualified to comment on the validity of the Fraser *et al.* (2020) epidemiological study, either in methodology or in interpretation. However, it should be pointed out that other work has found no effect of the intake of milk and dairy products on the incidence of breast cancer or that any association before the menopause, was in the negative direction. Others have found associations for particular milk products. Therefore, the only possible inference one can draw is that one or more of the associations found in these various papers is invalid.

In the paper and in the press statement, Fraser *et al.* (2020) suggest 'bovine sex hormones' and 'endogenous serum IGF-1' levels as 'two possible mediating agents in a dairy milk breast cancer link'. I will restrict this commentary to any significance of oestrogens in milk. Since the 1970s there has been a steady stream of original papers (some, sadly, merely repetitive), reviews (of variable quality) and commentaries (of even more variable quality) on the topic. Because of this plethora I will not, therefore, give detailed references in the discussion that follows but simply mention here a list of reviews that provide references plus the other sources I have used (Hamon *et al.*, 1981; Hamon *et al.*, 1990; Heap and Hamon, 1979; Heap *et al.*, 1983; Heap *et al.*, 1984; Heap *et al.*, 1986; Janowski *et al.*, 2002; Kuhl, 2005; Parodi, 2012; Peaker and Neville, 1991; Peaker and Taylor, 1990; Snoj and Majdič, 2018).

A key feature of dairying systems is that the dairy cow is for part of the year both lactating and pregnant. As pregnancy advances oestrogens appear in milk. The unconjugated oestrogens 17β-oestradiol and oestrone are at similar concentrations to those in maternal plasma, however, the major oestrogen in milk is oestrone sulphate, produced by the gravid uterus, which is concentrated in milk compared to arterial blood. It is secreted along with major milk proteins and lactose by the Golgi vesicle route. Milk for human consumption avoids a short period in very late gestation (cows are 'dry' at this stage) when the mammary gland itself produces oestrogens *de novo*.

On qualitative grounds, it is very easy to erect 'plausible hypotheses' linking oestrogens in milk to breast cancer. Oestrone sulphate taken orally has oestrogenic properties in women; it is or was a common means of administering therapeutic doses of oestrogen. Ingested oestrogens hitch a ride on an enterohepatic cycle of oestrogen metabolism. Endogenous oestrogen metabolites are secreted into bile and are then partly reabsorbed from the intestine. Oestrone sulphate is absorbed from the gut intact while metabolism to more active forms by sulphatases occurs in a number of organs. Although oestrone has one-tenth of the biological activity of 17β-oestradiol, conversion of the former to the latter can occur to form an equilibrium between the two in the presence of the enzyme 17β-hydroxysteroid oxidoreductase. That enzyme is expressed primarily in the ovaries and placenta but also in the mammary epithelium. Therefore, both systemically and locally, oestrone sulphate can be converted to oestrone and oestradiol.

For consumers of milk one obvious question is whether oestrogens are destroyed by processing and/or conversion into dairy products. Only small changes have been found after pasteurisation, homogenisation or souring and some methods of sterilisation. By contrast, no oestrone sulphate was found in UHT milk or in dried baby 'formula'. I will not discuss dairy products further since the stimulus for the present commentary was the quantity of liquid milk consumed.

Since the oil-water partition coefficients of free oestrogens are in the oil direction and that of oestrone sulphate is towards water, concentrations in milk fat compared with the aqueous phase of milk reflect those differences. Similarly, high fat dairy products have greater concentrations of free oestrogens. It was because there was no apparent difference in the incidence of breast cancer between full-fat milk and fat-reduced milk consumption that Fraser *et al.* (2020) sought an explanation for a cancer-promoting substance in the aqueous phase.

Therefore, all evidence indicates that the oestrone sulphate, together with the very low concentrations of oestrone and 17β-oestradiol, in milk must be considered as a source of biologically active oestrogens in those ingesting that milk. However, when the quantitative aspects of oestrogen absorption from milk were compared to endogenous oestrogen production that 'plausible' hypothesis (of a link between milk oestrogens and breast cancer) fell apart. The important question for any quantitative calculation is: what is the concentration of oestrone sulphate (and free oestrogens) in milk actually consumed by the consumer? The volume of milk produced and the concentration of oestrogens of all types varies in individual cows with stage of lactation and stage of pregnancy. Depending on the calving pattern of a herd as a whole, the concentrations of oestrogens in the bulk milk leaving the farm each day may vary throughout the year. Similarly, the milk reaching the consumer, gathered from farms across a region, will have varying concentrations.

There have been a number of studies over the past forty years or so on individual cows in different countries but astonishingly few analyses of milk at the point of sale. Taking the few data, oestrone sulphate was in the range 130–500 pg/ml, oestrone 8–20 pg/ml and 17β-oestradiol 5–21 pg/ml. Milks from individual cows in the U.S.A. were found by Macrina *et al.* (2012) to have lower concentrations of oestrone sulphate than those reported by earlier authors. Whether the lower values were related to differences in

https://doi.org/10.1017/S0022029920000370 Published online by Cambridge University Press

analytical methodology or to the fact that the highly-bred, rbGH-treated Holstein cows had markedly higher milk yields than, say, the Jersey cows used in the original UK studies, is not known. But, as will be seen below, these differences in concentration make little or no material difference when the quantity of oestrogen consumed in milk is compared with the quantity of endogenous oestrogen produced each day.

Assuming that all the oestrogens in milk enter the peripheral circulation, there have been several comparisons of this exogenous supply with the endogenous production rate determined by isotope kinetic measurements in human subjects. Some calculations have appeared in the literature; others have been done in confidential reports to industry or regulatory bodies in various countries. I will give two examples:

Macrina *et al.* (2012) calculated, using American measures, that the oestrogens in three servings of whole milk (a total of 710 ml) represent only 0.01–0.1% of the daily endogenous production rates for prepubertal girls and boys, women and men.

In view of the claim of Fraser *et al.* (2020) that 157 ml of milk per day has an effect on the chances of developing breast cancer, I have recalculated the Macrina *et al.* (2012) figures accordingly. However, to produce a worst-case scenario of oestrogen action, I have assumed that all the oestrone and oestrone sulphate is converted to the 10× more biologically active 17β-oestradiol. Thus, in this worst-case scenario, the total oestrogen concentration in milk is expressed as 17β-oestradiol equivalents, in other words as an index of oestrogenic activity. Using the lowest recorded daily production rate of 17β-oestradiol (30 µg/d), that is in premenopausal women in the early follicular phase of the menstrual cycle (and ignoring the production of oestrone, again for a worst-case scenario), the supply in milk then represents 0.01% of daily endogenous production. That percentage will be even lower at other stages of the menstrual cycle where endogenous production rates of 17β-oestradiol may be up to 21 times higher. For post-menopausal women, the corresponding figure is 0.017%.

Using the same approach I have taken the highest concentration (500 pg/ml) of oestrone sulphate recorded for commercial dairy milk, that obtained at the start of these studies in the late 1970s in Cambridgeshire, UK. For the early follicular phase of the cycle 157 ml would, and again assuming total conversion to 17β-oestradiol and ignoring endogenous oestrone production as a worst-case scenario, represent 0.03% of daily production. For post-menopausal women the figure is 0.05%. Once again, I reiterate that all of these figures are worst-case.

Figures for oestrogens entering the circulation are an underestimate of oestrogen action in post-menopausal women, for whom extragonadal sites of oestrogen production with local action is the norm. Simpson (2003), for example, showed that in a breast tumour oestrogen concentrations are an order of magnitude higher than in the peripheral circulation. The addition of minute quantities of oestrogen from ingested milk is thus even less likely to have any effect.

It is because the maximum contribution of oestrogens in milk to total oestrogen production in the consumer, whether it be prepubertal children, men or women at all stages of life, is so low that regulatory and advisory bodies do not consider oestrogens in milk to be of any risk to health or development. For example Macrina *et al.* (2012) wrote of their calculation: '*This is below* [*US*] *FDA guidelines, which state that no physiological effects occur when consumption is <1% of the endogenous quantities produced by the segment of the population with the lowest daily production*'.

Drinking a litre of milk per day would only raise the contribution of milk oestrogens to <0.35% of total oestrogen production, again, to stress, with worst-case scenario calculations. Drinking 3–12 l of milk per day would be needed (depending on the range of concentrations recorded in commercial milk supplies) to exceed the 1% guideline of the FDA. Another way of putting the contribution from milk in perspective is to consider the contribution of oestrogens in milk to the total amount circulating in extracellular fluid. Using 17β-oestradiol equivalents as above, the maximum contribution from 157 ml would be 2% in those women with the lowest oestrogen concentrations in the circulation, i.e. those taking the contraceptive pill who are in the anovulatory phase of the cycle.

The same considerations apply to progesterone (which with oestrogen causes mammary cell proliferation), present mainly in the milk fat fraction. Taking reported concentrations of progesterone in milk, 157 ml would represent 0.012% of endogenous progesterone production at the stage of the menstrual cycle when production is at a minimum, falling to 0.08% in the pre-ovulatory phase and 0.001% in the mid-luteal phase. Even if all milk supplied to the consumer came from pregnant cows, the corresponding figures would be 0.34, 0.23 and 0.03%

Can the view that oestrogens and progesterone in milk have no material effect on women consuming milk be challenged on other grounds? After all, hormones are not nutrients and their intake cannot necessarily be treated in the same way. Endocrinology is a matter of concentrations, of pulsatile or steady rates of secretion, of receptor affinities, of receptor recycling and of duration of response to activation. I can, though, envisage no means by which oestrogens from milk could, in the face of overwhelming endogenous production, interfere in any of these processes. But is there any way, so far overlooked, whereby oestrogens from milk could influence the endogenous oestrogen economy of women or any target organ? The reader may now have noticed that this field of research is distinctly lacking in direct experimental evidence. Furthermore, and regrettably, some experimental evidence is not useful in the present context, for example, those that show the biological activity of oestrogens in milk on mammary development in rodents or in organ culture. It is all a question of quantity. After all, almonds contain very small quantities of cyanide but we do not treat the consumption of a single nut as harmful.

The dearth of direct experimental evidence persists despite there being a direct test possible for the hypothesis that oestrogens in milk are absorbed and have an effect on the concentrations of endogenous oestrogens in blood. One longer-term study, in Japan, on two individuals has been interpreted in that manner. However, a quantitatively important uptake of oestrogens cannot be inferred since it is possible that the macronutrients in milk do, with time, lead to an increase in endogenous oestrogen concentrations in individuals with low dietary energy and protein intakes.

As might be expected from the vast amount of research on oral contraceptives and on hormone replacement therapy, there is a great deal of information available on the time-course of concentrations in blood of a variety of oestrogens and progestogens after oral administration of pharmacological doses. Similar studies could be done after the ingestion of milk and/or milk containing oestrogens tagged with stable isotopes. Human nutrition has the reputation as a weak scientific field. One of the reasons is that it is often impossible to perform definitive studies on human subjects. But when a hypothesis that could be tested does emerge from the seemingly endless and contradictory epidemiological

https://doi.org/10.1017/S0022029920000370 Published online by Cambridge University Press

studies, should not those organisations which fund such work use their resources to commission those experiments?

On a final note, any attempt to link the presence of biologically active substances in milk to an effect in those ingesting the milk, whether a mother's own young or the consumers of dairy milk and products, is fraught with difficulty. In an attempt to put some sort of perspective on the many and often fanciful claims in the case of the former, Peggy Neville and I proposed nearly 30 years ago a set of criteria that must be met in order for a proposed effect in the mother's own young to be valid. Simple modifications to those criteria, with enforcement by referees and editors, for the consumption of dairy or other food products that contain biologically active substances might prevent the publication of 'plausible hypotheses' that become highly implausible when exposed to the harsh light of quantitative analysis and direct experiment.

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