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He Y, Tao Q, Zhou F, Si Y, Fu R, Xu B, Xu J, Li X, Chen B. The relationship between dairy products intake and breast cancer incidence: a meta-analysis of observational studies. BMC Cancer. 2021;21(1):1109.

What We Know, Think We Know, or Are Starting to Know

Breast cancer will affect 1 in 7 women in the UK in their lifetime, and is the most common cancer type in the population, accounting for 15% of all cancer cases each year [(1)]. Obviously from the foregoing stats, it is the most common cancer in women, averaging 150 diagnoses every day [(1)]. Breast cancer risk is influenced by several factors, including age, genetics, estrogen-receptor status, and menopausal status.

With any cancer type, my default position is to tread carefully with placing nutrition on too much of a pedestal. This is not to downplay the effects of diet, but to place it above the factors listed above would be to grossly overestimate the role of nutrition in determining any cancer outcome [(2)]. Nevertheless, diet may certainly interact with those factors to influence the overall risk profile, and should be considered within the risk equation.

A battleground in the conversation regarding nutrition and cancer has been dairy. You' ve probably seen the critically illiterate Netlfix documentaries, the hyperbole over IGF-1, the claims about hormones, puss, etc. Needless to say this isn' t exactly a scientific conversation, whether documentaries wheel David Katz out on screen or not.

Most people are genuinely surprised when the hyperbole is removed, and a number of cohorts have found that higher dairy intakes are associated with lower breast cancer risk in premenopausal and postmenopausal women [(3-6)]. These effects may also depend on other important factors, specifically oestrogen and progesterone receptor status [(3-6)]. It has also been clear that the associations are most persistent for low-fat dairy, rather than full-fat dairy.

So we have potential modifying effects of diary type [low fat vs. full fat], menopausal status, and other variables which appear to influence associations between dairy consumption and breast cancer risk. The present study, published this week, is the most recent meta-analysis of observational studies on dairy intake and breast cancer.

The Study

The researchers conducted a search of studies published up to January 2021, with the following inclusion criteria:

- The study was a prospective cohort study or clinical case-control study in design;
- The main exposure of interest in the primary study was dairy foods;
- The main outcome of interest in the primary study was breast cancer [BC];
- The primary study reported hazard ratios and corresponding 95% confidence intervals [CI].

The primary aim of the study was to evaluate the effects of all dairy products. Secondary aims explored the effects of different dairy food forms: fermented [yogurts, cheese] vs. non-fermented, and high-fat vs. low fat.

*Geek Box: Case-Control Study

Prospective cohort studies take a cohort of people from the population, and follow them prospectively, i.e., over time. The advantage to this design is that exposures - like diet, smoking, etc. - can be assessed before a disease develops in the participants, and this reduces the potential for recall bias. Another advantage of prospective cohort studies is the potential sample size, which can range into the thousands to hundreds of thousands of participants. However, this comes with a potential disadvantage in terms of gathering more granular detail regarding exposures and participant characteristics, which would be prohibitively expensive to do with a cohort of, for example, >100,000 people. To navigate this potential hurdle, some additional study designs have been used, in particular case-control study designs. In a case-control design, several healthy participants are selected as controls for each case of an outcome, e.g., each case of a disease that has diagnosed. In this design, the researchers identify cases of their outcome of interest - we'll stick with breast cancer as our example - that have already occurred, or as they occur if the parent study is a prospective cohort, and then select up to 4 to 5 healthy controls to match with a case of BC. Ideally, they will seek controls who have a similar risk profile to the cases of BC, only the controls do not have the diagnoses itself. For example, if premenopausal BC was the outcome of interest, the researchers would want to have the controls also be premenopausal women. The case-control study would then compare, for example, dietary intake or estrogen-receptor status in the healthy controls vs. the BC cases. While case-control studies have some advantages, they can face some logistical hurdles, in particular if more than one disease outcome is of interest - which is common in prospective cohort studies - then it can be highly inefficient, as each case of each different disease would require its own set of healthy controls to be matched with. In addition, they require careful statistical analysis and adjustment for relevant confounders to make the comparison between cases and controls as equivocal as possible. However, case-control designs have the advantage of lower cost and more efficiency in execution, particularly where the outcome of interest is a single disease endpoint.

Results: A total of 36 studies were included in the analysis, 14 of which were prospective cohort studies and 22 of which were case-control studies. In the cohort studies, there were a total of 912,975 participants and 25,097 cases of BC. In the case-control studies, there were a total of 106,257 participants and 18,543 cases of BC.

- ***Total Dairy Intake*:** Compared to the no/rare dairy intake, total dairy consumption was associated with a 5% [HR 0.95, 95% CI 0.91 – 0.99] lower BC risk. There was no significant association when analysed by menopausal status. However, total dairy intake was associated with significantly lower risk in hormone-receptor-positive BC; 21% [HR 0.79, 95% CI 0.68 – 0.92] lower for estrogen-receptor-positive [ER+] and 25% [HR 0.75, 95% CI 0.58 – 0.97] for progesterone-receptor-positive [PR+] [more under ***Interesting Finding***, below].
- ***Fermented vs. Non-Fermented Dairy*:** Fermented dairy foods were associated with a statistically significant 4% [HR 0.96, 95% CI 0.93 – 0.99] lower BC risk in postmenopausal women only. There were no other significant effects of fermented dairy on premenopausal BC risk, or modification by hormone-receptor type. There were no significant associations for non-fermented dairy in any population.
- ***High-Fat vs. Low-Fat Dairy*:** Total high-fat dairy consumption was associated with a 6% [HR 1.06, 95% CI 1.00 – 1.13] increase in BC risk in women overall, but there was no association when analysed according to menopausal status. Low-fat dairy product consumption was not associated with BC risk in women overall, however in premenopausal women low-fat dairy was associated with a statistically significant 6% [HR 0.94, 95% CI 0.89 – 1.00] lower BC risk.

The Critical Breakdown

Pros: The analysis included studies published up to January of this year makes this the most recent synthesis of the evidence on this issue. The study used the Newcastle-Ottawa Quality Assessment Scale (NOS) checklist, a straightforward, convenient grading tool to assess the quality of non-randomised trials included in a meta-analysis. The cohorts were well distributed between Europe [*n* = 13], North America [*n* = 11], and Asia [*n* = 9]. The total study sample had an enormous number of participants and cases of BC, strengthening the ability to detect associations and have meaningful subgroup comparisons [i.e., high-fat vs. low-fat dairy]. The study conducted a number of relevant subgroup analyses on factors like menopausal status, estrogen-receptor and progesterone-receptor status, and dairy food type.

Cons: The study doesn' t state how the exposure of interest was quantified, i.e., presuming it was a highest vs. lowest comparison but, in fact it appears the exposure was defined dichotomously, i.e., "consume dairy" vs. "don' t/rarely consume dairy". This is shoddy, and gives us no indication of dose-responses or levels of intake. It leaves us with a very poorly defined exposure, which is never helpful in either observational research or intervention studies. The majority of studies included in the meta-analysis were case-control studies, which are more prone to recall bias than prospective studies [which measure diet *before* the onset of disease, thus limiting the potential for retrospective bias]. The authors refer to the included studies as "clinical trials", despite the analysis clearly being confined to observation research. They do not, inexplicably, present their analyses in funnel plots – just a table of the subgroup analyses. So we don' t know which studies contributed to statistical weight, etc. How this got past peer review without a funnel plot is anyone' s guess.

Key Characteristic

The study looked at key potential moderating factors which had previously been observed in the research on diet and BC, in particular the type of dairy and menopausal status. These analyses were had large sample sizes for these comparisons. For example, the analysis of low-fat dairy and premenopausal B included half-a-million participants and 17,873 cases of BC.

Does this help us reconcile apparent inconsistencies in the evidence? Two recent studies have found opposed findings to the present study. In the Swedish Mammography Cohort published this year, fermented dairy [>3 servings per day yogurt/cheese] was associated with 72% lower risk in postmenopausal women with estrogen and progesterone *negative* receptor status [(6)]. Then in a pooled analysis of 21 cohort studies also published this year, yogurt intake of >60g/d and cheese intake >25/g were associated with 10% and 15% lower risk of BC, respectively, again in ER-negative status [(5)]. This did not vary by menopausal status.

Thus, while the present study was useful in its incorporation of a large sample size and number of cases, it does not go further to providing a more clear signal from the noise.

Interesting Finding

There was a significant 21% lower risk of BC in women positive for the estrogen receptor [ER+]. Now, why is this interesting? Because of the hyperbole that tends to be spouted in relation to dairy intake, “but hormones tho” is one of the most common. However, this claim is divorced from the evidence. In the These associations in the US Cancer Prevention Study II Nutrition Cohort [CPS-II] were stronger in women with oestrogen-receptor positive (ER+) tumours, with a 33% risk reduction in ER+ participants [RR 0.67, 95% CI 0.51-0.88] [(3)]. The present study found the greatest magnitude of effect in both hormone-receptor-positive types, both estrogen and progesterone. Taken together with prior research, evident from the research regarding breast cancer is that attempting to classify potential risk associated with dairy consumption according to hormone-dependence, such as breast cancer, may be an oversimplification. And the putative mechanism associated with dairy and cancer risk, i.e., IGF-1, may not necessarily be operable in all circumstances.

Relevance

Overall, the present study found more modest effects in BC risk reduction with dairy intake, compared to prior research. In the CPS-II, 2-3 servings of dairy per day was associated with a 19% reduction in breast cancer risk [RR 0.81, 95% CI 0.69-0.95] compared to <0.5 servings per day, an effect driven by low-fat dairy consumption when low-fat and high-fat sources were analysed separately [3]. In the Nurses' Health Study, there was a 32% lower risk [RR 0.68, 95% CI 0.55-0.86] for the highest category of dairy intake, but this time in *premenopausal*, not postmenopausal, women [7]. Similar to the CPS-II study, this effect was strongest for low-fat dairy.

Thus, the finding of a signal among the noise for low-fat dairy, but no significant associations for high-fat dairy, is consistent with this prior research [3-7]. In addition, when separated by menopausal status, low-fat dairy had the most significant effect on lowering BC risk in premenopausal women which has also been shown in prior research [7].

But let's also remind ourselves of the confidence intervals Research Lecture, where we discussed how to think about different effect sizes and the precision of their estimate [i.e., the confidence intervals around the estimate]. We discussed the importance of distinguishing "statistical significance", which is cute but meaningless in isolation, from magnitude of effect and precision. In the present study, with the exception of the hormone-receptor outcomes, the magnitude of risk reduction is in the range of 4-6%. The effect size is so modest that, in the context of the other risk factors which influence BC risk, it would be overstating the case to consider dairy "protective against" [to use the common phrase] BC overall.

Rather, it is likely that specific factors converge – menopausal status, low-fat dairy foods, fermented dairy foods, hormone-receptor status – to elicit more robust reductions in risk. It should also be noted that these differences between receptor status and menopausal status, and the associations with food exposures, are not unique to dairy. Indeed, we covered similar ground in a previous Deepdive on soy and soy isoflavone intake and BC risk. All of this speaks to the complex heterogeneity of BC itself, and the challenges in superimposing a complex heterogenous exposure like diet on top of it.

Any of these food-based considerations now come with an environmental caveat. Moderation analysis from previous research has suggested that the effect of dairy may be in contributing to calcium and vitamin D status, and both of these nutrients have been independently associated with lower BC risk from dairy intake [3,4]. Thus, the consideration becomes whether adequate calcium and vitamin D from non-dairy sources suffice, and this is something to be teased out in future research.

Application to Practice

This much is clear: it is difficult to mount an evidence-based case that dairy consumption poses a risk for breast cancer. There may be some signal for high-fat dairy, but the overall body of evidence is relatively consistent in a reduction in BC risk with low-fat dairy intake. The present study suggests this effect may be much smaller than prior research has demonstrated. The most pragmatic conclusion at this juncture in the evidence would be that dairy is not necessary for modifying BC risk, but in women who do consumed dairy, opting for low-fat versions may be prudent, and opting for fermented foods like yogurts and cheeses would be congruent with the evidence. The strongest case that could be made for deliberate inclusion would be low-fat dairy produce in women with hormone-receptor-positive status.

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