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Tantamango-Bartley Y, Knutsen SF, Jaceldo-Siegl K, Fan J, Mashchak A, Fraser GE. Independent associations of dairy and calcium intakes with colorectal cancers in the Adventist Health Study-2 cohort. Public Health Nutr. 2017;20(14):2577–2586.

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

Historically, a major focus of dietary guidelines in Western countries has been dairy produce, consumption of which has emphasised the high calcium content of dairy foods [(1)]. However, this does somewhat of a disservice to dairy as a composite food group. Dairy is a major source of iodine in the population, one reason why it is considered critical to infant development, and contains high levels of magnesium and phosphorous, two minerals also important for bone health [(1)]. It is arguable the most effective source of dietary protein for maintaining musculoskeletal health over the lifespan, while emerging recent suggests the fat in whole-milk sources of yogurt and cheese may have certain benefits for cardiometabolic health [(2)].

And, while these are all facts, it is also true that ethical and environmental considerations are now important determinants of individual dietary choices, and many may wish not to consume dairy for these reasons. However, these considerations do not invalidate the research in relation to the health effects of the food group: these are distinct, and should be considered distinct. For the purposes of this Deepdive, therefore, we are only concerned with an analysis of the study, and context of the findings, in relation to the health effects aspect.

However, pay attention to the online dialogue, which is being polite about the level of conversation, about dairy and you will hear one word over and over: “cancer”. This tends not to be in a positive, or protective, sense. But this isn’ t reflective of the evidence, which is complex and goes both ways: dairy has been associated with increased risk for certain cancers, for example prostate, and associated with reduced risk of others, in particular gastric and breast cancers [(3-5)].

A research question that has been a focus of the cancer research has been whether any effect is derived from the food itself, or specific nutrients provided by the food, in particular calcium. This study evaluated the independent effects of dairy and calcium on colorectal cancer risk in a large cohort.

The Study

The Adventist Health Study-2 [AHS-2] is a large prospective cohort study that began in 2002 to investigate the relationship between diet and cancer. The interest in establishing a cohort study in Seventh Day Adventists [SDA] stemmed from their health-focused lifestyle habits: abstinence from smoking and alcohol, high physical activity levels, and promotion of a vegetarian dietary pattern. However, within the SDA community there is a wide variance in dietary habits, including lacto-ovo-vegetarians [i.e., consume dairy and eggs], pescetarians [i.e., consume fish], semi-vegetarian [i.e., consume meat infrequently], and omnivorous diets.

The initial cohort studies in the SDA community were confined to California; the AHS-2 expanded this to included the entire United States and Canada. 96,194 participants entered the study in 2002; 65.1% female and 34.9% male, and 26.9% black participants [remainder non-Hispanic white participants].

Recruitment was conducted through SDA churches over 8 weeks, with churches having an enrolment target relative to the size of the congregation. Enrolment required completion of the baseline questionnaires, including a food frequency questionnaire [FFQ], which was validated in both white and black subgroups in the cohort, including culture-specific food items for the black SDA group [e.g., plantains, poke, rice and beans]. To assess dairy specifically, the total calories from, and grams per day intake, of milk, cheese, and yogurt, were calculated. Calcium intake was specifically calculated from diary sources, total diet, and supplements, respectively.

The relevant exposures of interest in the study were dairy foods and calcium. The outcome was incidence and mortality from colorectal cancer. The results were presented as hazard ratios [HR] and 95% confidence intervals. The basic analysis model* adjusted for race and gender. The fully adjusted model included family history of colorectal cancer, education level, minutes of vigorous physical activity per week, body mass index [BMI], alcohol consumption, smoking status, history of peptic ulcers, diabetes, or polyps, medication use, and dietary factors: fibre intake, unprocessed meat, processed meat, fish, and poultry.

*Geek Box: Adjustment Models

Reading nutritional epidemiology, you will continually encounter a long list of variables [generally referred to as 'covariates'] that the investigators adjusted for. In statistics, the term 'adjustment' means to control, i.e., remove from the equation, a variable that might influence the association between the exposure of interest and the outcome of interest. By adjusting for these factors, it provides a more direct estimate of the effects of the exposure on the outcome. The term 'model' refers to the particular set of variables which have been added to the analysis. There may be different combinations of variables included. Every specific group of variables that is adjusted for is referred to as a model. Basic models tend to adjust for factors like age, gender, ethnicity, BMI, or whichever combinations of these basic factors the authors deem relevant. When multiple variables are included in a model, this is known as 'multivariate analysis' or a 'multivariate model'. In nutritional epidemiology, there are two levels of variables we want to account for in a multivariate analysis: potential confounding by lifestyle factors [smoking, alcohol, BMI], and potential confounding by correlated dietary factors [other nutrients]. Dietary factors can be analysed by using a substitution analysis: this is where the effects of replacing one nutrient with another are modelled, for example, the effect of replacing saturated fat with polyunsaturated fat. A single study might have three models; an 'Unadjusted Model', where the results are displayed before adjusting for any variables; a 'Basic Model' generally adjusts for typical lifestyle factors, like smoking, alcohol, and/or BMI; and a 'Fully Adjusted Model', where all variables that the investigators have deemed important to control for are added.

Results: 96,001 participants were included in analysis. The average duration of follow-up was 7.8-years. Comparing high vs. low* quintiles of calories from dairy intake, and after adjusting for total calcium, the hazard ratios and 95% confidence intervals were:

- Rectal cancer: 69% reduction in risk [HR 0.31, 95% CI 0.09-0.88]

Calories from dairy were significantly associated with lower risk of colorectal, after adjusting for non-dairy calcium:

- Colorectal cancer: 23% reduction in risk [HR 0.77, 95% CI 0.59-0.99]

In relation to specific foods, the only significant association comparing high vs. low levels of intake was in relation to milk:

- Colorectal cancer: 37% reduction in risk [HR 0.63, 95% CI 0.43-0.89]
- Colon cancer: 33% reduction in risk [HR 0.67, 95% CI 0.45-0.99]

In relation to calcium intake from all sources [total diet, dairy, supplements], the following associations were found:

- Colon cancer: 45% reduction in risk [HR 0.55, 95% CI 0.28-0.98]

Supplemental calcium was also associated with a significant reduction in risk:

- Colorectal cancer: 20% risk reduction [HR 0.80, 95% CI 0.65-0.98]

*Geek Box: Exposure Contrasts in Epidemiology

Nutritional epidemiology faces two particular challenges when it comes to assessing diet-disease relationships: narrow variability in daily intake, and measurement error in dietary assessment methods. Dietary intake tends to vary within a narrow range; we don't tend to go from eating 5% fat one day to 55% the next. And for nutrients, once we are within an adequacy range of intake, we may be talking about gram or milligram differences in intake. Take sodium, for example; we may often be trying to compare 1,500mg to 3,000mg. The relevance of this is that the size of the difference in intake will generally relate to the effect size of the result. If we compared the effects of 15g fibre per day vs. 11g fibre per day, we may not see a big difference in any biological outcomes: if we compared 40g per day to 11g per day, we would see some significant differences in the effect of fibre. In nutritional epidemiology, intakes of the food or nutrient of interest will be divided up into levels: tertiles [thirds], quartiles [fourths] or, commonly, quintiles [fifths]. Often, 'null' results or a lack of effect may simply reflect that there wasn't an adequate contrast in exposures. Therefore, one place to always look in the data of a prospective cohort study is the tables which show the levels of intake per unit of the exposure. For example, in this study, total diary intake in calories per day ranged from 394kcal/d in the highest quintile to 29kcal/d in the lowest; total calcium ranged from 2057mg/d in the highest quintile to 577mg/d in the lowest. These are sufficiently wide variations in exposure to determine a 'true' effect of comparing the high vs. low quintiles.

The Critical Breakdown

Pros: The AHS-2 cohort is a large cohort with a wide range of dietary habits, and dietary intakes; there was a sufficient contrast in exposures* - dairy intake and calcium - in the cohort. The cohort included a significant proportion of black participants, in contrast to many of the major US cohort studies. Dairy and calcium were investigated separately, which is important as the health effects of dairy are often over-simplified to relate to calcium intake. The validation process for dietary assessment was quite strong.

Cons: The confidence intervals in the study, although the findings are positive, are very wide for certain key findings. Recall from last week' s Geek Box on confidence intervals, that narrower intervals give us more certainty that the true effect lies within that range. Wide intervals indicate a wider margin of uncertainty in the results. For example, the 95% CI for colon cancer and total calcium intake is 0.28-0.98; this means the effect could be as little as a 2% reduction in risk [0.98] or a 72% reduction in risk [0.28]. While the true effect may lie in that range, these differences in potential effect size are huge. Given that black participants consumed less dairy, but high dietary calcium, it would have been interesting if data was presented for both ethnic groups for comparisons of effects of dietary patterns.

Key Characteristic

Analysing the separate effects of dairy and calcium, which most - if not all - studies prior to this publication had not done. The adjustment for calcium from dairy and non-dairy [including supplements] yielded different findings.

When adjusting for total calcium, the association between total calories from dairy and rectal cancer was significant: this suggests an effect of dairy independent of all calcium from dairy, other dietary sources, and supplements.

When adjusting for non-dairy calcium [i.e., other dietary sources and supplements, but not calcium from dairy], the association between calories from dairy and colorectal cancer risk was significant: this adjustment for non-dairy calcium indicates that the association with dairy may include an effect of dairy calcium.

Ultimately what this indicates is that 'food vs. nutrients' is not a simple dichotomy [more on this under ***Interesting Finding***, below]; a food may have effects itself due to other constituents of the food matrix, and it may have an effect due to the properties of a nutrient it contains.

Interesting Finding

This was an interesting analysis in the context of the 'food vs. nutrients' debate, as the effect of a nutrient is not necessarily always independent of the food it is consumed in, and vice versa.

What this analysis indicates is that dairy itself has benefits independent of its calcium content - as we stated above, the list of nutrients in dairy is extensive: magnesium, iodine, zinc, phosphorus, vitamin K, manganese, conjugated linoleic acid [CLA], lactoferrin, and protein.

Given the consistent associations between dairy and reduced risk for bowel cancers, what do we know mechanistically that could explain these effects? The fact that milk had the strongest relationship of any single dairy food analysed indicates a potential role for lactoferrin, a protein which - outside of human milk - has highest levels in cows milk [6]. Mechanistic research indicates a beneficial effect of lactoferrin on bacterial composition in the gut, stimulation of immune and anti-inflammatory processes in the colon [7].

Another element of dairy foods that may be of particular benefit to intestinal health is the role of dairy fatty acids. Dairy is one of the few dietary sources of butyrate, a short-chain fatty acid [SFCA] which is primarily produced by colonic bacteria degrading dietary fibres; butyrate exerts several immune-modulatory and anti-inflammatory effects in the colon [8]. Finally, CLA is another SCFA for which dairy is the primary dietary source, and which also has mechanistic research indicate indicating an anti-carcinogenic effect [9].

Relevance

The AHS-2 cohort is characterised by a generally healthy overall profile of the participants. While this is often construed to mean that any benefit in the results reflects these wider lifestyle factors, the fact is that these factors are known, and can be controlled for.

In this sense, the AHS-2 cohort represents a good cohort to determine effects of foods or nutrients on outcomes, in fact because they are generally healthy; the effect of the food/nutrient, if positive, therefore is still evident after adjusting for these healthy factors.

The findings in this cohort have also been observed elsewhere, with the World Cancer Research Fund [WCRF] ongoing analysis of diet and cancer concluding that milk and calcium reduce colorectal cancer risk. Other analysis have shown this, in different populations, for dairy intake, in addition to milk specifically [10,11].

Application to Practice

While the 'food vs. nutrients' aspect of this study is interesting, this is more from an academic perspective. **The practical perspective always comes back to the fact that people eat foods, not nutrients.** Thus, advice to consume milk, yogurt, and cheeses [a definition which includes foods like cottage cheese]. remains constant here.

It also bears repeating that if these recommendations do not align with an individual's ethical framework, then there is no 'need' to consume any food. From an environmental perspective, if someone chooses to consumed dairy, an average of 250g/d - with a maximum of 500g/d - is supported by the evidence for planetary impacts of diet [12]. Finally, context of wider diet pattern is always important: dietary fibre and the pronounced protective effect on bowel cancers should not be forgotten!

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