dairy foods and cancer prevention

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About a third of the most common cancers can be prevented through diet, weight management and physical activity.[1]

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Since these are modifiable factors, change of lifestyle could help to ease the immense burden of cancer on individuals, families and health care systems. Diet (or foods) can have effects that either promote or prevent cancer. Despite many studies being conducted each year to unravel the complex link between dairy consumption and cancer, several questions remain unanswered.

Health and nutrition professionals need to be able to critically judge the wealth of published information to inform their professional decisions and viewpoints. However, a recent study among South African nutrition professionals revealed very low attitude scores in respect of dairy and the development of cancer.[2] The finding was interpreted as being related to the novelty or complexity of the relationship.

This review is published in response to South African nutrition professionals' expressed attitude[2] and hence aims to empower nutrition professionals in critically evaluating the strength of current evidence that describes possible links between dairy intake and cancer. We first propose a framework that can be used as a tool for evaluating research and then present a summary of the strength of current evidence that suggests a link between dairy consumption and cancer. The paper closes with an integrative, working conclusion and recommendations for South African nutrition practitioners.

1 A framework for judging the evidence

At least three questions should guide the nutrition professional when evaluating whether dairy is related to cancer development:

- **What research method was used?**
- **What type of dairy is referred to?**
- **What type of cancer is referred to?**

Figure 1 shows a framework that puts these questions in context. Research methodology occupies the central position in the diagram, because it establishes the link between exposure and outcome.

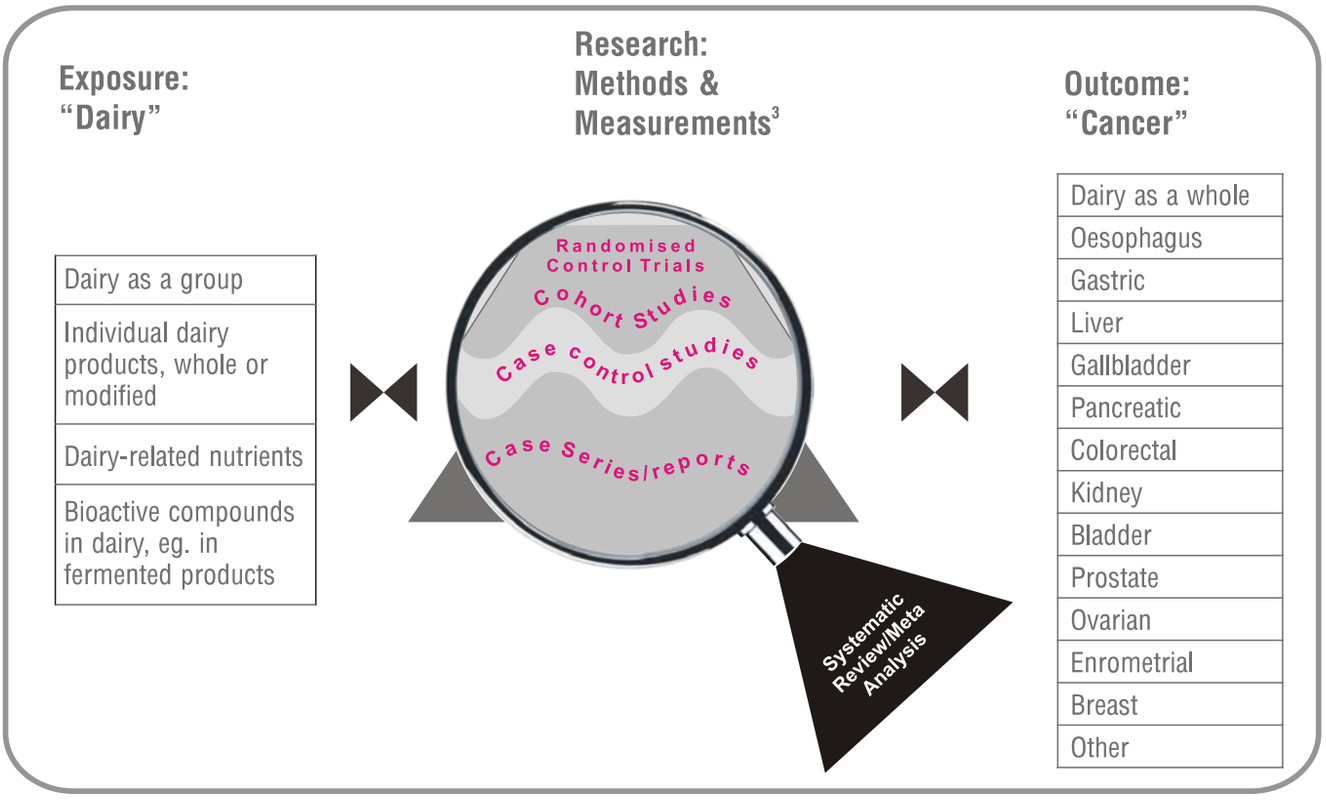

Figure 1: Framework for evaluating evidence linking dairy to cancer

1.1 Research: Methods and measurements

Research methods have traditionally been ranked into an evidence pyramid. Clinical textbook information, case series and reports are at the base of the hierarchy (lowest scientific validity), followed by observational research such as case-control and cohort studies. Randomised control trials are at the top of the 'direct' methods. Above these, in the apex – either attached to or separated from the pyramid – are systematic reviews and meta-analyses. Such evidence pools the data from a number of primary studies, and so acts as a lens through which the other types of evidence are viewed.[3] To address the criticism of oversimplification, the boundaries between the levels in the pyramid are wavy to 'GRADE'[4] the quality of 'direct' methods. High-quality studies are characterised by adequate designs and statistical considerations of sample size and analyses, in addition to clear descriptions of the population and geographical site to which the findings refer. The latter is of particular importance in evaluating the dairy-cancer link as differences in risk may be related to different ethnicities, as implied by Lu et al[5], or due to regional differences in the composition of dairy.

It is acknowledged that some clinical epidemiologists and research design specialists may prefer a circular arrangement of research methods as opposed to a pyramid (e.g. Tugwell and Knottnerus).[6] In such an arrangement human experiments are complemented by real-life observational studies. Initial exposure–outcome links seek confirmation by basic experiments, which shed light on mechanisms and dose-effect relationships. Indications of quantities (doses) may be important for quantitative dietary guidelines, i.e. recommended number of servings of, for example, dairy.

The methodological quality of systematic reviews that investigate the link between cancer and dairy cannot necessarily be taken for granted[7] and a critical 'GRADEing'[4] of the research (for example, with the AMSTAR tool[8]) is recommended. Nevertheless, most experts consider credibly performed systematic reviews and meta-analyses of high-quality studies to be the strongest evidence currently available to nutrition professionals.

This comprehensive approach to evaluating available studies was followed by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) in their groundbreaking Second Expert Report.[9] For this report, about half a million studies investigating the link between cancer and the lifestyle factors food, nutrition and physical activity were scrutinised. To account for the latest evidence, various follow-up 'Continuous Update Projects' (CUPs) constitute a comprehensive, ongoing programme to analyse global research. In all these reports, the current state of understanding is assigned to one of the following categories, listed in descending order of strength of evidence:

- convincing
- probable
- limited – suggestive
- limited – no conclusion.

A cause-effect relationship should be inferred only if different types of well-designed study consistently link an exposure to an outcome. In studying the link between dairy and cancer, dairy consumption is the '**exposure**' and cancer is the '**outcome**'.

1.2 Dairy intake: Exposure

Defining and measuring **dairy intake** refers to the second question to be asked when an association between dairy and cancer is of interest (Figure 1). As a dietary exposure, dairy products refer to a complex group of foods. Studies vary in how such consumption data are defined and collected.[10] Sometimes dairy is studied as a group, but increasingly individual dairy products are investigated. An example is a meta-analysis of intakes of various types of dairy product and the risk of non-Hodgkin lymphoma: it emerged that an increased risk was associated with overall dairy consumption, but not with yoghurt.[11] Similarly, Rafie et al[12] focused on the association between kefir (fermented milk) intake and cancer.

The terminology and classification related to dairy are ambiguous and not consistent across research studies. Butter is usually excluded from the analyses, but not always. When the focus is at the food level, specific forms of individual dairy products are often investigated, for example, whole milk versus low-fat or fat-free versions (e.g. Lu et al[5]).

However, in the case of colorectal cancer, the inverse relationship between dairy products and cancer risk appears to hold regardless of the fat content of milk, yoghurt and cheese.[13]

The effect of dairy-associated nutrients, such as calcium and vitamin D, has been investigated in numerous studies. Examples of such studies are shown in Table 1 (see page 5). However, inferences should be considered with caution as calcium from dietary sources and from supplements may have been considered in some studies. Similarly, practices of vitamin D fortification differ across countries. In South Africa, for example, vitamin D fortification of dairy is not compulsory. Investigations into the association between dairy intake and cancer have recently shifted their focus to bioactive constituents in dairy. This includes the role of certain fermented dairy products in modulating the gut microbiome, which, in turn, may affect the association with certain cancers.[14]

Even if the exposure (i.e. the type of dairy product/food intake being assessed) is clearly defined, its measurement is challenging. This particularly complicates interpretation of the results from retrospective observational studies. The cancer process is usually prolonged and for some types of cancer many years can pass before diagnosis. Nutrition can play a part at many points during the multistage process of carcinogenesis: from initiation, through promotion, to tumour formation.[9] The reference period of a dietary assessment (e.g. a food frequency questionnaire) should be matched to the development of a particular cancer. This may be extremely challenging as recall/reporting bias can become a real threat. In addition, the quantification of intake (how much was consumed) remains problematic in dietary assessment. Establishing dose–response associations and thus what quantity constitutes a protective or causative intake level continue to largely elude researchers. Although biochemical markers of dietary intake are an objective, albeit expensive, measure, they are still in the developmental stage and their use is associated with complexity.

1.3 Cancer: Outcome

Cancer, the third element of the framework in Figure 1, is actually a group of more than 100 different diseases.

What these diseases have in common is that a change in the genetic information in the cells results in unlimited replication, evasion of apoptosis (i.e. the regulated process of programmed cell death), sustained angiogenesis (i.e. growth of new blood vessels to supply nutrients to the new growth), invasion of adjacent tissue and metastasis.[9] Although the umbrella term 'cancer' is occasionally used, it is more appropriate to specify a particular cancer, as the aetiology of the different types of cancer, including the link to diet, is disease specific. It has even been implied that subtypes of some cancers (e.g. prostate cancer[15]) may have different dairy-related risk factors. The way in which the association with the exposure, i.e. dairy, is expressed usually refers to incidence, yet in some analyses (e.g. Lu et al[5]) mortality (i.e. death as a result of cancer) is reported.

2 Current strength of evidence linking dairy to cancer

In a meta-analysis of 11 population-based cohort studies, Lu and colleagues[5] investigated the association between mortality due to cancer as a whole and total dairy product intake. They reported a non-association in men and women alike.

As mentioned before, the link is more often investigated with regard to a specific cancer site or dairy product, and based on incidence. Table 1 summarises the findings from the authoritative WCRF/AICR report of 2007[9] and the various subsequent CUPs.

The following findings emerge:

- The WCRF and CUPs investigated the role of dairy for a total of 13 different cancers through systematic reviews and meta-analyses. The cancer sites were mainly from the gastrointestinal and urogenital systems. For the majority of cases there is currently not enough evidence to make any valid conclusions.

- There is currently no *convincing* evidence that dairy either increases or decreases risk in any of the cancer sites listed in Table 1. The report concluded that for cancers such as lung cancer, the current evidence shows that a substantial effect of dairy on the risk of developing this cancer is unlikely.[29]

- The following findings emerged with regard to cancers of the gastrointestinal tract:
  > Milk probably decreases the risk for colorectal cancer.[9,21] In addition, the subsequent CUP report[21] concluded that high calcium intake probably decreases the risk for colorectal cancer. There is limited suggestive evidence that vitamin D reduces the risk for this cancer, but that cheese increases the risk. This difference between the effect of different dairy products (non-fermented milk, solid cheese and fermented milk) with regard to the association with colorectal cancer was confirmed by Ralston et al.[30] Kongerslev Thorning et al[31] extend this finding in a recent narrative review, where they claim that 'consumption of milk and dairy products probably protects against colorectal cancer'. This research group offered similar statements with regard to bladder, stomach and breast cancer.

  > There is consensus that insufficient research is available to reach a conclusion with regard to cancer of the oesophagus, liver, gallbladder and pancreas. In the evidence matrix of the WCRF/AICR report,[9] dairy products are not mentioned in relation to pancreatic cancer. This indicates that the limited available studies still do not allow for a conclusion. Genkinger et al[31] published a pooled analysis of[14] cohort studies investigating the link between dairy and pancreatic cancer, and concluded that there is no association between consumption of dairy foods, calcium or vitamin D during adulthood and pancreatic cancer risk. This conclusion is shared by Kongerslev Thorning and colleagues.[31] The lack of a clear association between dairy and gastric cancer (Table 1) has also been noted by Tian et al (cited by[32]), although the possibility of differences among dairy products may exist.[33]

- Regarding cancers of the urogenital tract the following findings emerge:

  > The WCRF/AICR report[9] concluded that diets high in calcium probably increase risk for prostate cancer. In 2009, Parodi[34] labelled this association as 'very modest' and the risk level was subsequently reduced to 'limited suggestive' in the CUP of 2014.[24] In both reports this risk level was associated with milk and dairy as a group.

In contrast, whole milk intake was singled out by Lu et al[5] as contributing to an elevated prostate cancer mortality risk in men. This link was confirmed through a linear dose-response relationship. Aune et al[15] detailed the association by stating that 'high intakes' of dairy products, milk, low-fat milk, cheese, and total dietary and dairy calcium may increase total prostate cancer . risk'. They were not able to single out whether fat and calcium are the components associated with this increased risk.
The possibility that subtypes of prostate cancer may have different links to dairy was raised by these authors.

> In 2015, a report of a WCRF/AICR-associated CUP concluded that limited and inconclusive evidence exists for linking intake of milk, yoghurt and cheese individually, and also serum 25-hydroxy vitamin D, to the risk of developing *bladder cancer*.[23]

According to a narrative review by Lampe,[14] consumption of cultured dairy products appears to be inversely related to the risk, suggesting that the influence of live microbes on the gut microbiome requires further research. In a meta-analysis of various epidemiological study designs that investigated the association between bladder cancer and milk individually and dairy as a group, Li et al[35] noted that there was no overall association between the exposures and outcome, despite inverse relationships being observed in the USA and Japan. Kongerslev Thorning et al[31] concluded that, in general, an inverse association has been documented between milk and dairy products and bladder cancer. It therefore appears that different researchers interpreted existing data differently.

Table 1: Summary of strength of evidence linking dairy to cancer according to WCRF/AICR 2007[9] and CUP reports[16-28]

Dairy products and dairy-related nutrients	CANCER SITE: Oesophagus	Stomach	Liver	Gallbladder	Pancreas	Colorectal	Kidney	Bladder	Prostate	Ovarian	Endometrial	Premenopausal	Postmenopausal
	GASTROINTESTINAL								UROGENITAL			BREAST	
Milk and dairy products as group	limited – no conclusion [16]	limited – no conclusion [17]			limited – no conclusion [20]		limited – no conclusion [22]		limited - suggestive increased risk [9,24]	limited – no conclusion [25]	limited – no conclusion [26]	limited – no conclusion [27]; limited - suggestive decreased risk [28]	limited – no conclusion [27]
Milk						limited - suggestive decreased risk [9,21]		limited - suggestive decreased risk [9]; limited – no conclusion [23]					
Yoghurt								limited – no conclusion [23]					
Cheese						limited - suggestive increased risk [9,21]		limited – no conclusion [23]					
Diets high in calcium (including supplements)		limited – no conclusion [17]	limited – no conclusion [18]	limited – no conclusion [19]		probable – increased risk [21]	limited – no conclusion [22]		probable – increased risk [9]; limited - suggestive increased risk [24]	limited – no conclusion [25]		limited - suggestive decreased risk [28]	limited - suggestive decreased risk [28]
Foods/supplements containing vitamin D/serum 25-hydroxy vitamin D		limited – no conclusion [17]	limited – no conclusion [18]	limited – no conclusion [19]		limited - suggestive increased risk [9,21]		limited – no conclusion [23]					
Lactose										limited – no conclusion [25]			

KEY:

Symbol	*Meaning*
■■■	Convincing – decreased risk
■■	Probable – decreased risk
■	Limited – suggestive decreased risk
▬	Limited – no conclusion
■■■	Limited - suggestive increased risk
■■	Probable – increased risk
■	Convincing – increased risk

- No conclusion regarding the link between dairy and breast cancer emerged from the CUP for breast cancer[27] owing to a lack of evidence at the time of the studies. Zang and co-workers[37] subsequently performed a systematic review and meta-analysis of mainly prospective studies and found that 'dairy consumption was inversely associated with the risk of developing breast cancer and this effect was dependent on the dose, dairy type, and time'.

3 Integrative conclusion and recommendations

Research into the association between cancer and nutrition, including dairy intake, is a dynamic field of investigation, with many original studies and numerous integrative knowledge synthesis studies (systematic reviews and meta-analyses) being published regularly. This umbrella review of systematic reviews and meta-analyses clearly shows that no definitive answers (convincing evidence) are available yet and that the link between a complex exposure (dairy consumption) and a complex outcome (cancer) does not have a simple answer. Consequently, none of the WCRF's[10] recommendations for the prevention of cancer (see Box below) explicitly refer to dairy. Matters such as weight management seem to be more important in this regard.

- **Be a healthy weight.**
- **Move more.**
- **Avoid high-energy foods and sugary drinks.**
- **Enjoy more grains, vegetables, fruit and beans.**
- **Limit red meat and avoid processed meat.**
- **For cancer prevention, don't drink alcohol.**
- **Eat less salt and avoid mouldy grains and cereals.**
- **For cancer prevention, don't rely on supplements.**
- **If you can, breastfeed your baby.**
- **Cancer survivors should also follow these recommendations.**

Box: Evidence-based recommendations to prevent cancer[1]

The World Health Organization has, for many years, promoted a general (as opposed to a disease-specific) approach to the prevention of non-communicable diseases (NCDs), including certain cancers. A prevention regime for one condition should not increase the risk for another. Population-based primary prevention should be relevant to the whole population.

There is extensive evidence that dairy intake is closely associated with the prevention of NCDs.[30] In addition, South Africa carries a double burden of nutrition-related disease: not only NCDs but also under-nutrition is rife. It follows that healthy eating guidelines for the country should be relevant for all.

Should the focus be only on cancer, dairy seems to offer substantial and robust health benefits to women in reducing the risk of the common and serious colorectal cancers. Based on current knowledge, the protective effect of milk and dairy on the common and serious colorectal cancers in men may outweigh a potentially increased risk of prostate cancer.[30] It is the responsibility of every nutrition professional to stay current in this field, for example by being familiar with the WCRF's Third Expert Report, which is expected in 2017.

In a holistic approach, where balance, variety, moderation and nutritional adequacy are valued, dietary recommendations cannot omit dairy.

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PLEASE ANSWER ALL THE QUESTIONS
(There is only one correct answer per question.)

1. Direct methods of research are ranked into an evidence pyramid. If these study methods are:
(a) Observational research such as case control and cohort studies
(b) Systematic reviews and meta-analyses
(c) Clinical textbook information, case series and reports
(d) Randomised control trails
Rank the order which will represent the correct order of the hierarchy, starting at the bottom working to the top.

[a] a;c;d;b
[b] c;b;a;d
[c] c;a;d;b

2. High-quality systematic reviews and meta-analyses studies that are characterised by adequate designs and statistical consideration of sample size and analyses, in addition to clear descriptions of population and geographical site to which the findings refer, are the strongest evidence currently available to nutrition professionals. This statement is particularly important when evaluating the _____
[a] dairy-colorectal cancer link
[b] dairy-bladder cancer link
[c] dairy-cancer link
[d] all of the above

3. The American Institute for Cancer Research used a hundred thousand studies to investigate the link between cancer and the lifestyle factors food, nutrition and physical activity
.[a] true
[b] false

4. When studying the link between dairy and cancer, dairy consumption is the (a)_____ and cancer is the (b)_____
[a] (a) exposure (b) outcome
[b] (a) cause (b) result
[c] (a) outcome (b) exposure

5. In the case of colorectal cancer, the inverse relationship between dairy products and cancer risk appears to hold regardless of the _____ content of milk, yoghurt and cheese.
[a] sugar
[b] lactose
[c] fat
[d] all of the above

6. South African fresh milk is fortified with vitamin D
[a] true
[b] false

7. Lu and colleagues investigated a meta-analysis of 11 population-based cohort studies, to report the association between mortality due to cancer as a whole and total dairy product intake. They reported a _____in men and women alike.
[a] probable decreased risk
[b probable increased risk
[c] non-association

8. Kongerslev Thorning et al claimed that 'consumption of milk and dairy products probably _____ colorectal cancer'. This research group offered similar statements with regard to bladder, stomach and breast cancer.
[a] protect against
[b] probably cause
[c] have a neutral effect on

9. A systematic review and meta-analysis of mainly prospective studies found that 'dairy consumption was _____ associated with the risk of developing breast cancer and this effect was dependent on the dose, dairy type, and time'

[a] directly
[b] inversely
[c] not

10. The World Health Organization has promoted a general (as opposed to a disease-specific) approach to the prevention of non-communicable diseases (NCDs), including certain cancers. There is extensive evidence that dairy intake is closely associated with the prevention of _____
[a] non-communicable diseases
[b] cancer
[c] all the above

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