CESP Center for Research in Epidemiology and Population Health

Dairy products and cancer prevention: fears and evidence

Marie-Christine Boutron-Ruault

INCA symposium

Paris 06/20/2013

Dairy contain many potentially beneficial components

- Dairy contain fats, mostly saturated fats, but some may be of special preventive interest such as CLA

- Fermented dairy products contain probiotics that may be of interest in colorectal cancer prevention

- Dairy consumption is the easiest way to get enough calcium, for bone health but also for colorectal cancer prevention

But

- Calcium may interfere with vitamin D conversion

- Dairy products contain essential amino acids

But

- Some dairy proteins may influence endogenous IGF production

So why is dairy considered a potential culprit regarding cancer risk?

- High dairy product intake is often part of the Western diet, which has been associated with an increased risk of several cancers including prostate, breast and colorectal cancers

- In the opposite the Mediterranean diet is associated with moderate dairy intake (e,g, Trichopoulou et al, 1 point for people with dairy intake below the median population intake).

- Some statements are widely spread in the general public by adepts of alternative medicines: e.g. "*milk is only for babies, no mammal drink milk when they become adults, thus dairy intake can be dangerous after infancy*"

- Milk contain growth factors including IGF1. High concentrations of IGF1 have been associated with an increased risk of some cancers. High milk intake has been associated with high IGF1 concentrations. Is there a causal relationship?

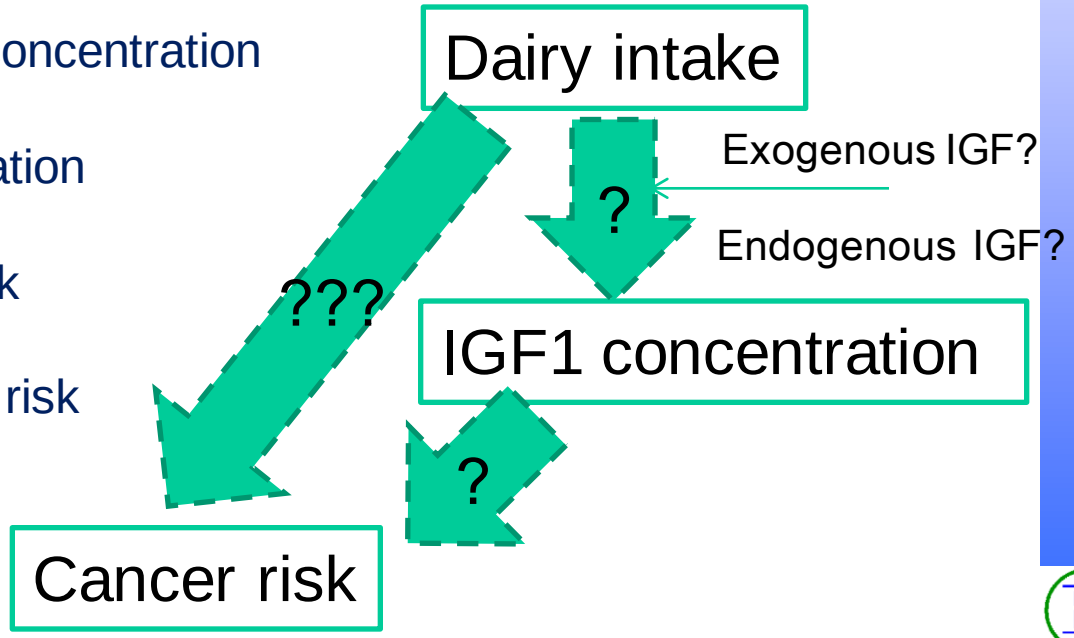
Milk, dairy and the growth factor pathway

Saisine AFSSA 2009-SA-0261: The Association des Familles de France worried about the potential carcinogenic effect of growth factors in milk

Multidisciplinary group including dairy specialists, scientists in experimental cancer research and epidemiologists

To determine whether :

- IGF from milk increase IGF concentration
- Dairy increase IGF concentration
- High IGF increase cancer risk
- Dairy intake increase cancer risk



Does IGF from milk increase IGF concentration? (1)

Growth factors in milk and dairy products

- The major growth factors present in milk and dairy are IGF, TGF-ß and EGF. The best known and most easily measured are IGF

- Undetectable IGF1 concentrations in UHT milk
Over 83% reduction in IGF1 concentrations during fermentation of lactose

- Absorption of IGF mostly by non-mature intestinal wall, absorption extremely reduced if any through adult intestinal wall

- Thus unlikely that IGF from milk or dairy products may significantly increase IGF blood concentrations

Growth factors in milk and dairy products

Group conclusion :

The reduced intake of raw dairy products, the effects of food preparation, the reduced digestive IGF-1 absorption and its digestive breakdown led us to consider that the contribution of exogenous IGF-1 from the overall diet to the circulating pool is probably low, although it cannot be precisely quantified to date.

Does dairy intake increase IGF concentration ?

Diet and IGF concentration

- **Observational studies**:

  Many food items have been associated with increased blood IGF concentrations in cross-sectional studies, but milk and dairy have been the most studied items

  Qin et al 2009, littérature review:
  10/13 studies reported a positive association with milk intake
  Less consistent association with non-milk dairy (3/12)

- **Intervention studies**

  Difficult to draw conclusions: heterogeneity of interventions, of populations (age groups), non-isocaloric comparison groups etc…

Diet and IGF concentration

Group conclusion :

Arguments in favour of an association between milk consumption and blood IGF-1 concentrations rely more on observational studies than on intervention studies, the methodology of which being often disputable.

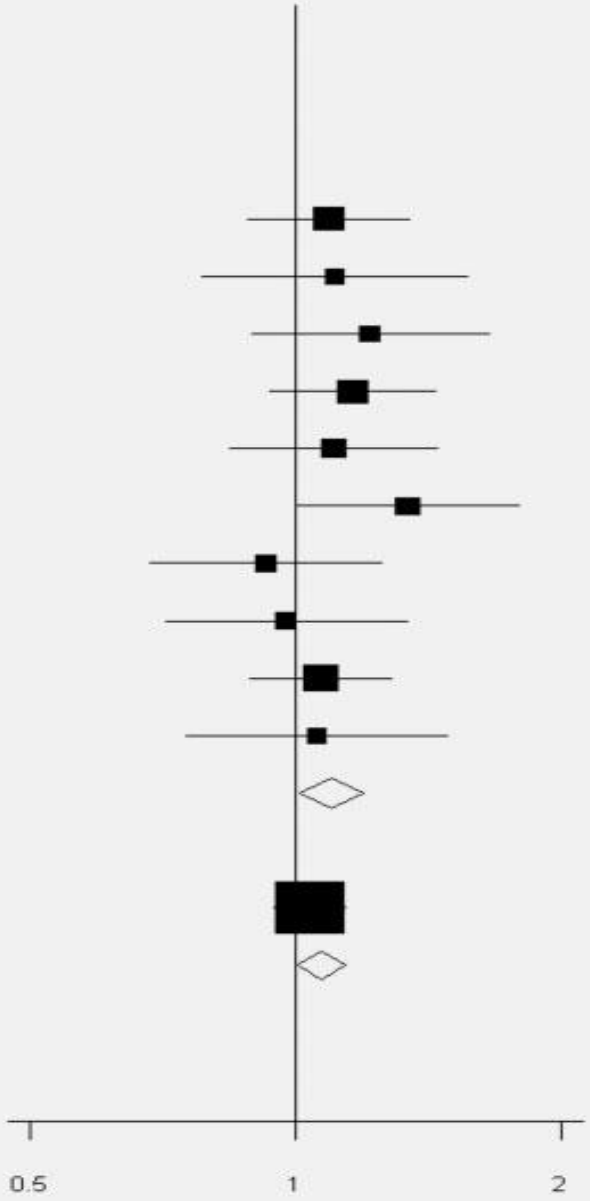
Further intervention studies in adults are requested. If they confirm an association, it would be attributable to a stimulation of endogenous synthesis rather than to absorption of exogenous IGF-1 from milk. When dairy products are considered as a whole, the association with increased IGF-1 is less consistent than with milk itself.

Other factors such as protein, energy and calcium could be associated with increased IGF-1 levels; there are complex relationships between energy intake or restriction and the BMI status

Are IGF concentrations associated with cancer risk

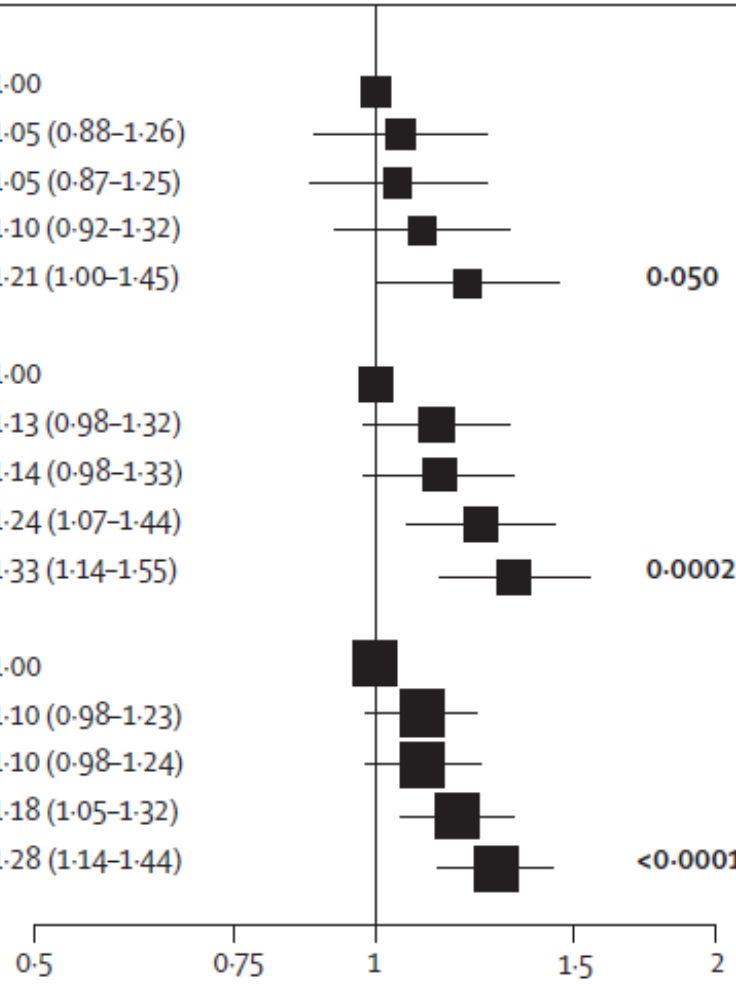
IGF-1 concentrations and colorectal cancer risk *(Rinaldi et al, 2010)*

Colorectal cancer and IGF1	Cases	Controls	RR	95%CI
Studies				
Ma J 1999	193	318	1.09	0.88-1.35
Giovannucci E 2000	79	158	1.11	0.78-1.56
Kaaks R 2000	102	199	1.21	0.89-1.66
Probst-Hensch 2001	135	661	1.16	0.93-1.44
Palmqvist R 2002	168	335	1.10	0.84-1.45
Wei EK 2005	137	262	1.34	1.00-1.80
Otani T 2007 - Men	180	359	0.93	0.68-1.25
Otani T 2007 - Women	175	338	0.98	0.71-1.34
Gunter MJ 2008	438	816	1.07	0.89-1.28
Max JB 2008	134	399	1.06	0.75-1.49
Pooled estimate	1741	3845	1.10	1.01-1.19
EPIC	1121	1121	1.04	0.94-1.14
Pooled all studies	2862	4966	1.07	1.01-1.14



IGF-1 concentrations and breast cancer risk *(Key et al, 2010)*

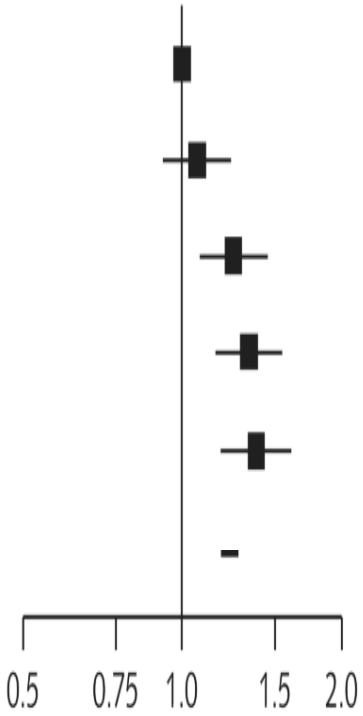
Hormone	Fifth	Cases/ controls	OR (95% CI)	p for trend
IGF1				
Pre-menopausal women	1	374/829	1·00	
	2	392/831	1·05 (0·88–1·26)	
	3	367/814	1·05 (0·87–1·25)	
	4	390/822	1·10 (0·92–1·32)	
	5	414/800	1·21 (1·00–1·45)	0·050
Postmenopausal women	1	508/1081	1·00	
	2	558/1069	1·13 (0·98–1·32)	
	3	573/1083	1·14 (0·98–1·33)	
	4	596/1060	1·24 (1·07–1·44)	
	5	618/1039	1·33 (1·14–1·55)	0·0002
All women	1	882/1910	1·00	
	2	950/1900	1·10 (0·98–1·23)	
	3	940/1897	1·10 (0·98–1·24)	
	4	986/1882	1·18 (1·05–1·32)	
	5	1032/1839	1·28 (1·14–1·44)	<0·0001



The Endogenous Hormones and Breast Cancer Collaborative Group

IGF-1 concentrations and prostate cancer risk *(Roddam et al, 2008)*

Concentration	Quintile	Case Patients/ Control Participants, *n/n*	Odds Ratio (95% CI)	Odds Ratio (95% CI)*	Chi-Square Statistic for Trend†
IGF-I	1	577/909	1.00		
	2	593/891	1.07 (0.92–1.24)		
	3	690/890	1.25 (1.08–1.45)		25.67
	4	716/874	1.34 (1.15–1.55)		*P* < 0.001
	5	723/872	1.38 (1.19–1.60)		



IGF concentration and cancer risk

Group conclusion :

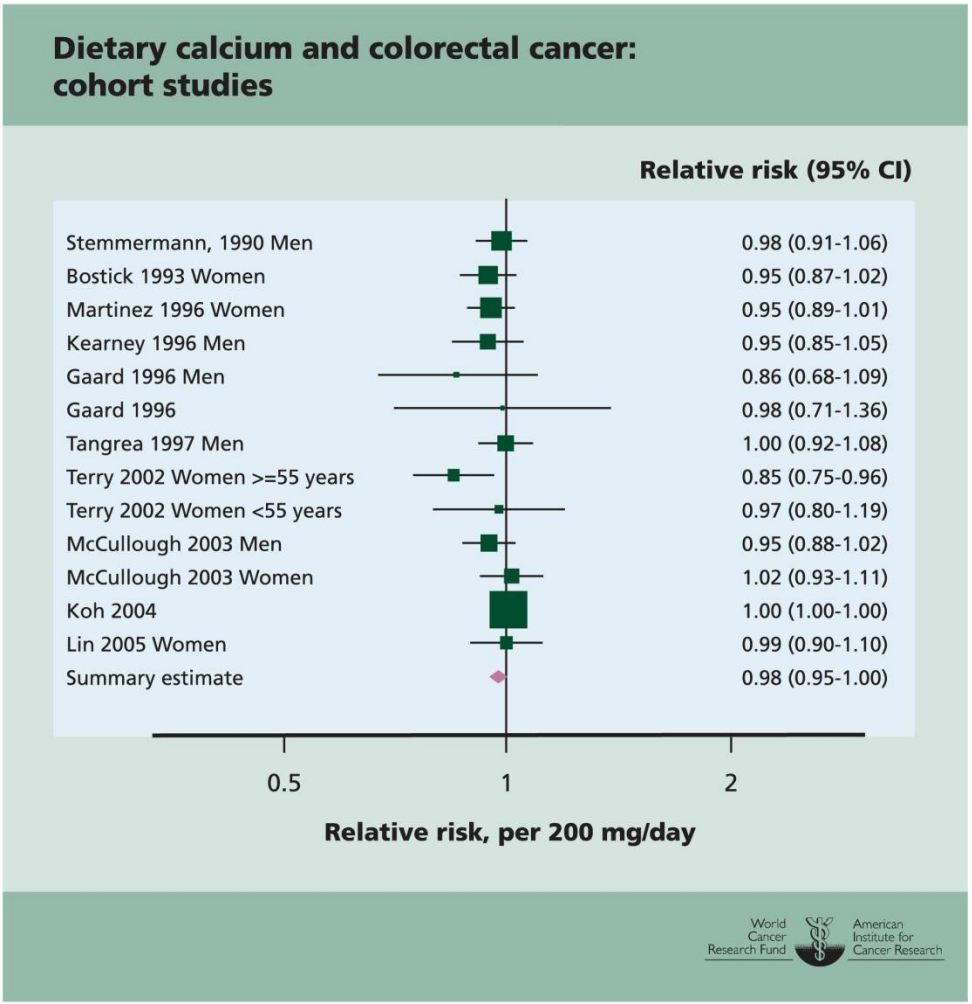
- For some cancers (ER + breast cancer, prostate cancer, colorectal cancer), available data lead us to conclude to a positive association between blood IGF-1 concentrations and cancer risk

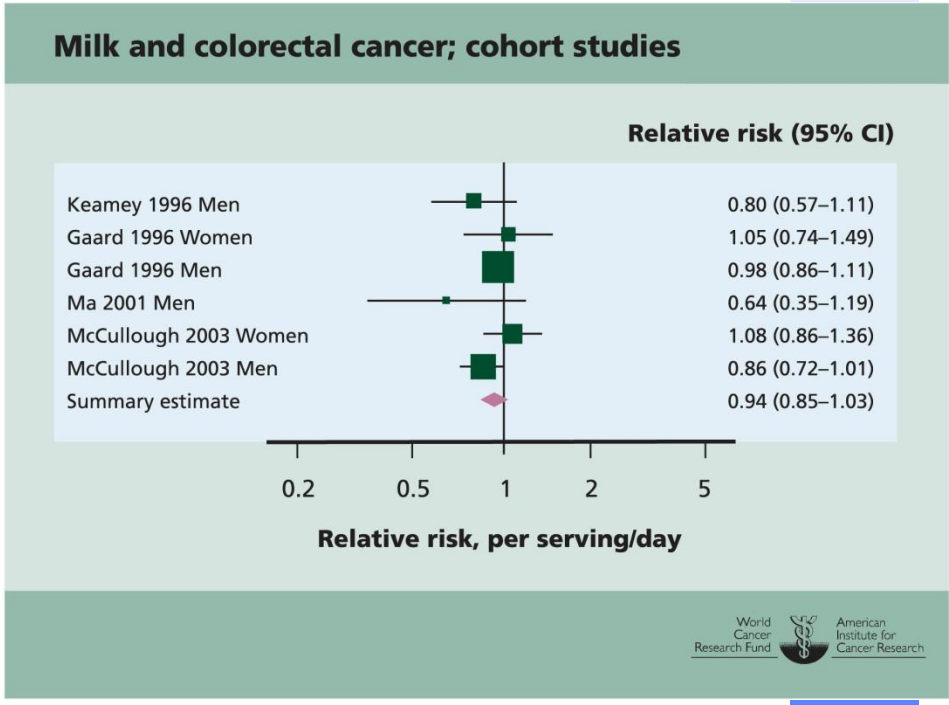
- The associations have been observed within the physiological range of IGF-1 and there is no data that could allow to estimate a risk associated with specific IGF-1 levels

- For other cancer sites, data are too scarce to enable reliable conclusions although positive associations cannot be ruled out

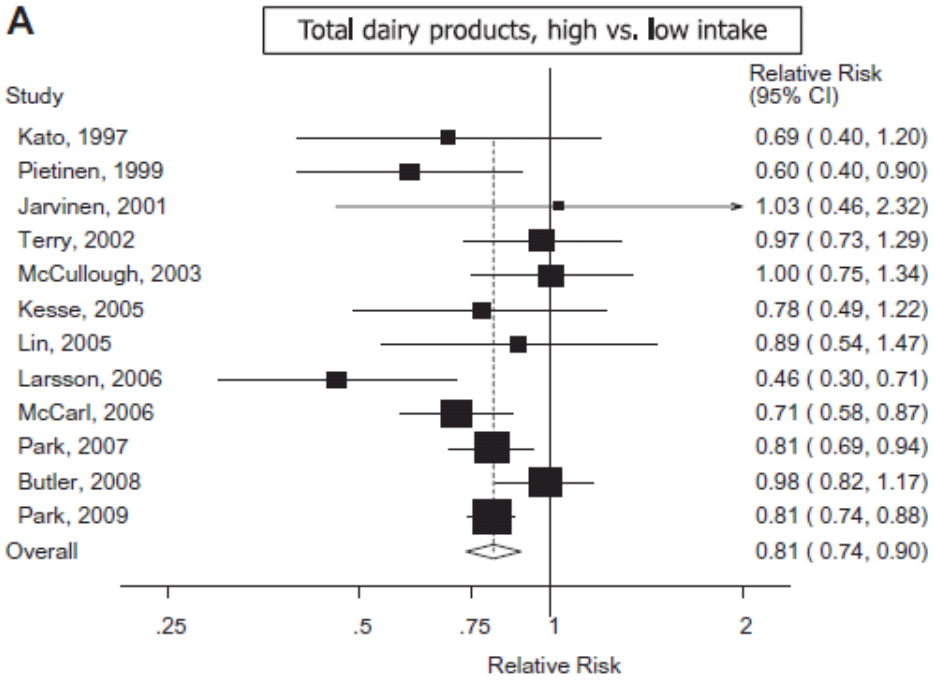
Is dairy intake associated with cancer risk?

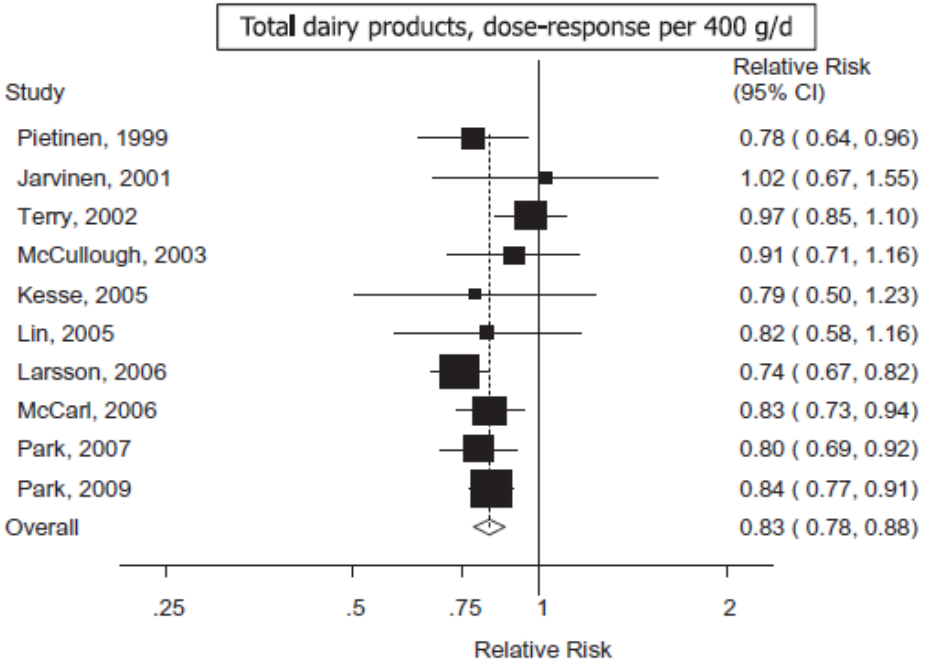
Calcium, milk and colorectal cancer: cohort studies (WCRF 2007)





Dairy & colorectal cancer risk





Aune D et al, Ann Oncol 2011

Dairy & Prostate Cancer

- A meta-analysis on 8 cohort studies found a 6% increase in prostate cancer risk per serving of dairy per day (AICR/WCRF - 2nd Expert Report. November 2007).

- In a 7.5 year prospective study of 43,435 Japanese men, those consuming the highest amount of dairy (=12 oz of milk/day) had a 63% ↑ risk of prostate cancer compared to men consuming the lowest (=2 oz of milk/day). (Kurahashi, et al. Cancer Epidemiol Biomarkers Prev. 2008 Apr;17(4):930-7).

Dairy intake and risk of prostate cancer Chagas 2012, Nutr Rev

Study	Country	Study design and number of subjects enrolled	Impact on incidence of prostate cancer
Bosetti et al. (2004)[27]	Italy	Case-control; 1,294 cases and 1,451 controls	Milk and dairy intake: OR 1.2 for 14 servings/week versus no servings/week No difference between whole milk, partially skimmed milk, skimmed milk, or yogurt
Torniainen et al. (2007)[28]	Sweden and Finland	Case-control; 4,153 cases and 2,315 controls	Low-fat milk: OR 1.73; 95% CI 1.16–1.39
Raimondi et al. (2010)[29]	Canada	Case-control; 197 cases and 197 controls	Total dairy intake: OR 2.19; 95% CI 1.22–3.94 for >468.9 g/day compared to <117.3 g/day Milk was the only dairy product positively associated: OR 2.27; 95% CI 1.25–4.09 for >408 g/day versus <117 g/day
Kesse et al. (2006)[30]	France	Cohort; 2,776 men	Dairy products: RR 4th quartile versus 1st quartile 1.35; 95% CI 1.02–1.78; *P* value 0.04 Yogurt: Increment of 125 g/day: RR 1.61; 95% CI 1.07–2.43; *P* value 0.02
Koh et al. (2006)[31]	USA	Cohort; 10,011 men	Dairy products: RR 1.05; 95% CI 0.84–1.31
Mitrou et al. (2007)[32]	Finland	Cohort; 29,133 men	Total dairy intake not associated with prostate cancer after an adjustment for calcium (*P* for trend 0.17)
van der Pols et al. (2007)[33]	England and Scotland	Cohort; 4,383 children followed up from 1937–1939 to 2005	No association with dairy intake Weak inverse association with high milk intake (>282 mL/day) during childhood (*P* for trend 0.11)
Rohrmann et al. (2007)[34]	USA	Cohort; 3,892 men	Dairy products: ≤1 serving/week compared with >5 servings/week (HR 1.65; 98% CI 1.02–2.66)
Kurahashi et al. (2010)[35]	Japan	Cohort; 43,435 men followed up for 7.5 years	RR for the highest versus the lowest quartiles of total dairy products, milk, and yogurt were 1.63 (95% CI 1.14–2.32), 1.53 (95% CI 1.07–2.19), and 1.52 (95% CI 1.10–2.12), respectively
Ahn et al. (2007)[36]	USA	Cohort; 29,509 men	Low-fat dairy products (>2.75 servings/day): RR 1.12; 95% CI 0.97–1.30
Park et al. (2007)[37]	USA	Cohort; 293,888 men	≥2 versus no servings of skim milk: RR 1.23; 95% CI 0.99–1.54; *P* for trend 0.01
Park et al. (2007)[38]	USA	Cohort; 82,483 men followed for 8 years	No association with dairy and milk intakes

Are there specific components in dairy that could have specific anti-cancer properties?

CLAs
Probiotics

CLA (conjugated linolenic acid)

- « The name CLA refers to a group of positional and geometric isomers of the essential N-6 fatty acid,linoleic acid, that is found in the meat of ruminants and dairy products. » (from Banni, 2002).
- The c9,t11 CLA représent about 90% of dietary CLAs (from Belury, 2002).
- There are 28 known isomers, the c9,t11 and t10,c12 isomers appear to be the most biologically active ones (from Kennedy et al., 2010).
- In animal studies, CLAs have been found to play a protective role towards cancer and atherosclerosis, to stimulate uimmune functions, to normalize glucose intolerance in type II diabetes, and to modify the body composition (from Bhattacharya et al., 2006).

CLA and cancer risk : epidemiological studies

- Only 5 available case-control studies

- Two French studies (*Chajès et al, 2002 and 2003*)

  no association between CLAs in fat tissue / in breast fat tissue, and breast cancer risk/ risk of BC metastases or death

- Swedish study (*Larsson et al, 2005*)

  dietary CLA inversely associated with colorectal cancer risk but (*2009*) no association with breast cancer risk

- US study (*McCann et al, 2004*)

  intake associated with decreased pre-menopausal ER-BC risk

Conclusion

- Dairy products are complex foods, and very heterogeneous in terms of their many components (calcium, fats, proteins, lactose, probiotics etc…)

- While dairy products and calcium are inversely associated with colon cancer risk, they are positively associated with prostate cancer risk. There is to date no strong convincing evidence of an association in either way with other cancer sites.

- Thus, while high IGF-1 concentrations have been associated with increased risks of colorectal, prostate and ER+ breast cancer sites, and high milk intake could be associated with increased IGF-1 concentrations, there is no evidence that dairy products increase the overall cancer risk through the IGF-1 pathway.

- Thus, with the possible exception of prostate cancer risk (in high risk subjects?), there is no strong evidence for changing the current recommendation of 2 to 3 dairy products per day.

- Studies that would evaluate the shape of the association between dairy intake and overall cancer risk and overall mortality are currently lacking and are requested before potentially modifying current recommendations.