

Micro-Nutrients in Milk and Dairy Products: New Insights and Health Benefits  
CERIN Symposium  
May 12, 2011 • Paris, France

# Dairy Products and Cancer: A Review of the Evidence

**Johanna W. Lampe, PhD, RD**

Division of Public Health Sciences

Fred Hutchinson Cancer Research Center, Seattle, WA



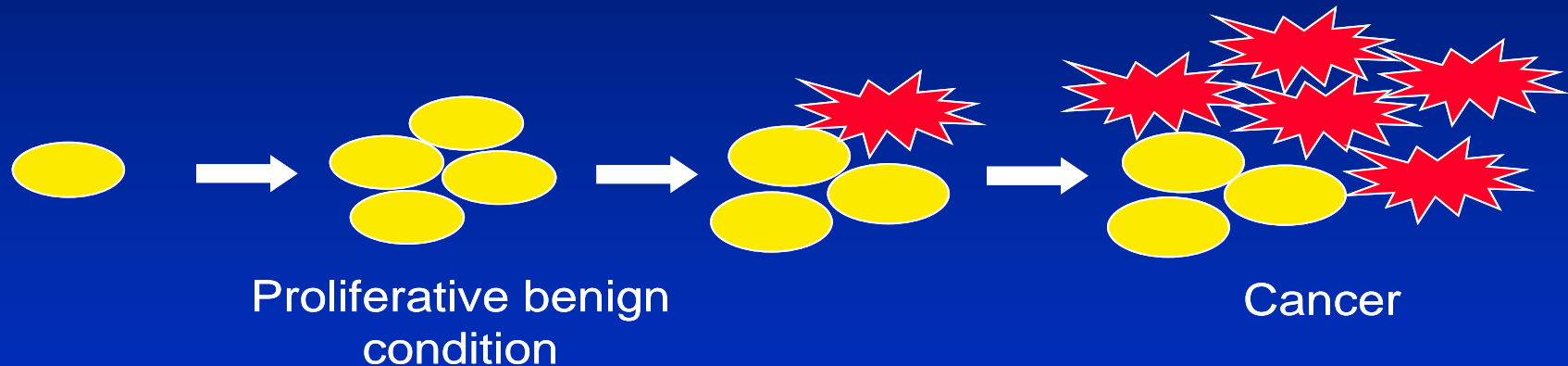
# Outline



- How do cancers develop?
- What do we know about dairy products and cancer risk and prevention?
  - In humans
  - In animals
- By what mechanisms might compounds in dairy products influence cancer risk?

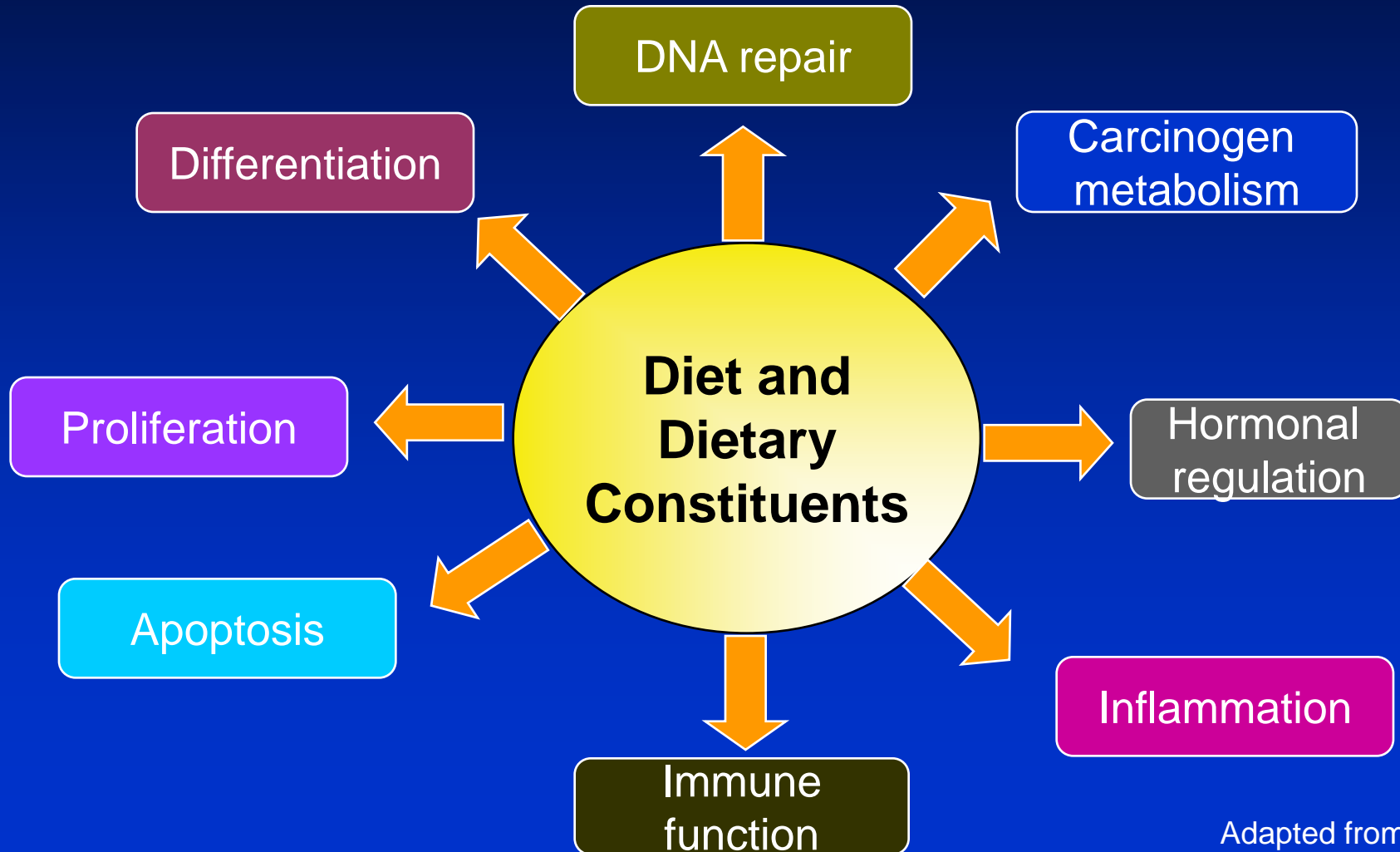
# Cancer

- Class of 100+ diseases in which a group of cells display:
- **uncontrolled growth**
- **invasion** that intrudes upon and destroys adjacent tissues
- sometimes **metastasis**, or spreading to other locations in the body via lymph or blood



- Starts from a single cell that has lost control of its normal growth and replication processes due to changes in genetic information in the cell.
- Effect of genetic alterations or damage accumulated within cells over time.

# Exposures and Cellular Processes Linked to Cancer



# The Cancer Process Over Time

Pro-cancer Effects

Anti-cancer Effects

Failed  
DNA Repair

DNA Repair

Proliferation

Apoptosis

Cell  
differentiation

Normal cell

Damaged DNA

Somatic alterations of genes

Abnormal  
DNA and cell division

Precancerous lesions/dysplasia

Cancer

Tumor Metastasis

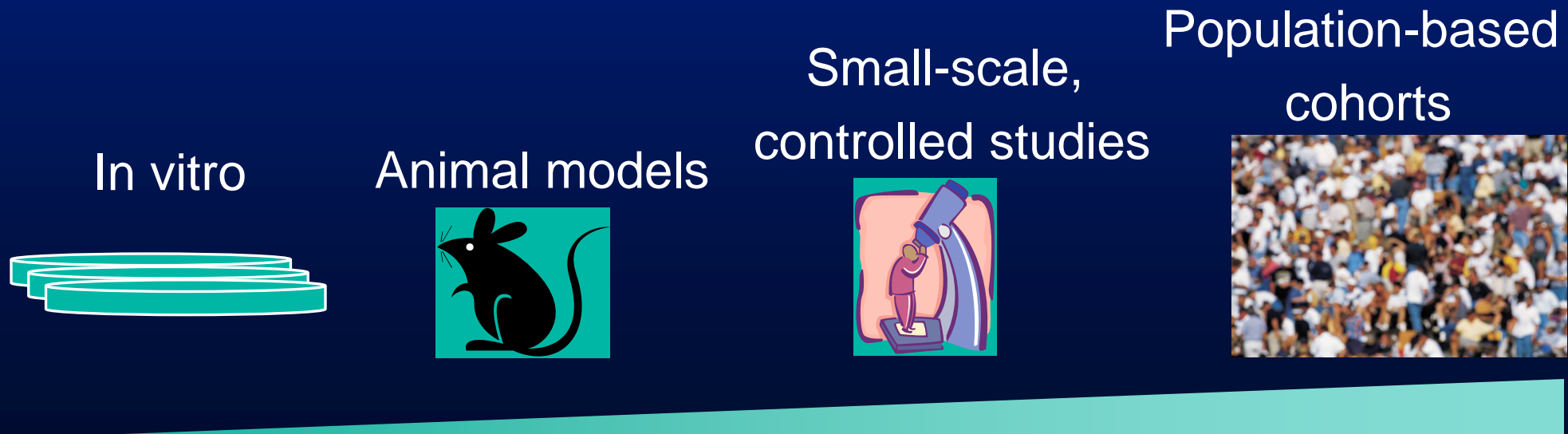
# Cancer Considerations

- Cancers come in different flavors –
  - Carcinogens can have cell-specific effects
  - Cancers arise in different cell types in an organ
  - Cells can go bad in different ways – different tumor types
- Need to be careful generalizing across cancers
- Cancer preventive agents or foods can affect risk of different cancers differently:
  - what may be protective for one cancer may be a risk factor for another

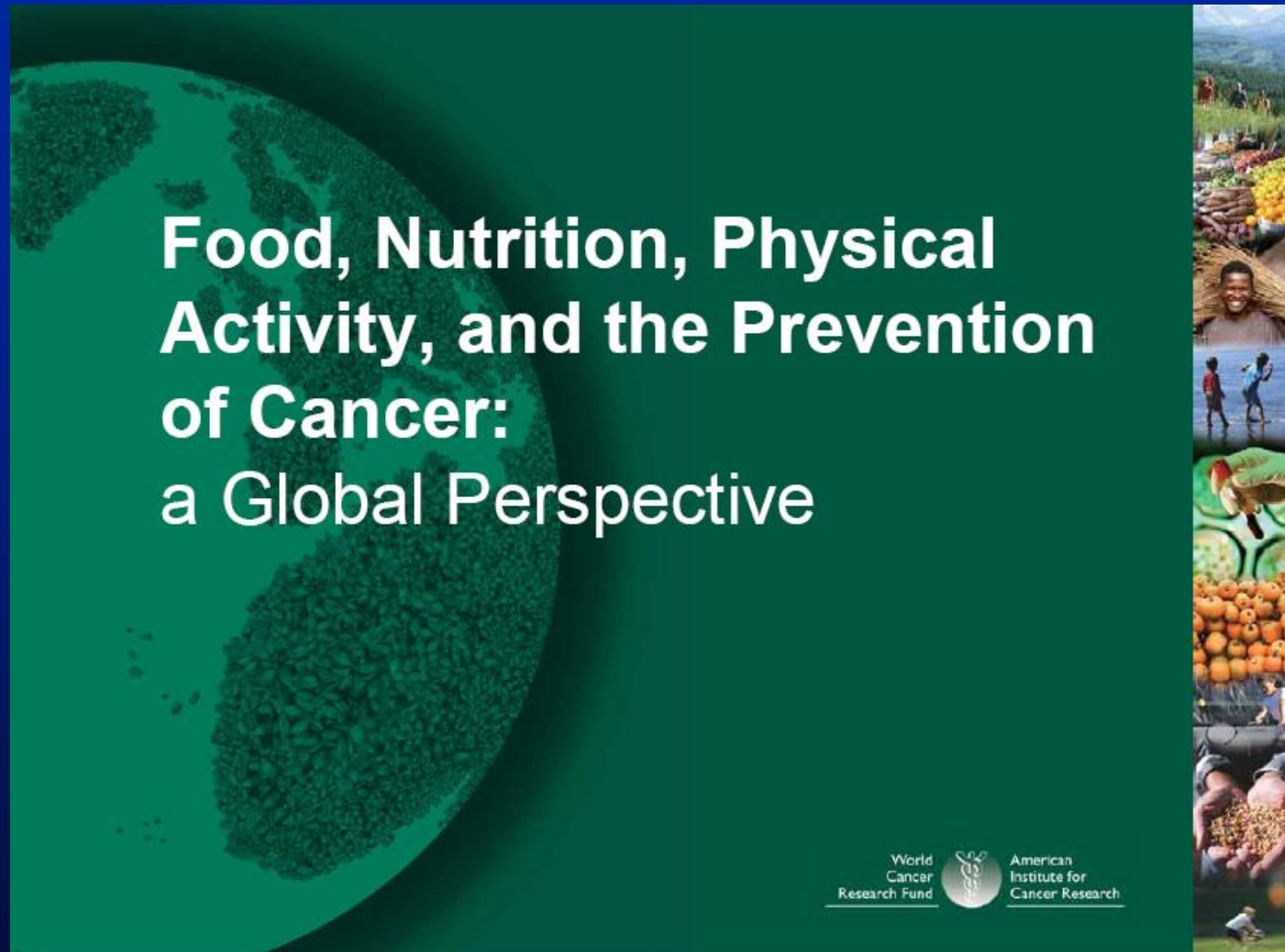
# Dairy Products and Cancer

## Sources and Weight of Evidence

- Across the continuum of research approaches
- Multiple human studies needed to provide sufficiently large sample sizes to evaluate effects at population-level.



# Milk, Dairy Products, and Risk of Cancer



<http://www.dietandcancerreport.org> 2007



# Milk, Dairy Products, and Risk of Cancer

## Summary of WCRF/AICR Report

- Examined milk and dairy product intake in relation to 15 types of cancer
  - No association observed for:  
*mouth; pharynx and larynx; nasopharynx; lung; stomach; gall bladder; liver; breast; ovary; endometrium; cervix; kidney; and skin*
  - Association reported for:  
*colorectal; bladder; prostate*

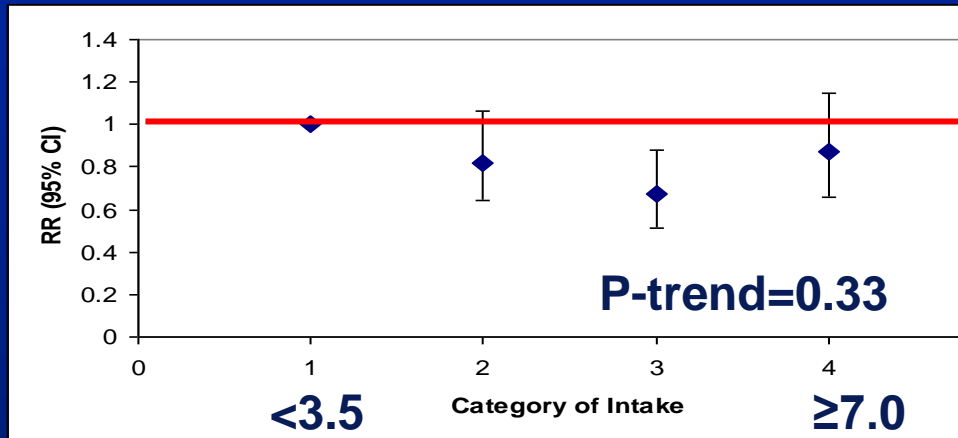


# Milk, Dairy Products, and Risk of Cancer: Evidence from Human Population Studies

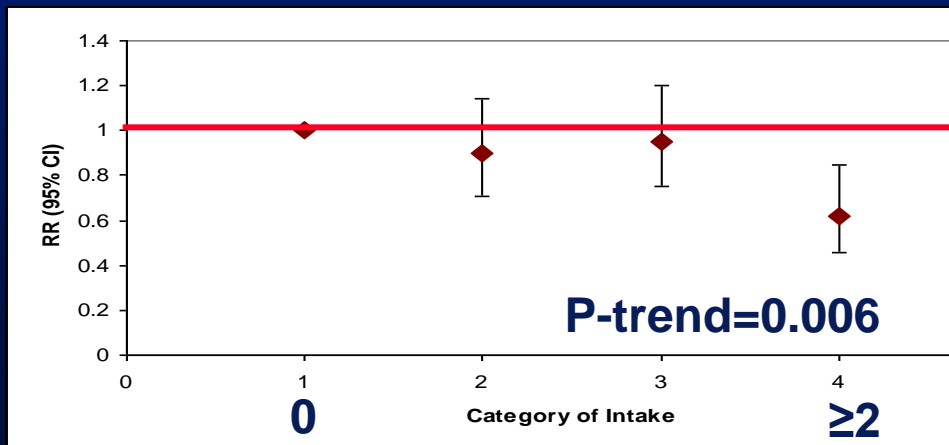
	DECREASED RISK		INCREASED RISK	
	Exposure	Cancer Site	Exposure	Cancer Site
<b>Convincing</b>	--	--	--	--
<b>Probable</b>	Milk	Colorectum	Diets high in calcium	Prostate
<b>Limited -- suggestive</b>	Milk	Bladder	Milk and dairy products	Prostate
			Cheese	Colorectum

# Dairy Products and Bladder Cancer Risk in a Swedish Cohort

## Total Dairy Products



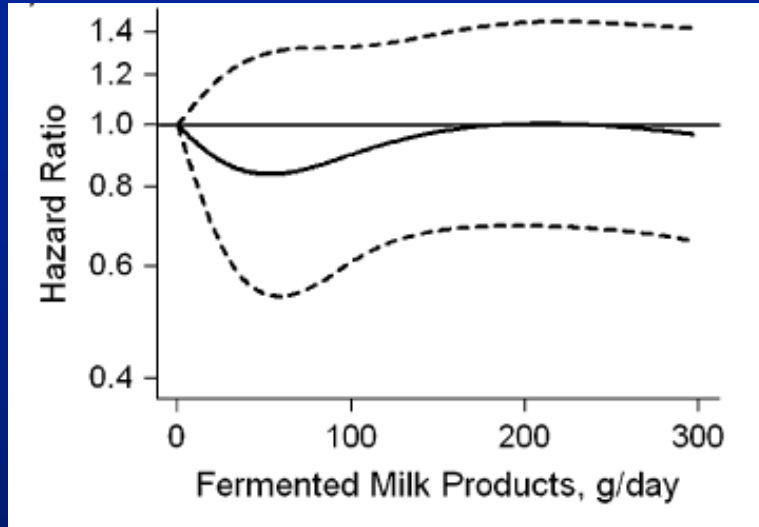
## Cultured Milk Products



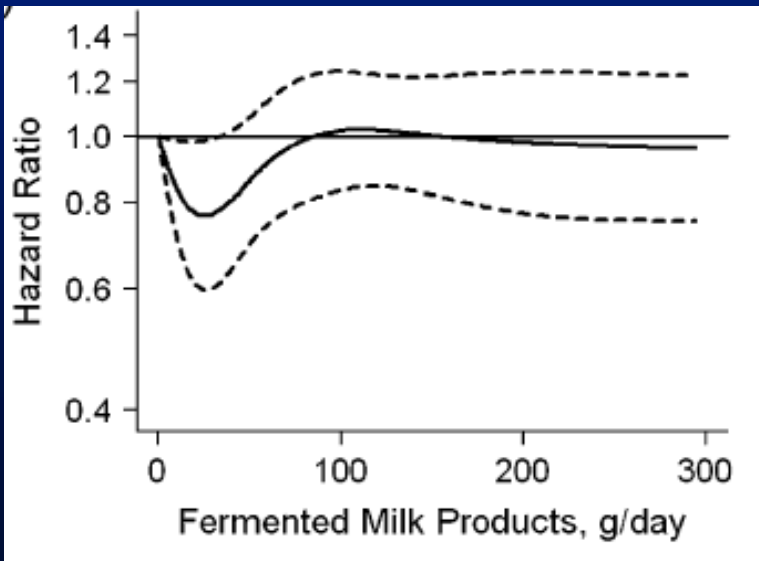
- Prospective cohort study of 82 022 Swedish men and women.
- Completed 96-item food frequency questionnaire in 1997
- 9.4 y of follow-up: 485 developed bladder cancer.
- No effect of total dairy, milk, and cheese, but 38% reduction in risk between no intake and highest quartile of cultured milk products.

# Fermented Products and Bladder Cancer in Dutch Cohort

Men



Women



- Prospective cohort study of 120 852 men and women in the Netherlands Cohort Study on Diet and Cancer.
- Completed 150-item food frequency questionnaire in 1986
- 16.3 y of follow-up: 1549 developed bladder cancer.
- No effect of total dairy, but men and women in 2nd quintile of cultured milk products had 29% lower risk of bladder cancer.

Models adjusted for age, smoking status, number of cigarettes smoked, smoking duration, and intakes of vegetables, fruits, meat, beverages, energy, and fat.

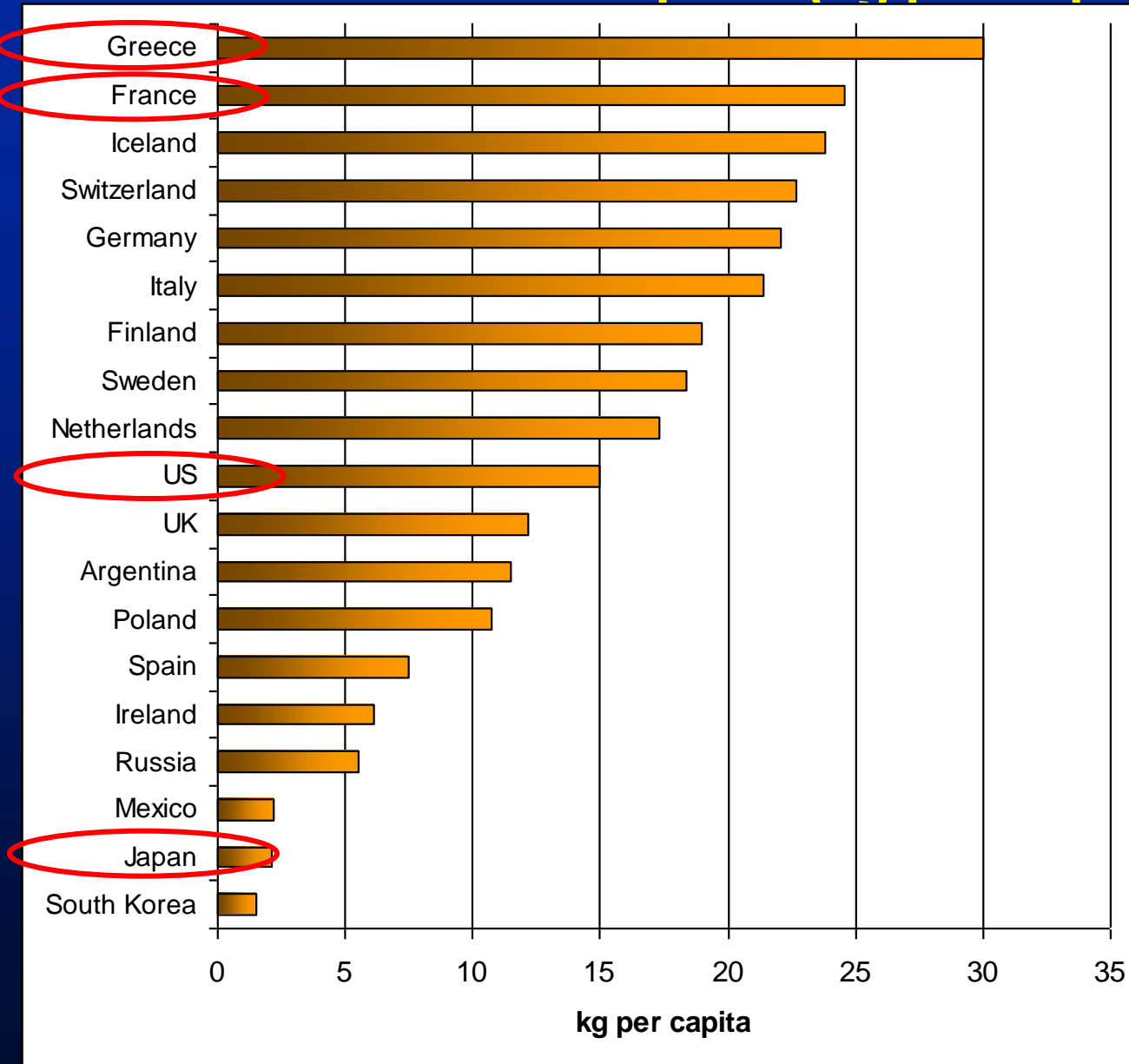
# Studying Dairy Products and Cancer in the Context of the Human Diet



- To date, most studies are in high-income populations
- Amounts and types of dairy products consumed vary by population
- Traditionally, diets that include dairy products also include other healthy and less healthy foods.
- Need to consider dairy intake in the context of the overall diet.

# Who Eats Cheese?

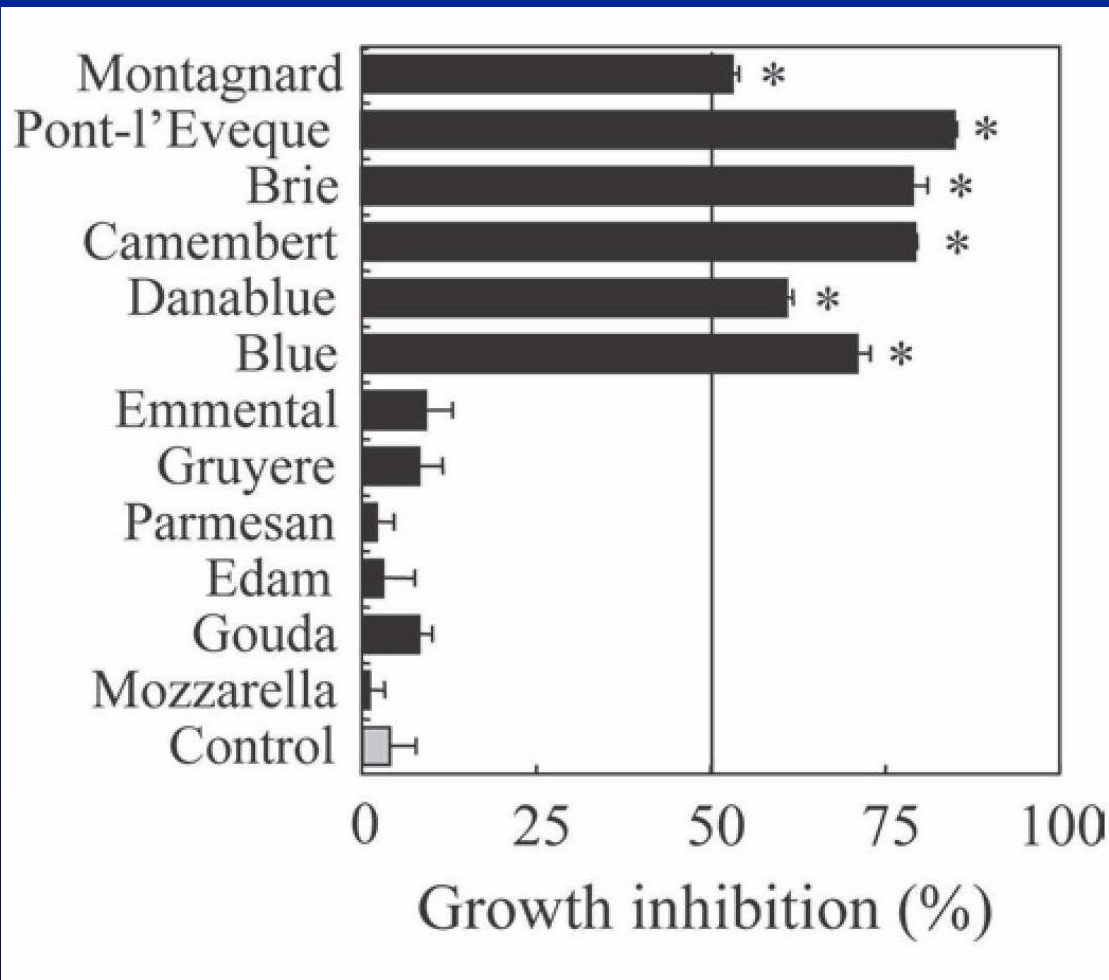
## Total Cheese Consumption (kg per capita)



Feta  
Emmental &  
Camembert

Mozzarella

# Cheese Type May Influence Cancer Risk: Effect of Cheese Extracts on Leukemia Cells



- Tested 12 cheese extracts on proliferation of human leukemia cells in culture
- Extracts of highly ripened cheeses inhibited growth of cells
- **Relevance of *in vitro* findings to humans?**
  - Bioavailability of active compounds?
  - Dose?

# What micro-nutrients and other compounds in dairy products may influence cancer risk?

## INCREASED RISK

- Calcium

## DECREASED RISK

- Calcium
- Microbial fermentation products
  - Peptides
  - Fatty acids – conjugated linoleic acids
  - Vitamins -- vitamin K -- menaquinones
- Microbes





# Calcium: Cell-Type Differences in Response

## *Increased Risk*

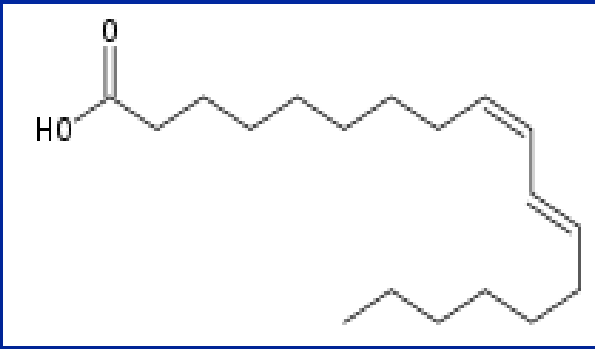
### Prostate Cancer

- Increases insulin-like growth factor (IGF) 1 signaling, which increases cell proliferation.
- Suppress circulating 1,25OH vitamin D

## *Decreased Risk*

### Colorectal Cancer

- High intracellular calcium favorably influences cell growth and apoptosis in colonic epithelium.
- Bind bile acids and fatty acids, preventing them from damaging colon cells.



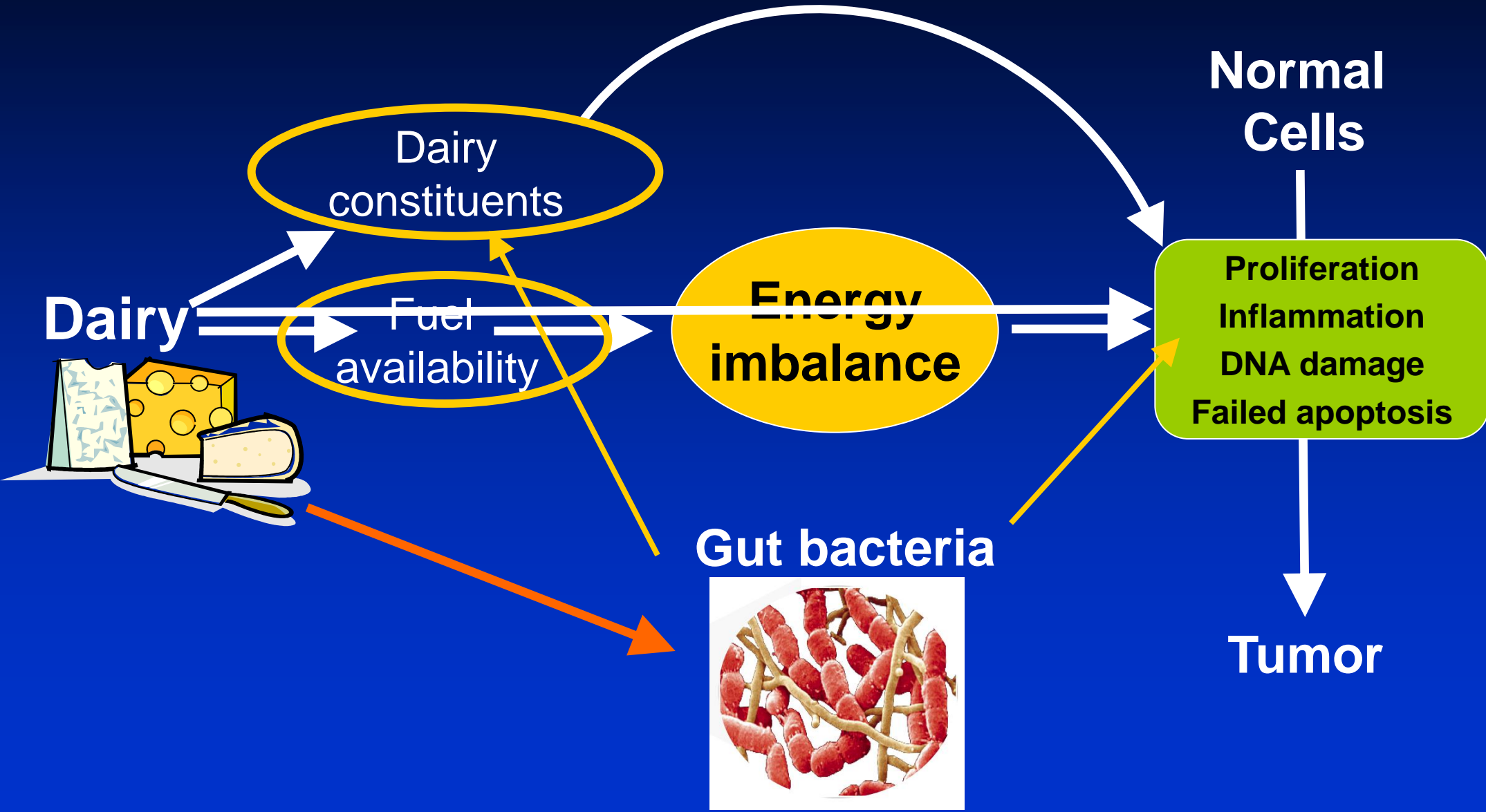
## Conjugated Linoleic Acid (CLA)

- Family of 28+ isomers of linoleic acid found especially in meat and dairy products derived from ruminants.
- Antioxidant and anti-inflammatory properties
- Anti-cancer effects in mice and rats
  - *Decreased growth of tumors in mammary, skin, and colon tissues.*  
Kelley et al, *J Nutr* 137:2599, 2007
- 4 epidemiologic studies of breast cancer inconclusive
  - *3 case-control studies and 1 cohort study*

Aro et al, *Nutr Cancer* 38:151, 2000 • Voorrips et al, *Am J Clin Nutr* 76:873, 2002

Chajes et al, *CEBP* 11:672,2002 • McCann et al, *CEBP* 12:1480, 2004

# Relationship of Dairy Products, the Gut Microbiome, and Cancer Risk



# Microbes and Cancer

- **Microbes as infectious agents**

- Account for ~20% of cancers worldwide
- Cervical, liver and gastric cancers
- Direct effects

- **Microbes as modifiers of physiology**

- **Microbes as modifiers of exposures**

- Metabolizing carcinogens, chemopreventive agents
- Affecting energetics

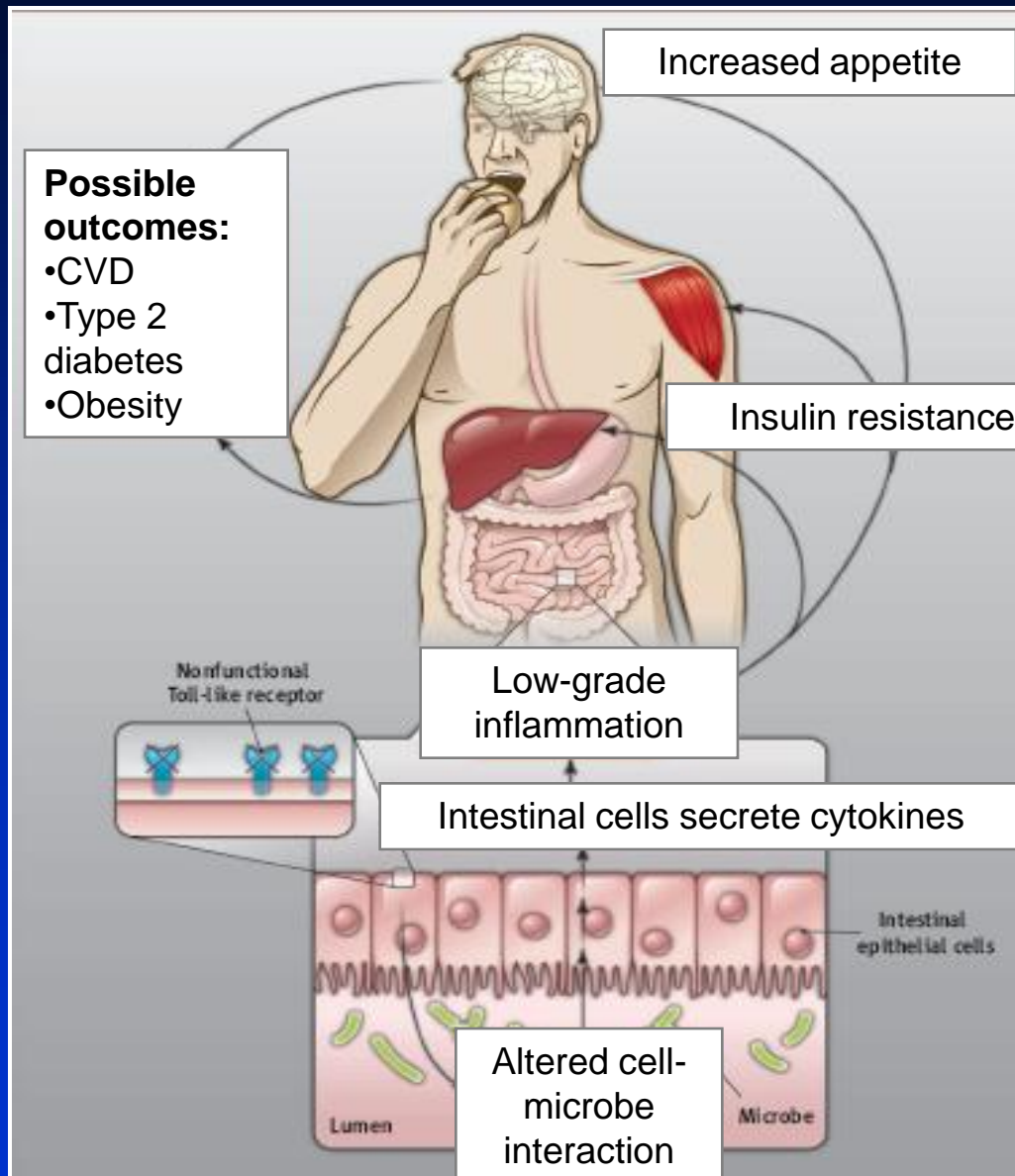
# Mechanisms by Which the Gut Microbiome May Directly Influence Cancer Risk

- Reduce competition by less-desirable bacteria
- Interact with mucosal-associated immune system
- Regulate tight junctions and mucosal barrier function in epithelium
- Influence signal transduction pathways relevant to cell proliferation and apoptosis
- The gut microbiota:
  - The largest collection of microbes in the human body: ~10-100 trillion organisms
  - 100s of species in 6 main phyla

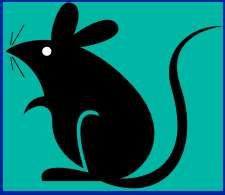
# Cultured Dairy Products as Modifiers of the Gut Microbiome and Gut Physiology

- Source of probiotics, mostly lactic-acid bacteria and bifidobacteria.
- Modulation of inflammatory processes in the gut and ultimately systemically.

# Gut Bacteria as Mediators of Diet-Disease Relationships: Obesity and Inflammation and Cancer



- Bacterial endotoxin activates the immune system through gut epithelial Toll-like receptor 4.
- Endotoxin (LPS) may play a role in activation of immune cells in adipose tissue.



# Effect of Cheeses on Gut Microbiome in Rodents

- Camembert and microbes from milk fermented with yogurt starters can survive intestinal transit
- Had a beneficial influence on intestinal metabolism
  - a decrease in azoreductase activity and NH<sub>3</sub> concentration
  - an increase in mucolytic activities.
  - the proportion of ursodeoxycholic resulting from chenodeoxycholic epimerisation was higher
  - $\beta$ -galactosidases were higher
  - azoreductases and nitrate reductases were lower.
- Camembert feeding did not modify intestinal bacterial populations



# Summary



- Limited evidence from human studies linking specific dairy products with cancer risk.
  - *Often evaluate dairy products generally, not specific products*
- Research from animal studies focus on effects of specific compounds
  - *Often fed at high doses*
  - *Relevance to human health?*
- Future research needs to study specific dairy products, taking into consideration the differences among products.