Nutrition and gastrointestinal cancer: An update of the epidemiological evidence

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NuGOweek 2017

Varna, Bulgaria

Epidemiology of colorectal cancer

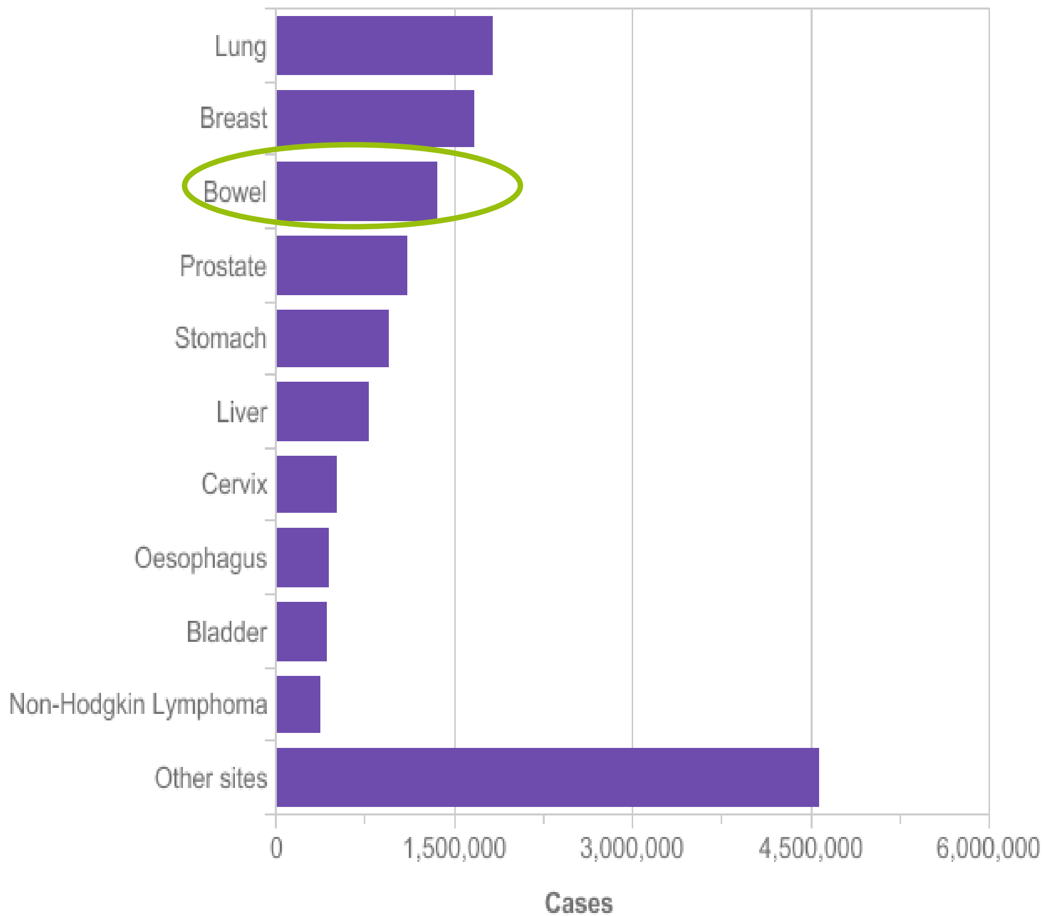
- Third most common cancer type

- Incidence

1.4 million new cases diagnosed in 2012

- Mortality

694,000 deaths in 2012

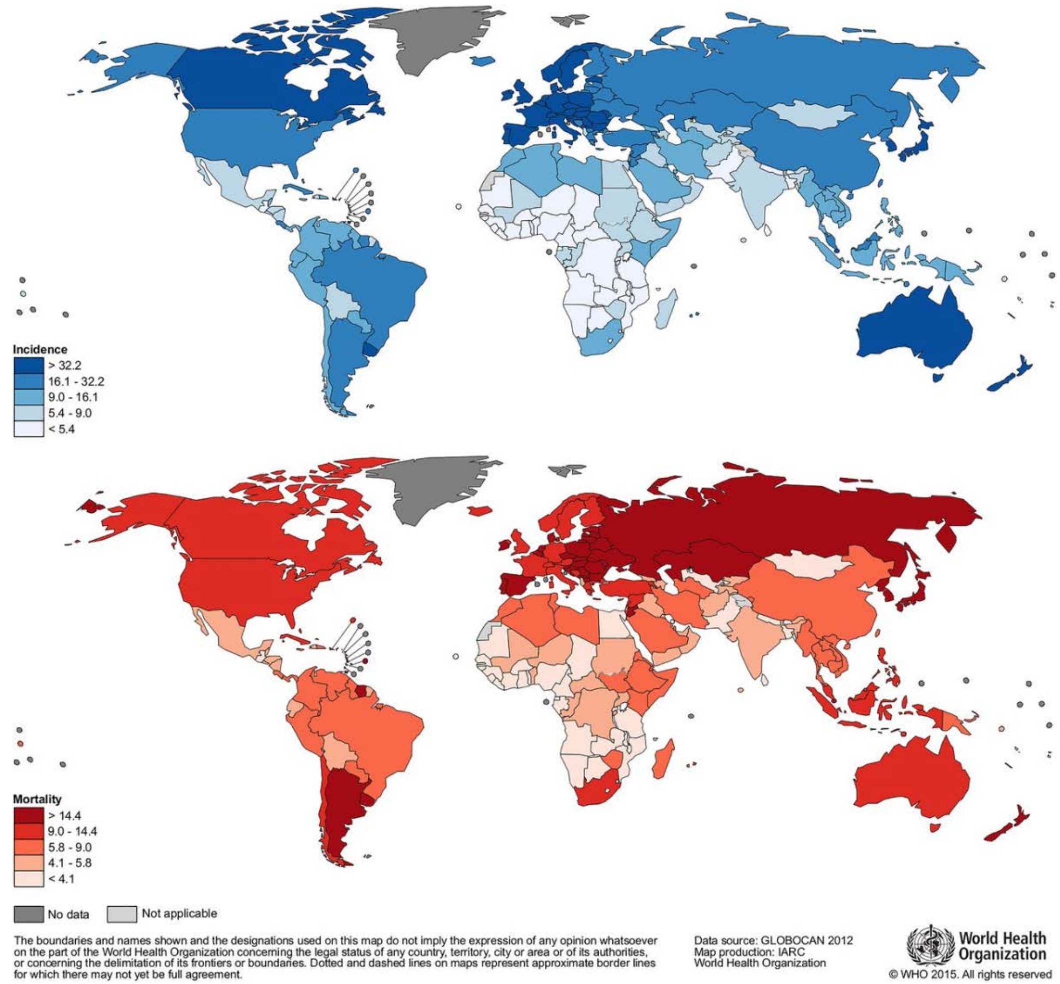


Total Number and Percentage of New Cases Diagnosed per Year, Worldwide

Ferlay et al. Int J Can 2014

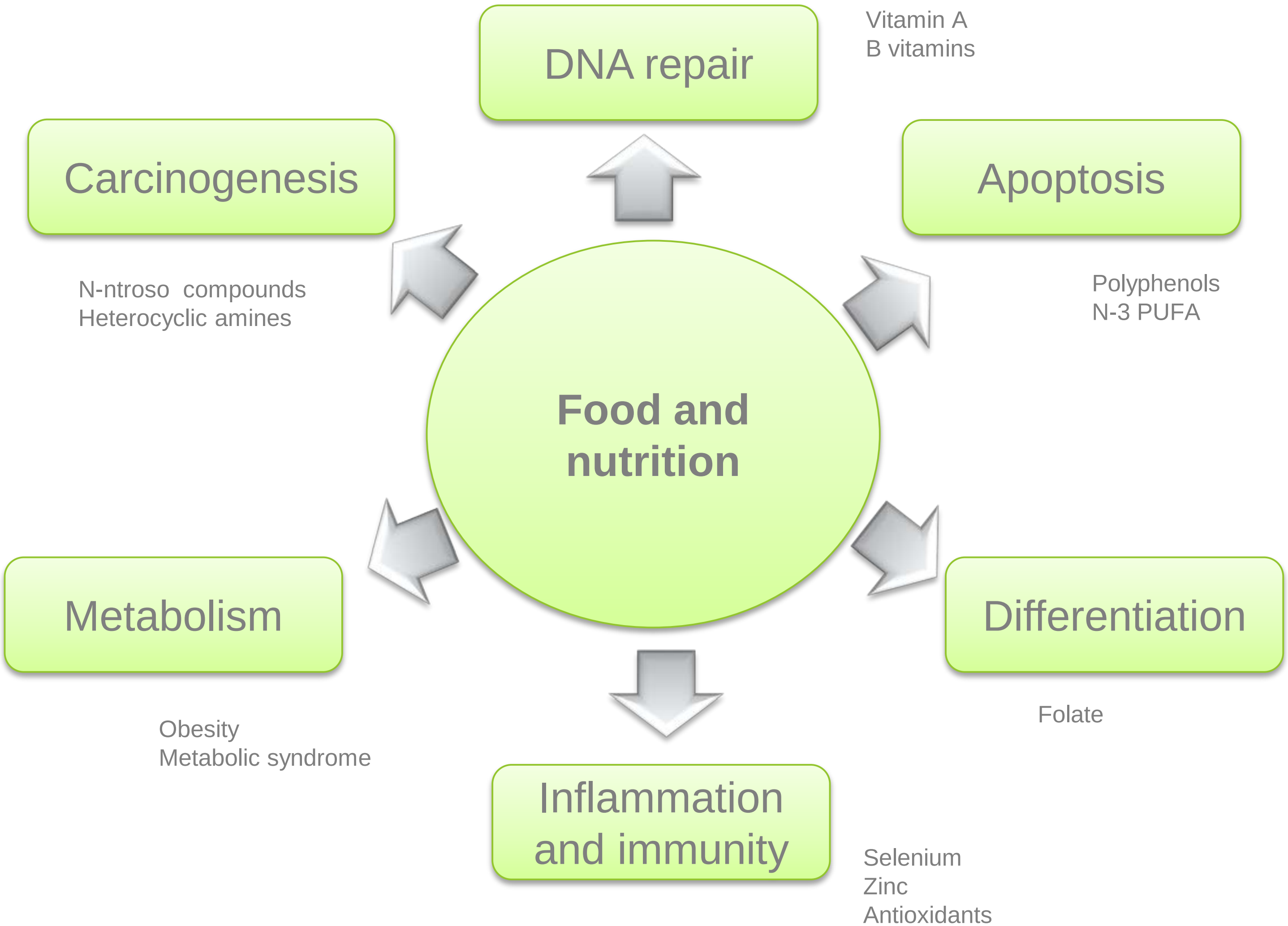
Epidemiology of colorectal cancer

- 54% of colorectal cancer cases occur in developed countries.
- More deaths (52%) in the less developed regions
- Increase by 60% by 2030
  - 2.2 million new cases
  - 1.1 million deaths



Arnold M et al. Gut 2016

Nutrition and cancer promoting mechanisms



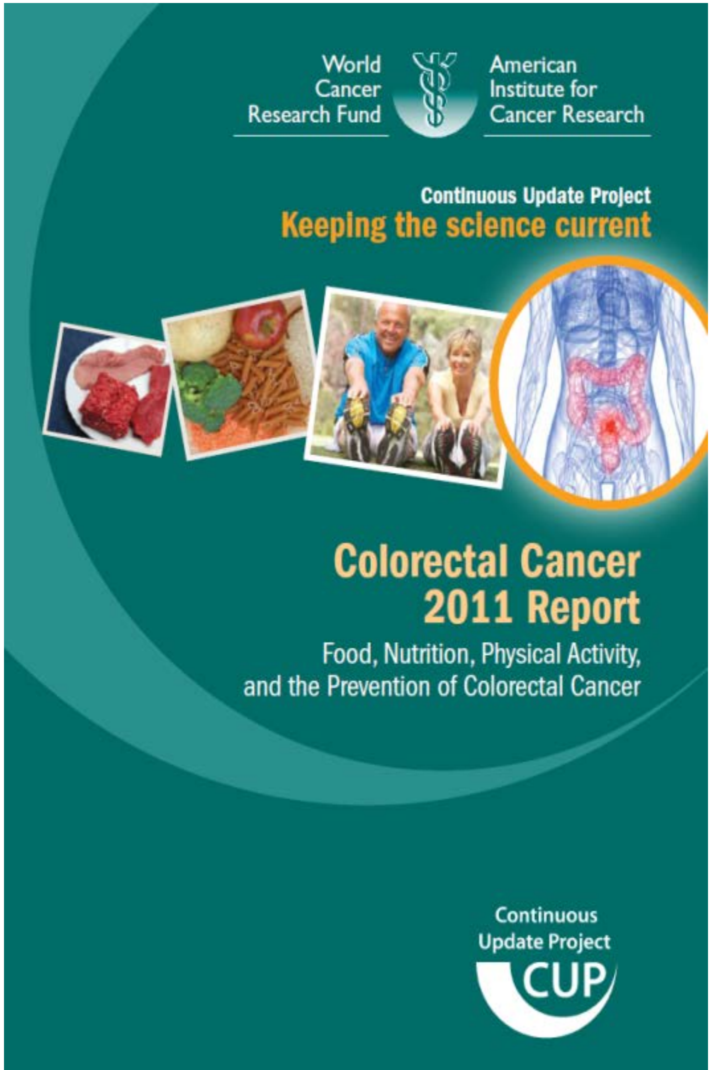
Objective

To review the meta-epidemiological evidence on the role of nutrition (including body composition) in colorectal cancer in order to identify potential targets for nutritional chemoprevention.

Methods

- **Umbrella review of evidence**
- **An online literature search**
  - MEDLINE, ISI Web of Science and Scopus
- **Studies published in English (up to June 2017)**
- **Inclusion criteria:**
  - Systematic literature reviews (SLRs) and meta-analyses (MAs) of observational studies
  - Most updated reviews and meta-analyses

Nutrition and colorectal cancer



FOOD, NUTRITION, PHYSICAL ACTIVITY AND CANCERS OF THE COLON AND THE RECTUM 2011

	DECREASES RISK	INCREASES RISK
Convincing	**Physical activity**[1,2] **Foods containing dietary fibre**[3]	**Red meat**[4,5] **Processed meat**[4,6] **Alcoholic drinks (men)**[7] **Body fatness** **Abdominal fatness** **Adult attained height**[8]
Probable	Garlic Milk[9] Calcium[10]	**Alcoholic drinks (women)**[7]
Substantial effect on risk unlikely	None identified	

1 Physical activity of all types: occupational, household, transport and recreational.
2 The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.
3 Includes both foods naturally containing the constituent and foods which have the constituent added. Dietary fibre is contained in plant foods.
4 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
5 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
6 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
7 The judgements for men and women are different because there are fewer data for women. For colorectal and colon cancers the effect appears stronger in men than in women.
8 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
9 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. The Panel judges that a higher intake of dietary calcium is one way in which milk could have a protective effect.
10 The evidence is derived from studies using supplements at a dose of 1200mg/day.

Red and processed meat

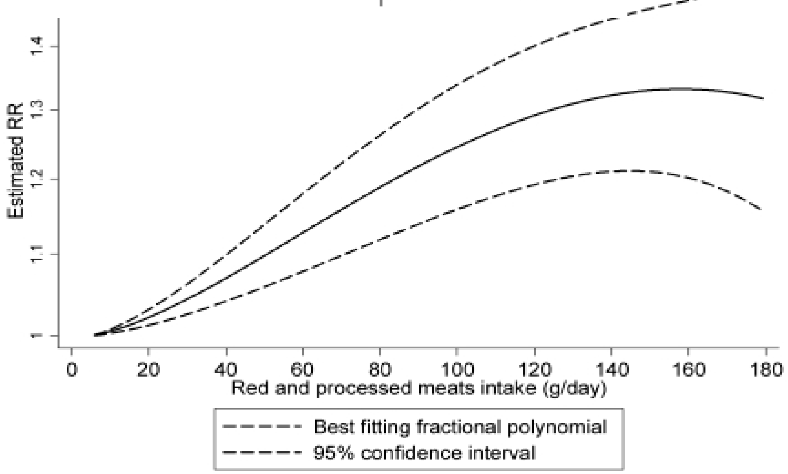
❖ Meta-anaylsis

– 13 prospective studies

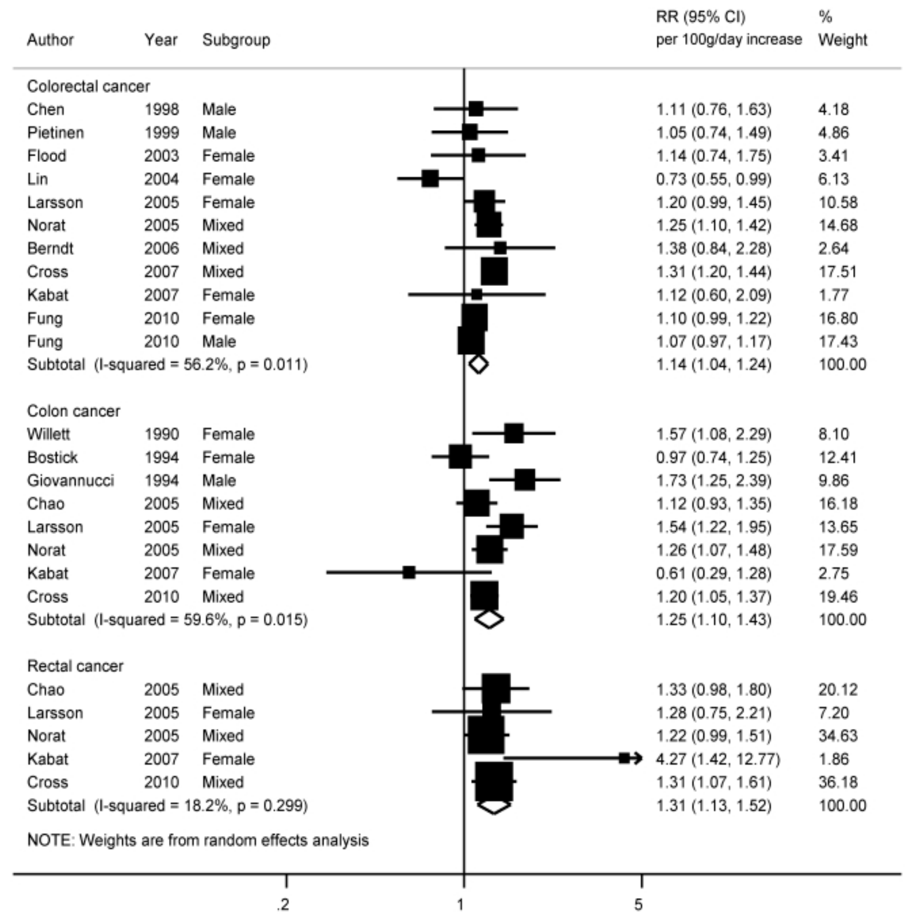
❖ Main results

– 14% risk increase in colorectal cancer for every 100 g/day increase of total red and processed meats

- Non-linear association
- Above 140 g/day, the risk increase is less pronounced.



Non-linear dose-response meta-analysis

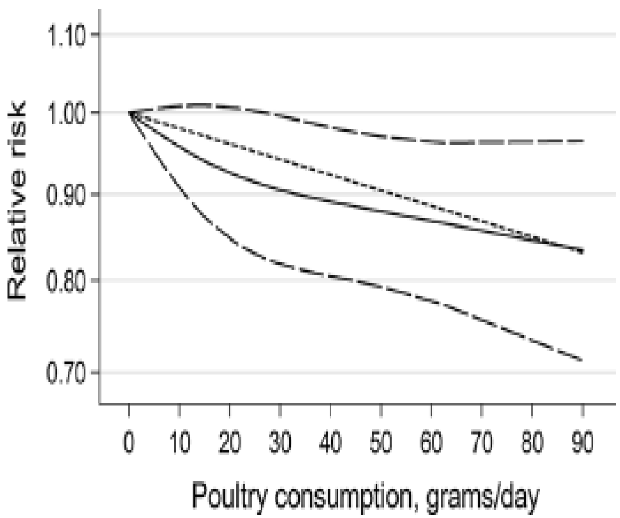


Meta-analyses of red and processed meat consumption and the risk of colorectal cancer

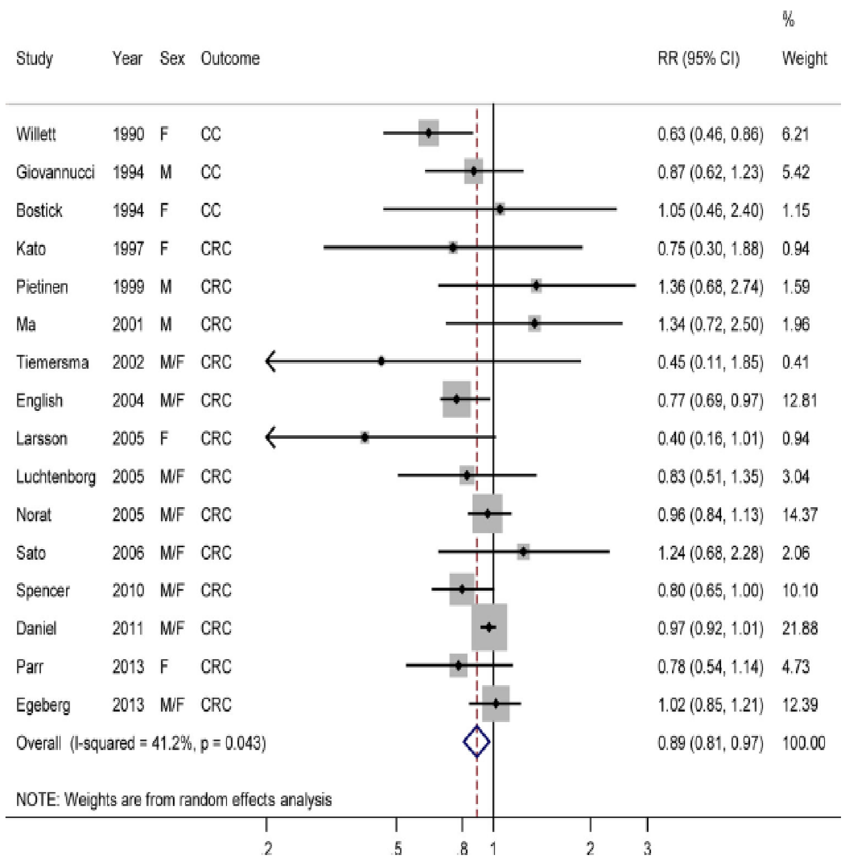
Chan D et al. Plos One 2011

Poultry and colorectal cancer

- **Meta-analysis**
  - 16 studies
- 11% lower risk for the highest versus lowest category of intake



Dose–response analysis between poultry intake and colorectal cancer



Meta-analysis of poultry intake and the risk of colorectal cancer

Shi Y et al. Eur J Nutr 2015

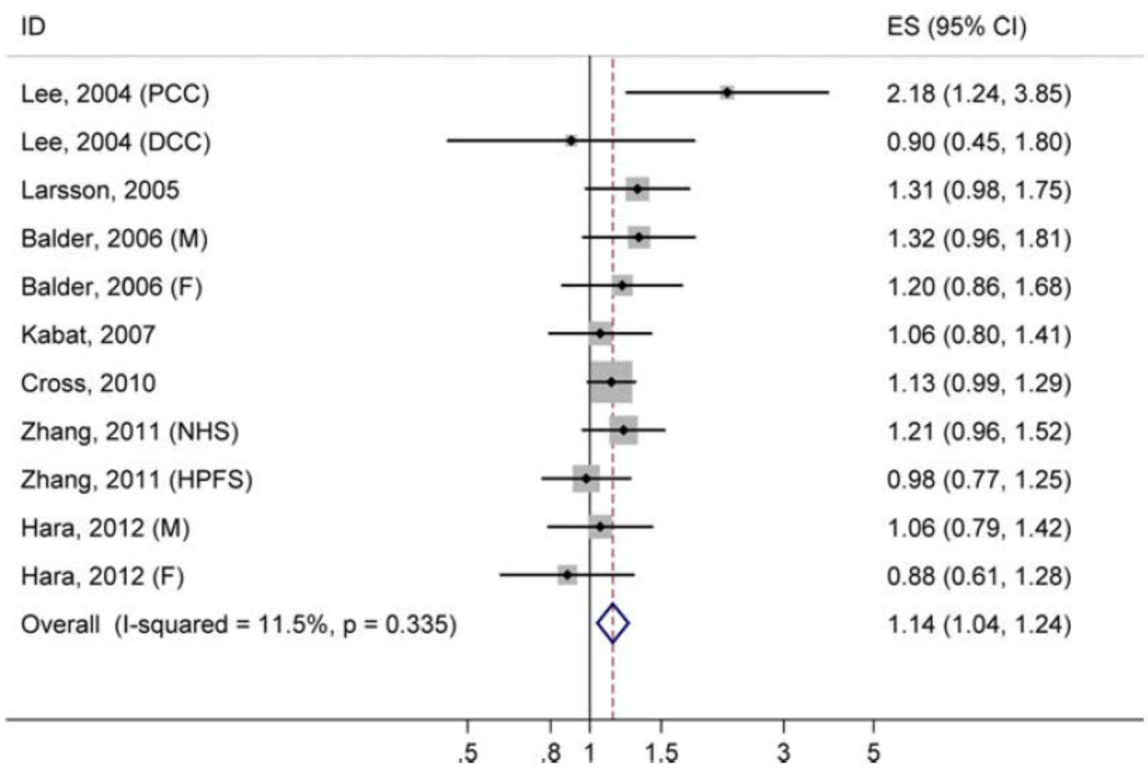
Heme iron

❖ Meta-anaylsis

– 7 prospective studies

❖ Main results

❖ 14% risk increase in colorectal cancer for high versus low heme iron intake



Meta-analysis of heme iron intake and the risk of colorectal cancer

Qiao& Feng Can Causes Control 2013

Alcohol and colorectal cancer

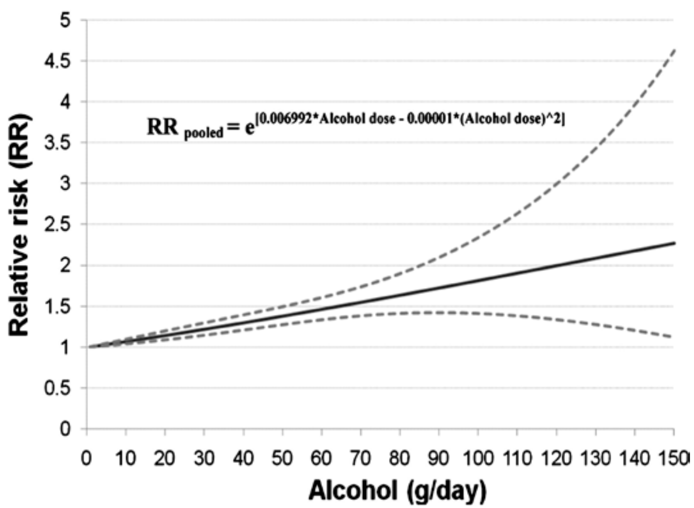
❖Meta-anaylsis

– 18 prospective studies

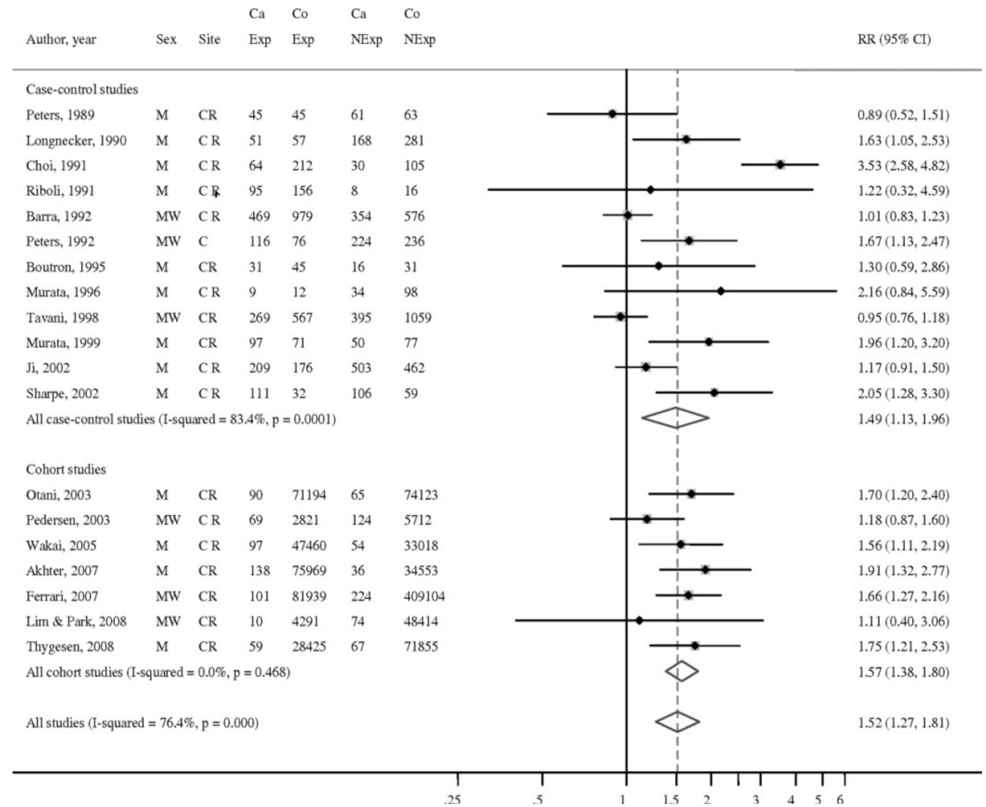
❖ Main results

– 21% higher risk for moderate alcohol drinking
– 52% higher risk for heavy (≥4 drinks/day) alcohol drinking compared to occasional drinking

7% , 38% and 82% higher risk for 10, 50, and 100 g/day of alcohol, respectively



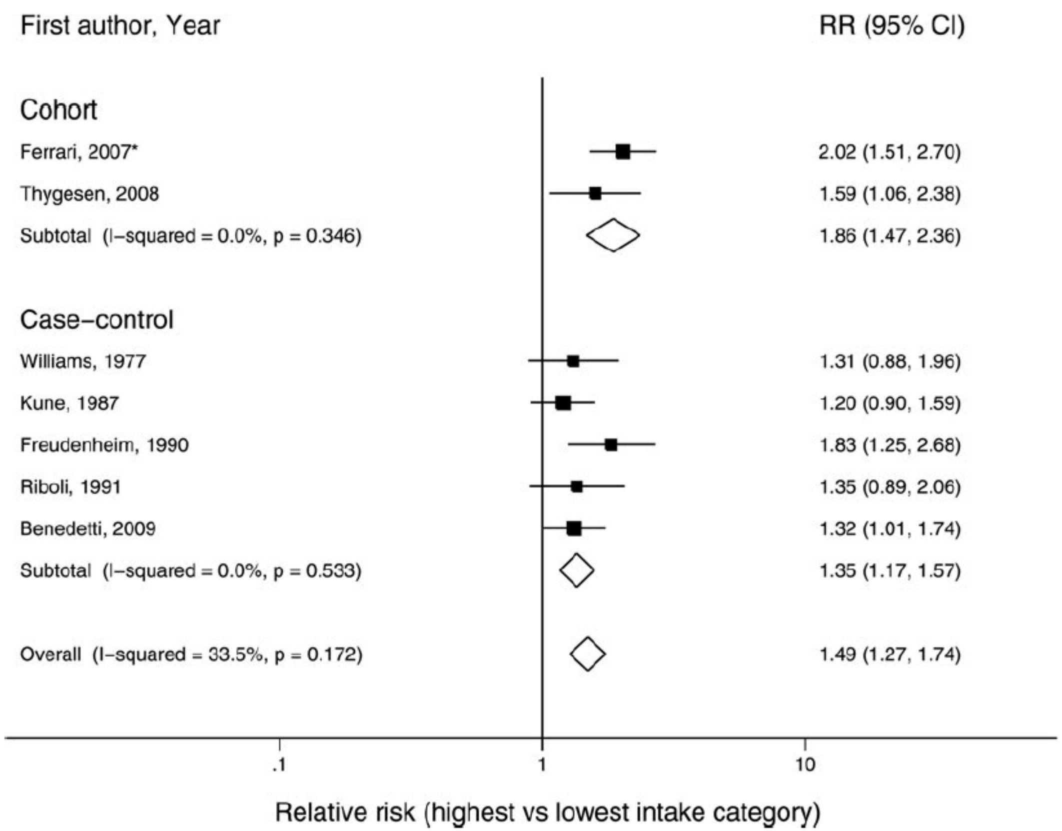
Dose-response meta-analysis of alcohol consumption



Meta-analysis of alcohol consumption (heavy versus occasional drinkers) and the risk of colorectal cancer

Fedirko V et al. Ann Oncol 2011

Lifetime alcohol



Meta-analysis of alcohol consumption measured during lifetime/over time and colorectal cancer

Jayasekara et al. Alcohol and Alcoholism 2016

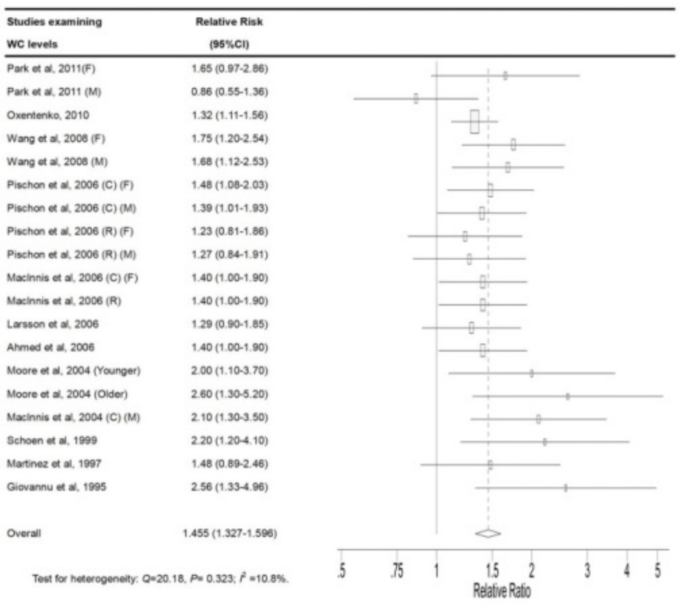
Obesity and colorectal cancer

❖Meta-anaylsis

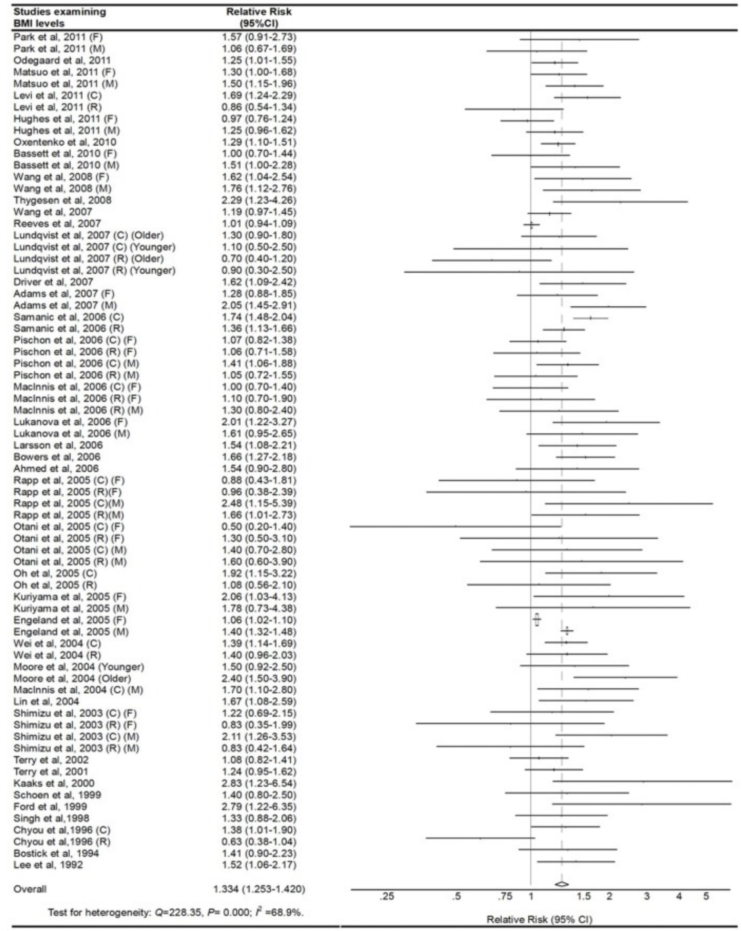
– 41 studies on general obesity
– 13 studies on central obesity

❖ Main results

– 33% higher risk for the obese vs. normal category of BMI
– 45% for the highest vs. lowest category of WC



Meta-analysis of general abdominal obesity (waist circumference) and the risk of colorectal cancer



Meta-analysis of general obesity (body mass index) and the risk of colorectal cancer

Ma Plos One 2013

Weight gain and colorectal cancer

❖ Meta-anaylsis

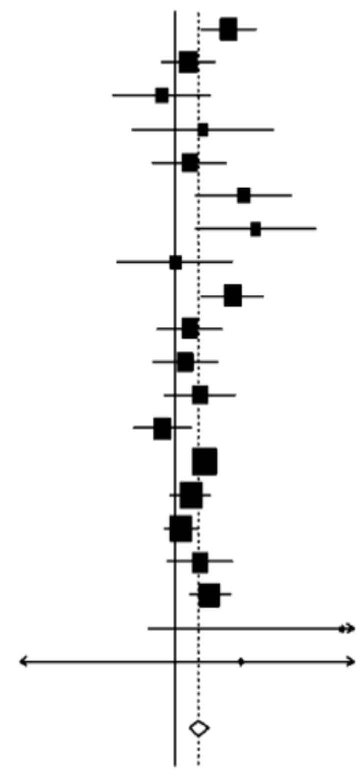
– 18 prospective studies

❖ Main results

– 22 % higher risk for high body weight gain (midpoint: 15.2 kg) compared with stable weight

Study	Design	Sex	Site	RR	95% CI
All					
Campbell *et al.* (22)	Case-control study	M	CRC	1.63	[1.27; 2.08]
Campbell *et al.* (22)	Case-control study	W	CRC	1.13	[0.89; 1.43]
Rapp *et al.* (19)	Cohort study	M	CC	0.89	[0.58; 1.37]
Rapp *et al.* (19)	Cohort study	M	RC	1.29	[0.68; 2.45]
Rapp *et al.* (19)	Cohort study	W	CC	1.14	[0.82; 1.60]
Thygesen *et al.* (18)	Cohort study	M	CC	1.86	[1.21; 2.86]
Bassett *et al.* (17)	Cohort study	M	CC	2.08	[1.21; 3.57]
Bassett *et al.* (17)	Cohort study	F	CC	1.01	[0.60; 1.68]
Campbell *et al.* (23)	Case-control study	M, W	CRC	1.68	[1.27; 2.22]
Laake *et al.* (16)	Cohort study	M	CC	1.15	[0.86; 1.53]
Laake *et al.* (16)	Cohort study	W	CC	1.10	[0.83; 1.47]
Hughes *et al.* (15)	Cohort study	M	CRC	1.26	[0.92; 1.73]
Hughes *et al.* (15)	Cohort study	W	CRC	0.90	[0.69; 1.17]
Renehan *et al.* (14)	Cohort study	M	CC	1.31	[1.18; 1.45]
Renehan *et al.* (14)	Cohort study	M	RC	1.16	[0.97; 1.39]
Renehan *et al.* (14)	Cohort study	W	CC	1.06	[0.91; 1.24]
Renehan *et al.* (14)	Cohort study	W	RC	1.26	[0.94; 1.68]
Aleksandrova *et al.* (13)	Cohort study	M, W	CRC	1.38	[1.14; 1.66]
Han *et al.* (11)	Cohort study	M	CRC	4.50	[0.79; 25.55]
Han *et al.* (11)	Cohort study	W	CRC	1.81	[0.14; 23.06]
I^2= 46.3%, *P* for heterogeneity=0.013				**1.24**	**[1.14; 1.36]**

Hazard ratio



P for non-linearity=0.463

Meta-analysis of weight gain in adult life and the risk of colorectal cancer

Schlesinger S Aleksandrova K et al. Obes Rev 2013

Physical activity and colorectal cancer

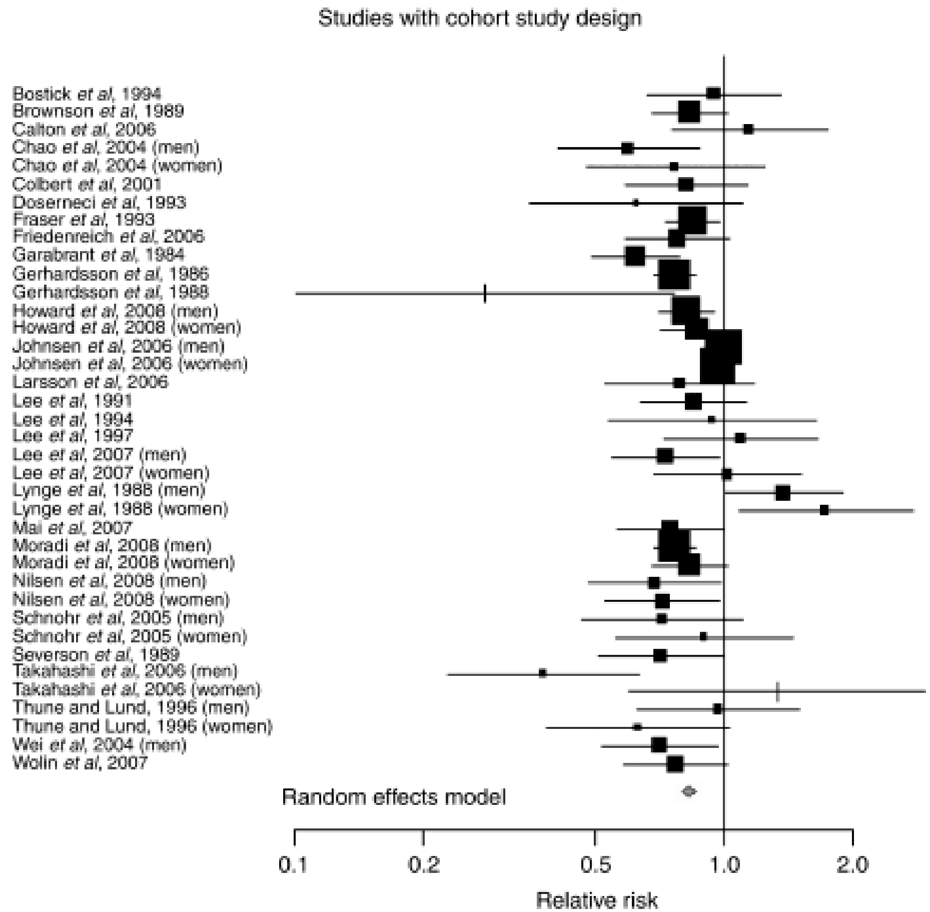
❖Meta-anaylsis

– 28 cohort

❖ Main results

- 17% lower risk for high vs. low physical activity

- Similar results for men and women



Meta-analysis of physical activity and colon cancer: cohort studies

Wollin K et al. Br J Can 2009

Dietary fibre

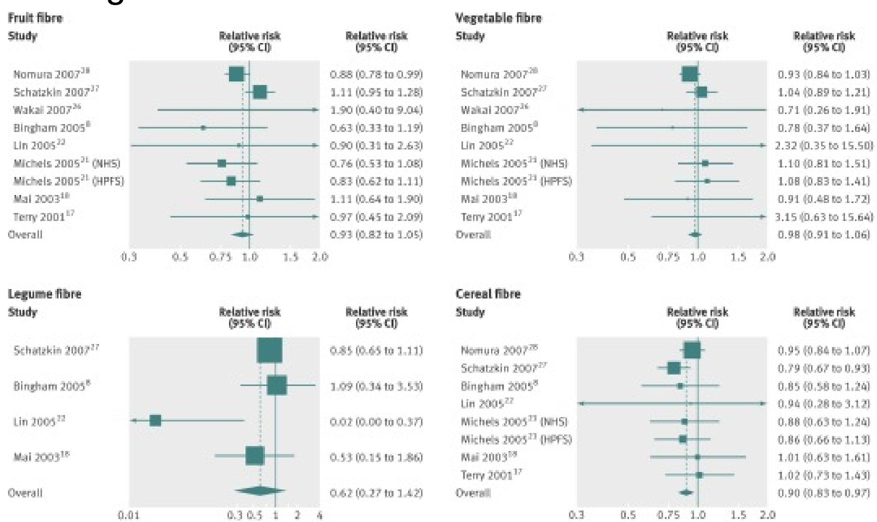
❖Meta-anaylsis

– 21 prospective studies

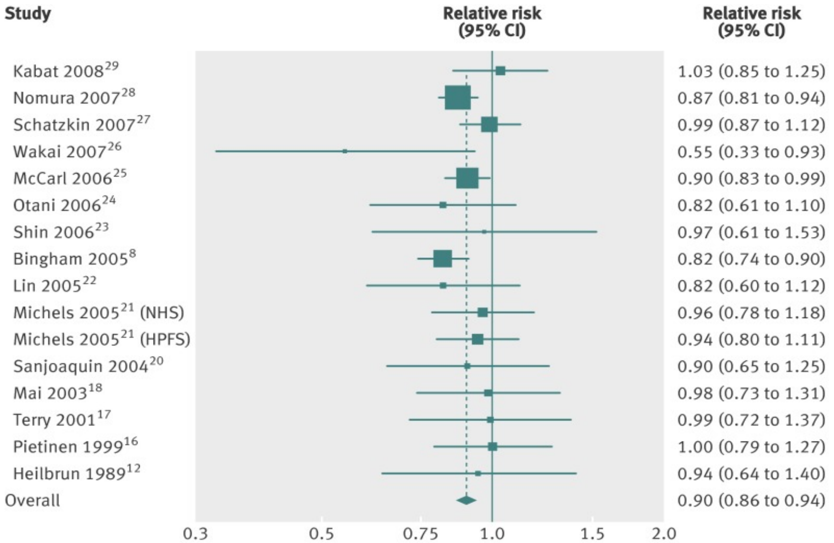
❖ Main results

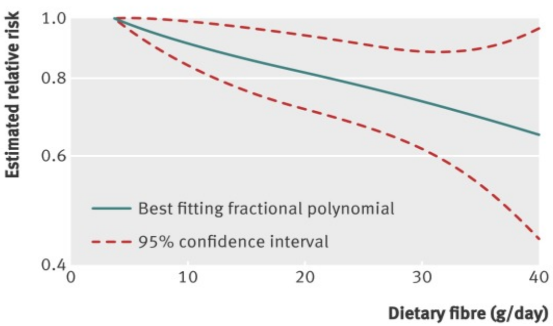
– inverse association between intake of dietary fibre, cereal fibre, and whole grains

– no significant evidence for fibre from fruit, vegetables, or legumes.



Meta-analysis of dietary fibre types and the risk of colorectal cancer





Dose-response analysis of dietary fibre and risk of colorectal cancer

Aune D et al. BMJ 2011

Fruits and vegetables intake and colorectal cancer risk

❖Meta-anaylsis

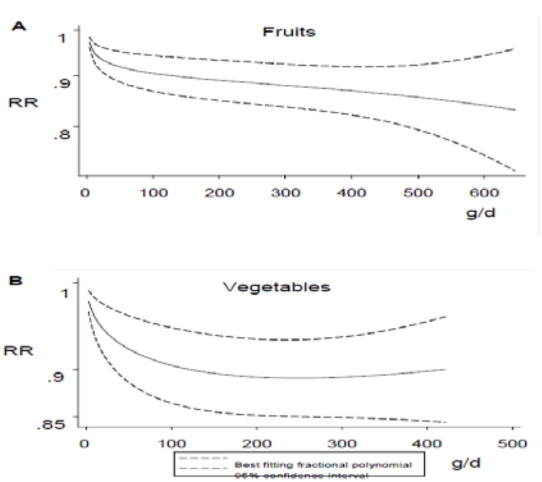
– 19 prospective cohort studies

❖ Main results

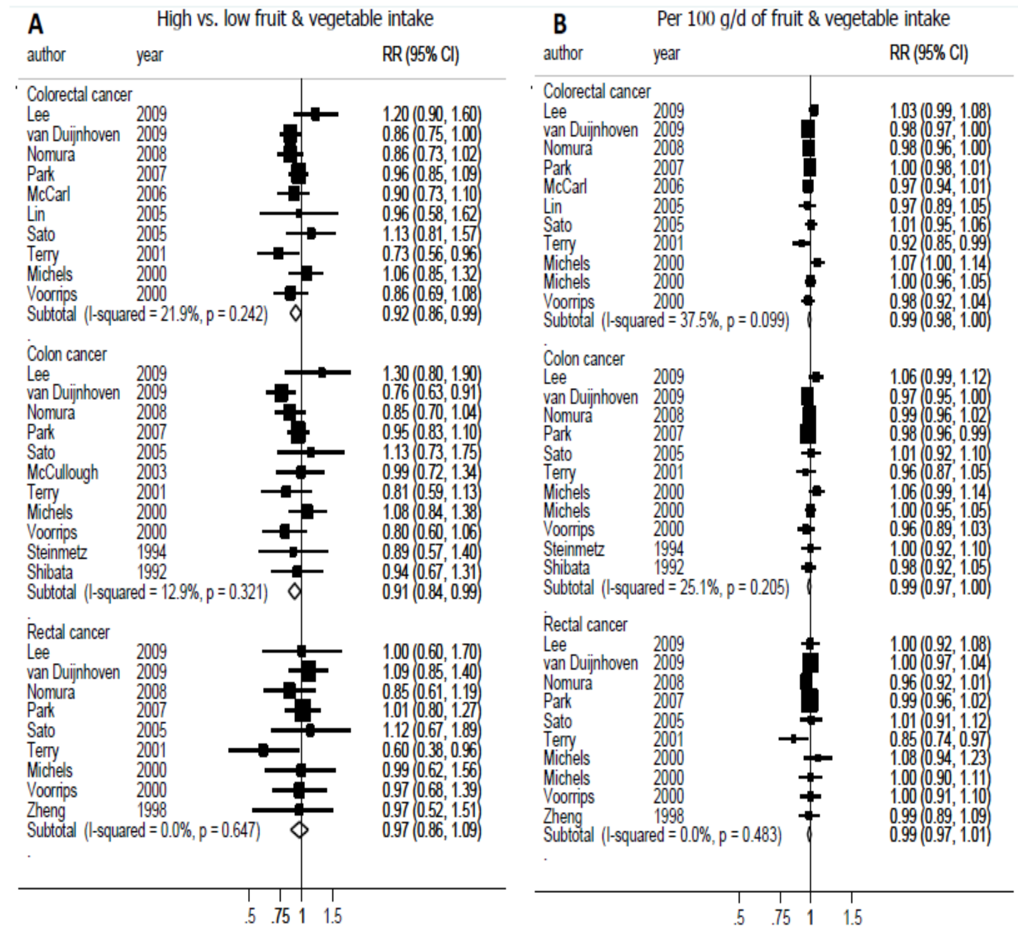
- 8 % lower risk for high vs. low intake

- Non-linear association
- Greatest reduction in risk when increasing intake from very low levels

Figure 5. Fruits and vegetables and colorectal cancer



Dose-response analysis of fruits and vegetables and risk of colorectal cancer



Keum N et al. Int J Can 2014

Dairy products

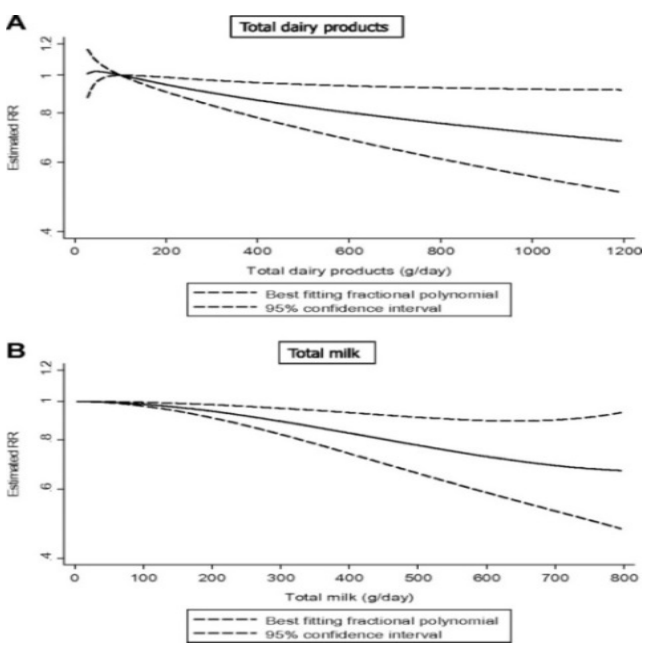
❖**Meta-anaylsis**

– 12 cohort studies

– **Main results**

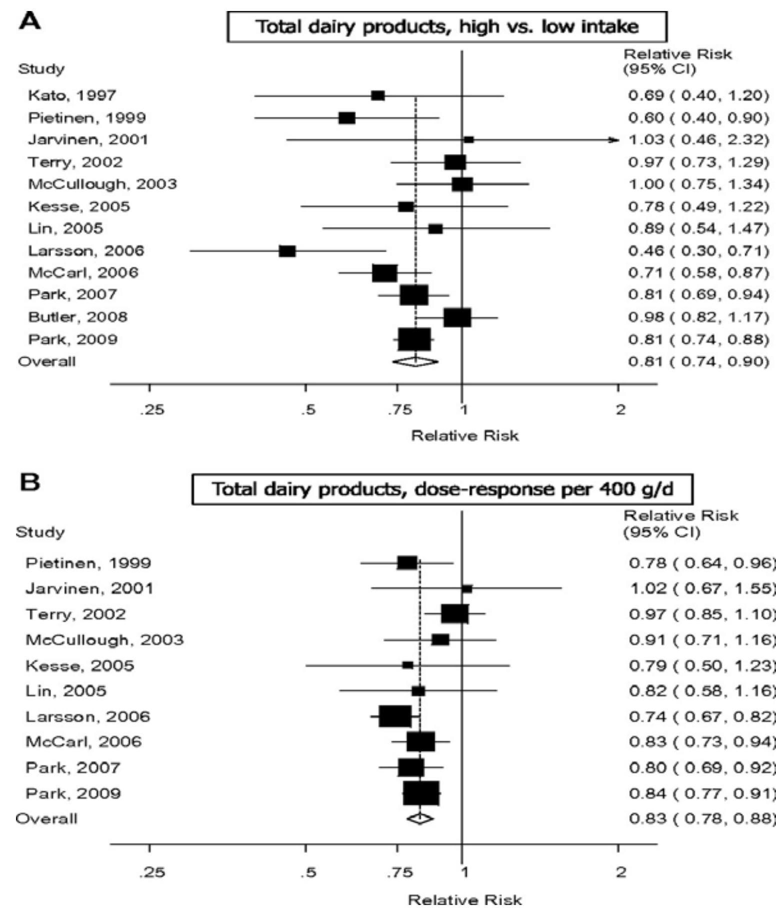
– 19% lower risk for colon cancer the high versus low intake

– **No association for rectal cancer**



Dose-response analysis of diary and milk and risk of colorectal cancer

Total dairy products and colorectal cancer



Meta-analysis of dairy products and the risk of colorectal cancer

Aune D. Ann Oncol. 2012

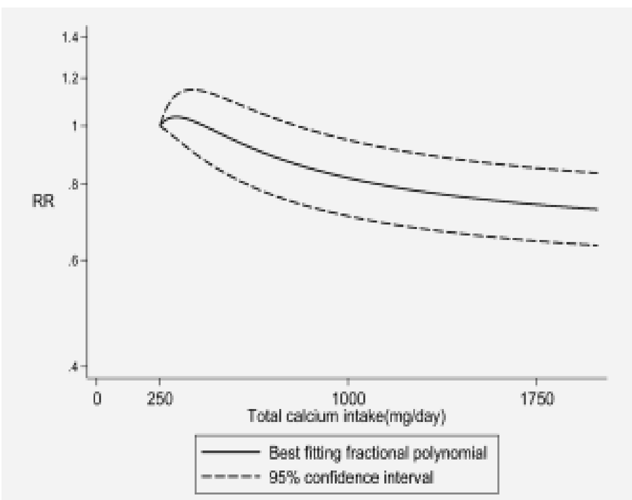
Calcium intake and colorectal cancer risk

❖Meta-anaylsis

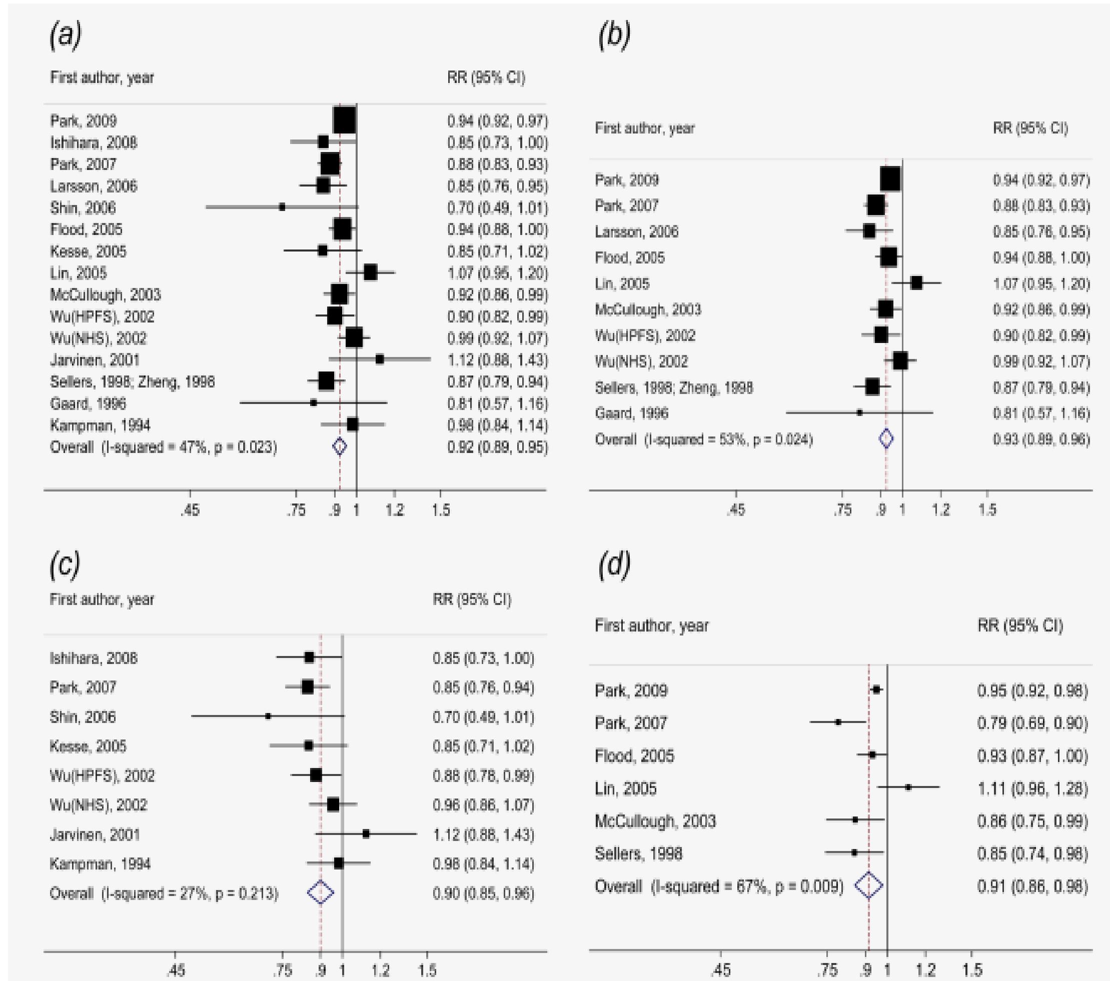
– 15 prospective cohort studies

❖ Main results

– Total calcium intake: 8% lower risk for each 300 mg/day increase
– Supplementary calcium: 9% lower risk for each 300 mg/day increase



Dose-response analysis of dietary calcium and risk of colorectal cancer



Keum N et al. Int J Can 2014

Vitamin D and colorectal cancer

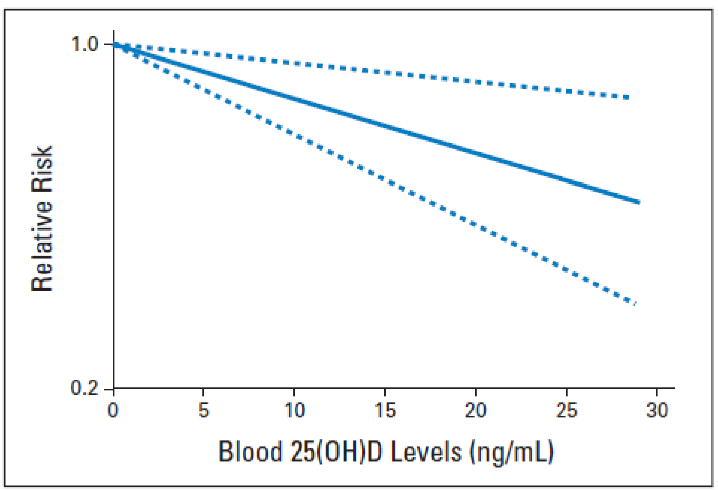
❖Meta-anaylsis

- 9 prospective cohort studies vitamin D intake
- 9 studies on 25-hydroxyvitamin D [25(OH)D]

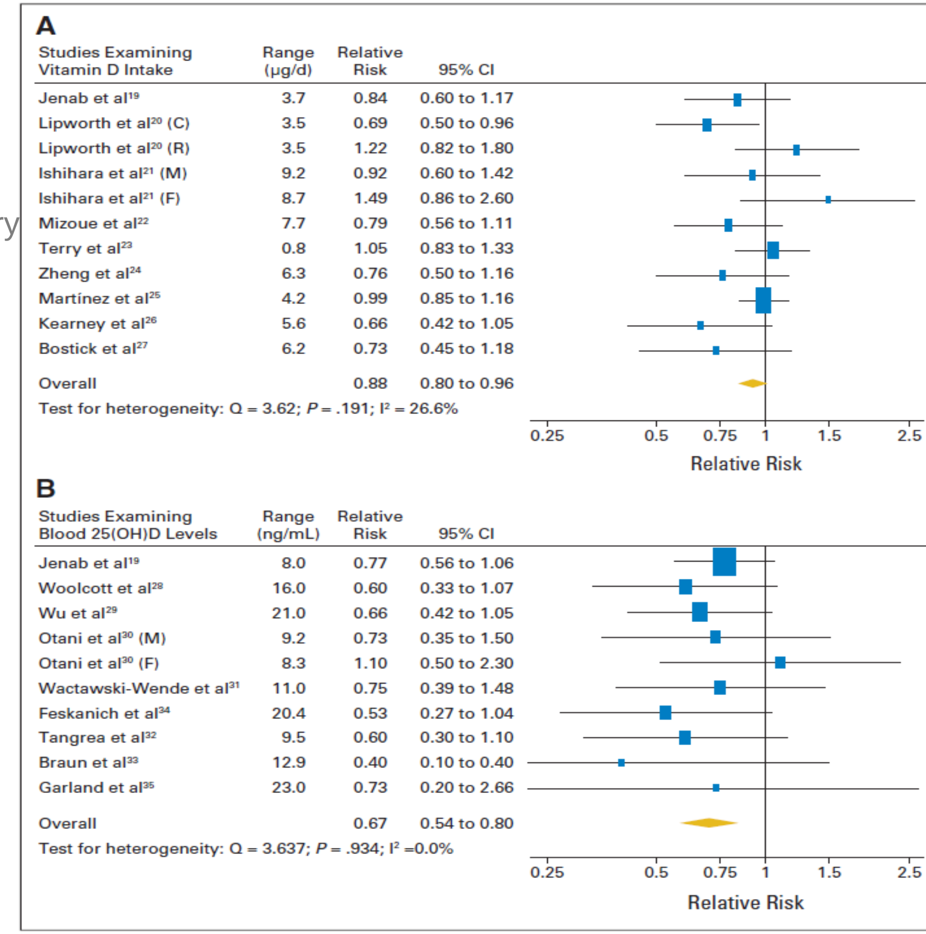
❖ Main results

- 12% lower risk for highest versus lowest category reported vitamin D intake
- 33% lower risk for blood 25(OH)D levels

A 10 ng/mL increment in blood 25(OH)D level conferred an RR of 0.74 (95% CI, 0.63 to 0.89)



Dose-response analysis of blood 25(OH) D levels and risk of colorectal cancer



Relative risks of colorectal cancer for the highest versus lowest categories of (A) vitamin D intake or (B) 25-hydroxyvitamin D [25(OH)D] blood level

Ma Y et al. J Clin Oncol 2011

Dietary supplements

❖Meta-anaylsis

– 25 prospective cohort studies

❖ Main results

- 8 % lower risk for use versus non-use of r multivitamins
-14% lower risk for calcium supplements

Inconsistent associations: supplemental vitamin A, vitamin C, vitamin E, vitamin D, garlic and folic acid.

Summary RRs of "use- no use" meta-analyses and "highest-lowest" meta-analyses for the association of dietary supplement use and colorectal cancer risk

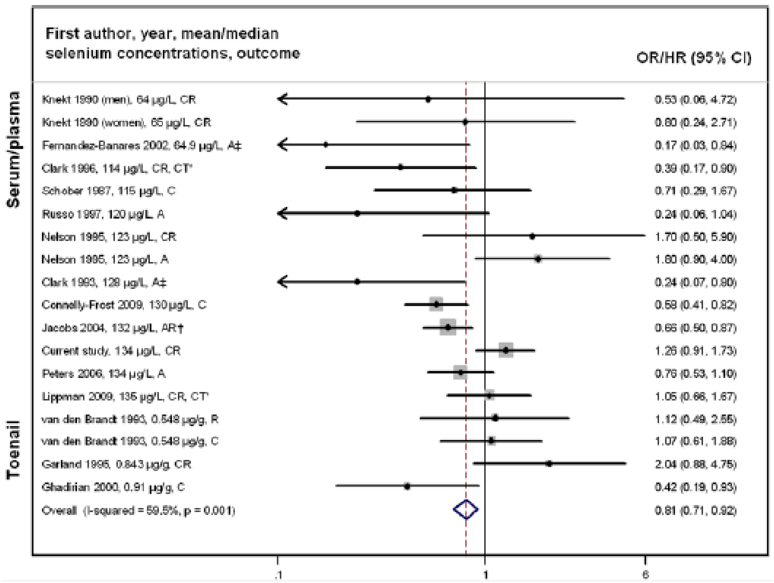
Dietary supplement	Summary RR	95% CI	I^2, $p_{\text{heterogeneity}}$	Included studies	Outcome[1]
Use-no use meta-analyses					
Multivitamins	0.92	0.87, 0.97	4.9%, $p = 0.39$	7[26–32]	CRC
Multivitamins (including Pooling Project)	0.92	0.86, 0.98	0.0%, $p = 0.43$	16[21,28,29,31]	CRC
Vitamin A	0.77	0.62, 0.94	0.0%, $p = 0.76$	2[33,34]	CC
Vitamin C	0.87	0.63, 1.21	77.4%, $p = 0.01$	3[33–35]	CC
Vitamin E	0.85	0.72, 1.01	20.0%, $p = 0.29$	5[33–36]	CC
Vitamin D	0.92	0.78, 1.09	53.9%, $p = 0.07$	5[34,37,38,40,41,]	CRC
Calcium	0.86	0.79, 0.95	63.7%, $p = 0.01$	8[34,37,40,42–46]	CRC
Garlic	1.24	0.99, 1.54	0.0%, $p = 0.34$	2[48,49]	CRC
Highest-lowest meta-analyses					
Vitamin A	0.79	0.62, 1.01	0.0%, $p = 0.97$	2[33,34]	CC
Vitamin C	0.85	0.68, 1.05	10.9%, $p = 0.33$	3[33–35]	CC
Vitamin E	0.82	0.67, 0.99	11.0%, $p = 0.34$	5[33–36]	CC
Vitamin D	0.87	0.62, 1.22	67.1%, $p = 0.03$	4[34,37,39,40]	CRC
Calcium	0.80	0.70, 0.92	49.2%, $p = 0.08$	6[34,37,40,42–44]	CRC
Folic acid	0.88	0.78, 0.98	6.2%, $p = 0.34$	3[32,35,47]	CRC

Heine-Bröring R et al. Int J Can 2014

Micronutrients

Selenium

❖ 12 observational studies and two clinical trials



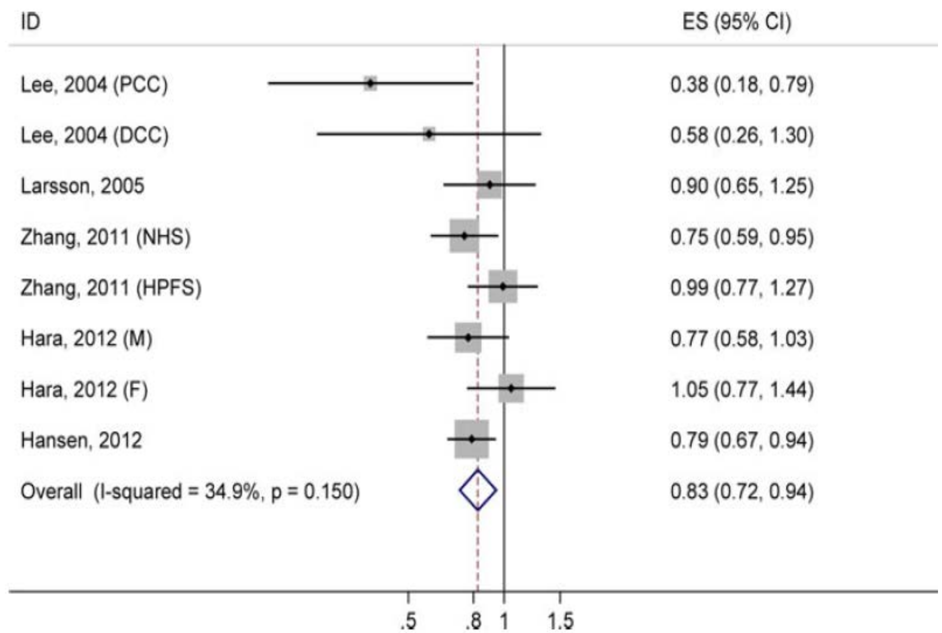
Meta-analysis of selenium and the risk of colorectal cancer*

*Ordered by biospecimen type (serum/plasma and toenail samples) and by selenium concentrations within each biospecimen type

Takata Y et al. CEBP 2011

Zinc

❖ 6 prospective cohort studies



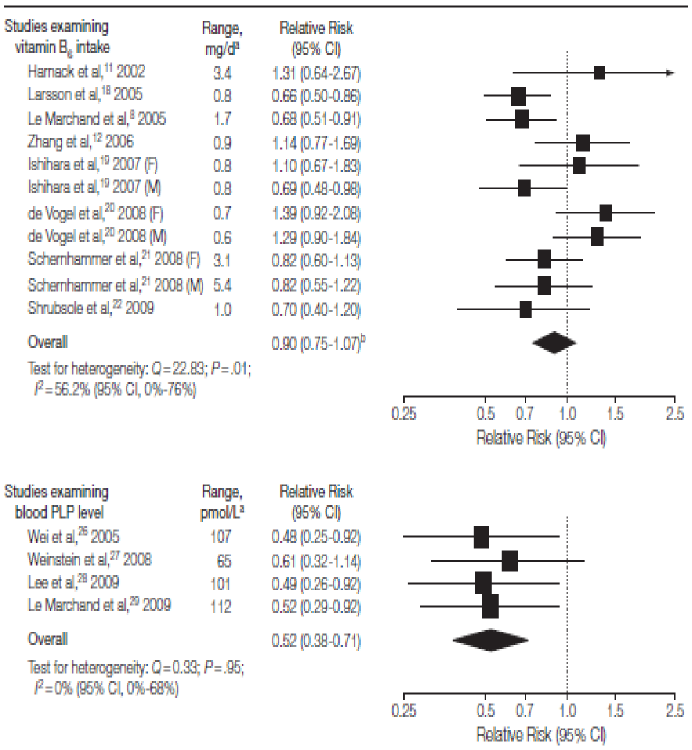
Meta-analysis of zinc and risk of colorectal cancer

Qiao& Feng Can Causes Control 2013

One-carbon metabolic pathway

Vitamin B 6

- 9 studies on vitamin B6 intake
- 4 studies on blood PLP levels

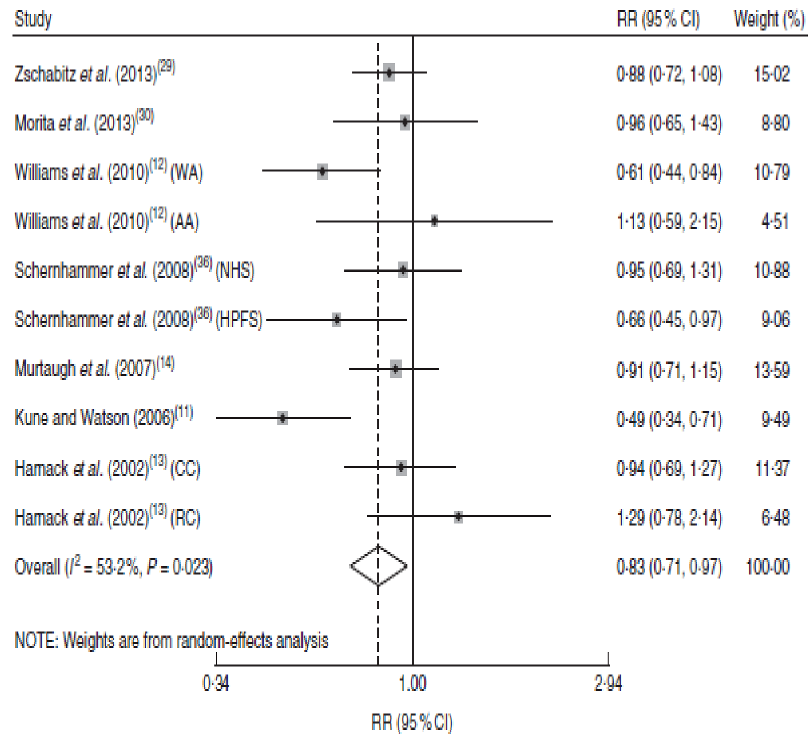


Meta-analysis of vitamin B6 intake or blood PLP Level and risk of colorectal cancer

Larsson S, Orsin N&Yolk A et al. JAMA 2010

Vitamin B 12

- 17 observational studies (incl 5 cohort studies)



Meta-analysis of vitamin B12 intake and risk of colorectal cancer

Sun NH et al. Public Health Nutrition 2015

Summary

- High body fatness (central adiposity): major risk factor for colorectal cancer

- Other established factors
  - alcohol, red and processed meat intake
  - whole grain intake

- Potential for chemoprevention through optimising micronutrient intakes:
  i.e. calcium, vitamin D, vitamin B6 and B12, zinc and selenium

- However, more data from radomised control trials would be needed

Outlook

- Further research focus on

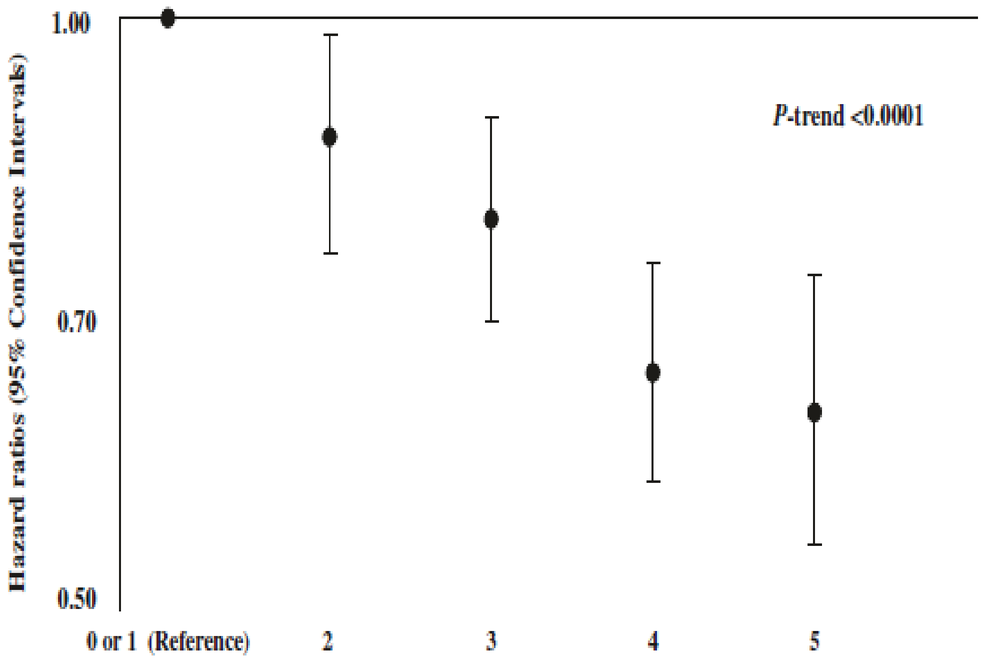
  - Complex dietary patterns&lifestyles
  - Micronutrients with chemopreventive potential
  - Targeted prevention via modulation of cancer-related biomarkers

- Prevention focus on
  - complex lifestyle recommendations
  - patient education about nutritional risks and benefits (i.e. processed meat)
  - identification of high-risk individuals
  - empowerment for behaviour changes

Combined impact of nutritional factors

Lifestyle factor	Index points	Description
Overweight and obesity[a]	0	Overweight or obese: BMI ≥25 kg/m^2 or waist circumference ≥94 cm for men and ≥80 cm for women
	1	Healthy weight: BMI 18 to 25 kg/m^2 or waist circumference <94 for men cm and <80 for women
Physical activity[b]	0	Low and very low physical activity: sedentary or standing occupation and recreational METs ≤57 for men and METs ≤82 for women
	1	High and very high physical activity: manual or heavy manual occupation and recreational METs >57 for men and METs >82 for women
Smoking	0	Smoking: current smokers
	1	Non-smoking: never or former smokers
Alcohol consumption	0	Heavy alcohol consumption: not adherent to alcohol consumption recommendations of WCRF/AICR (2007) [15] for two standard drinks a day (>24 g/day) for men and one standard drink a day (>12 g/day) for women
	1	Limited alcohol consumption: adherent to alcohol consumption recommendations of WCRF/AICR (2007) [15,16] for two standard drinks a day (≤24 g/day) for men and one standard drink a day (≤12 g/day) for women
Diet quality[c]	0	Unhealthy diet quality: 0 to 4 points of the diet index of colorectal cancer related foods
	1	Healthy diet quality: 5 to 8 points of the diet index of colorectal cancer related foods

Based on data from 350 000 men and women in the EPIC cohort



Number of lifestyle factors

Aleksandrova K et al. BMC Medicine 2014

THANK YOU FOR YOUR ATTENTION!

Biomarkers of Obesity

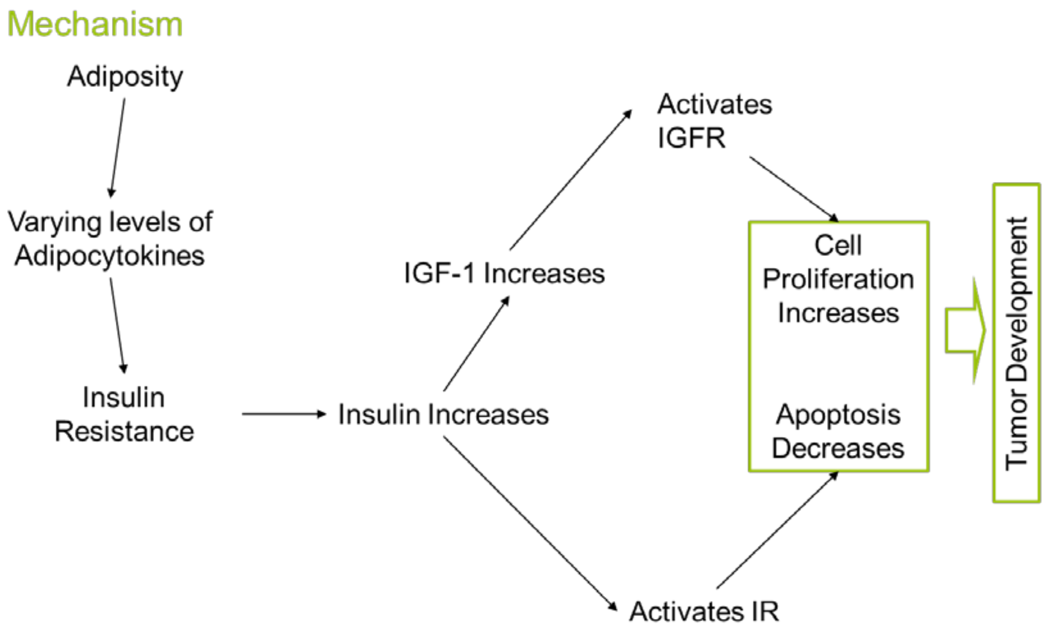
Adipose tissue

- Established relationship with insulin resistance
- Play a role in the regulation of insulin signaling and action

Source of inflammation

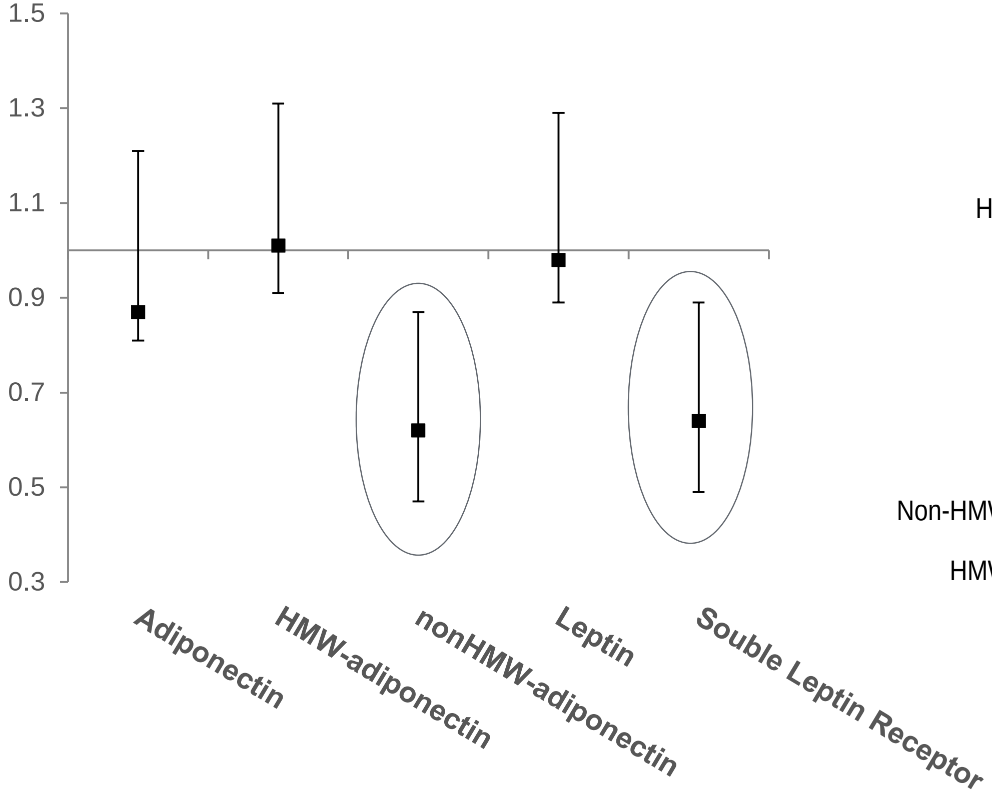
Adipocytokines

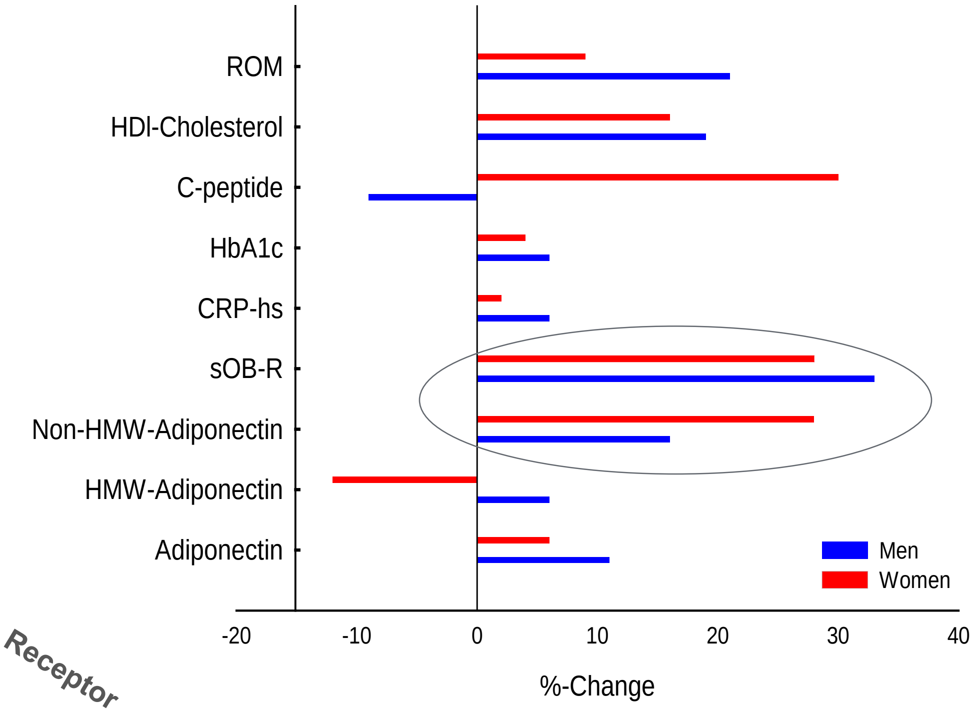
- Leptin
- Adiponectin
- IL-6
- TNFalpha
- Free fatty acids
- Resistin



Does obesity drive these changes in hormones or do hormones drive changes in body shape, weight, and adiposity?

Biomarkers of Obesity: Data from the EPIC cohort





Percent change in the association between abdominal obesity and colon cancer with adjustment for biomarkers

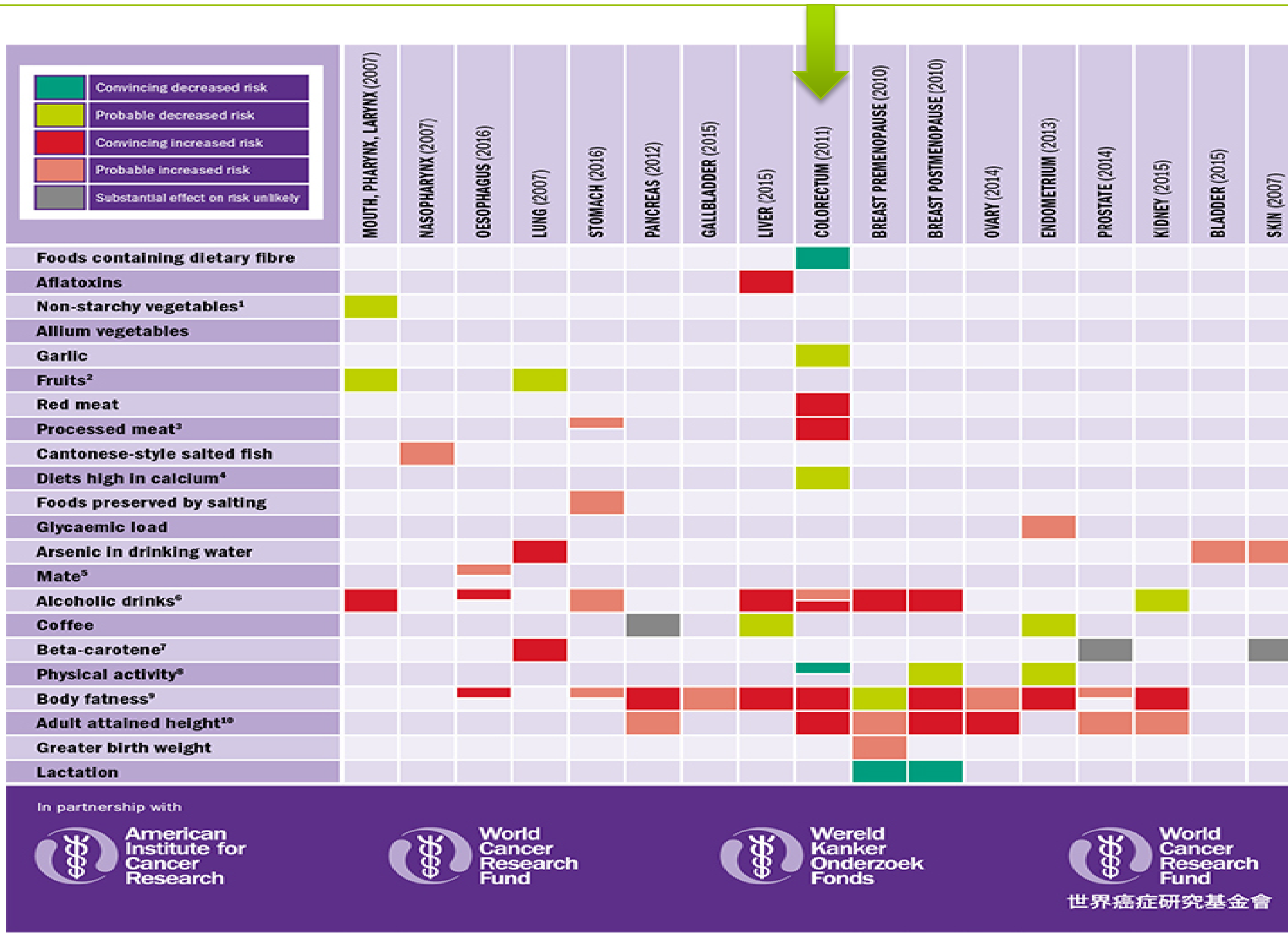
Multivariable-adjusted RRs associated with an increase in continuous log-transformed biomarker concentrations.

Models are stratified for EPIC center, age, sex, fasting status, date of blood collection, and adjusted for smoking status, education , alcohol, physical activity , red and processed meat, fish and shellfish ,fruits and vegetables , body mass index and waist circumference.

Evidence matrix

CUP Continuous Update Project

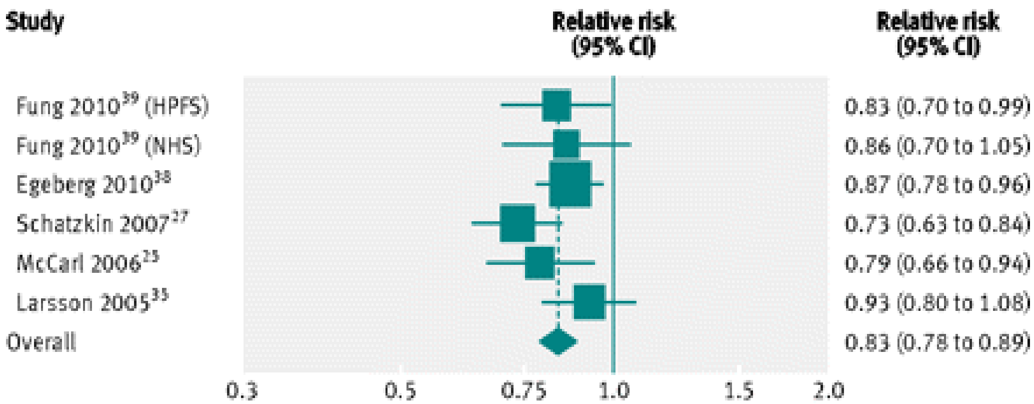
Analysing research on cancer prevention and survival

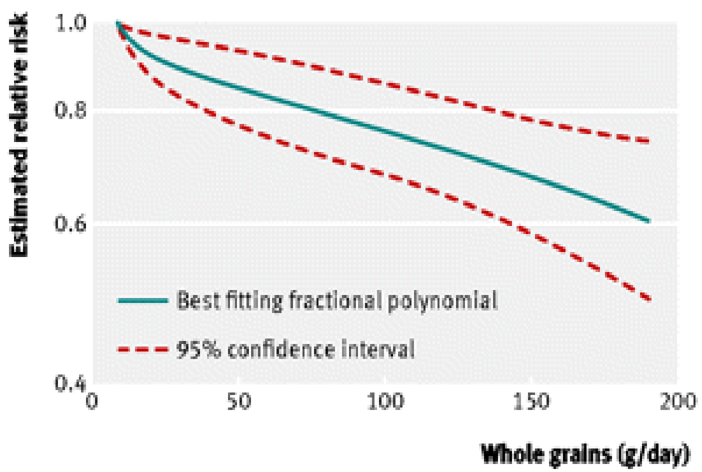


Whole grains and colorectal cancer

- **Meta-anaylsis**
  - 6 studies

- **Main results**
  - 10% reduction in risk of colorectal cancer for each 10 g/day intake of total dietary fibre and cereal fibre
  - 20% reduction for each three servings (90 g/day) of whole grain daily





Meta-analysis of whole grains and the risk of colorectal cancer

Aune D et al. BMJ 2011