Prevention of cancer – the influence of diet

Food Network, 2010
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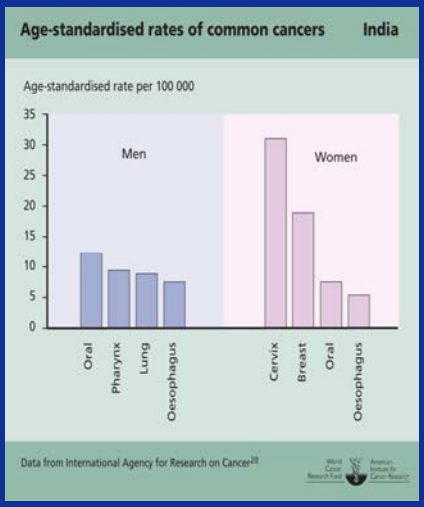
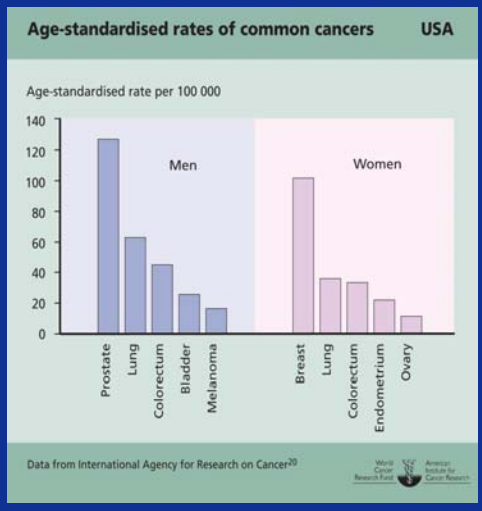
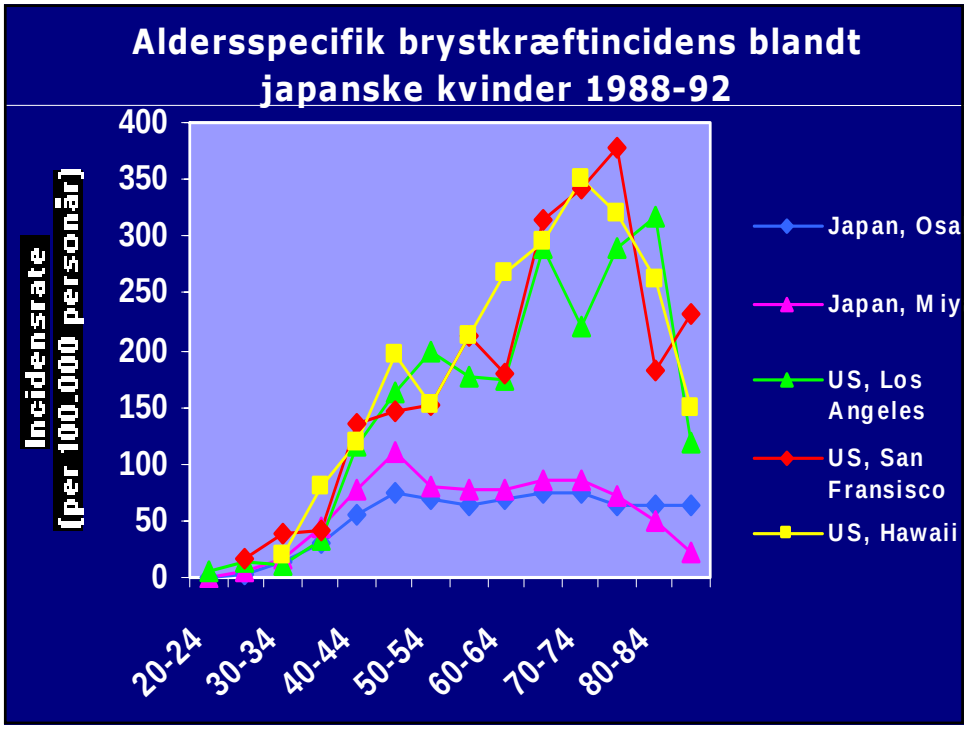
Risk of cancer – Indien / USA







Epidemiologic design/methods

- Population studies
- Case-control studies
- Prospective studies
- Intervention studies

Evidens for forebyggelsespotentiale

VEGETABLES,[1] FRUITS,[1] PULSES (LEGUMES), NUTS, SEEDS, HERBS, SPICES, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	Cancer site	Exposure	Cancer site
Convincing				
Probable	Non-starchy vegetables[1]	Mouth, pharynx, larynx Oesophagus Stomach		
	Allium vegetables[1]	Stomach		
	Garlic[1]	Colorectum		
	Fruits[1]	Mouth, pharynx, larynx Oesophagus Lung Stomach		
	Foods containing folate[2]	Pancreas		
	Foods containing carotenoids[2]	Mouth, pharynx, larynx Lung		
	Foods containing beta-carotene[2]	Oesophagus		
	Foods containing lycopene[2 3]	Prostate		
	Foods containing vitamin C[2 4]	Oesophagus		
	Foods containing selenium[2 5]	Prostate		

Micronutrients

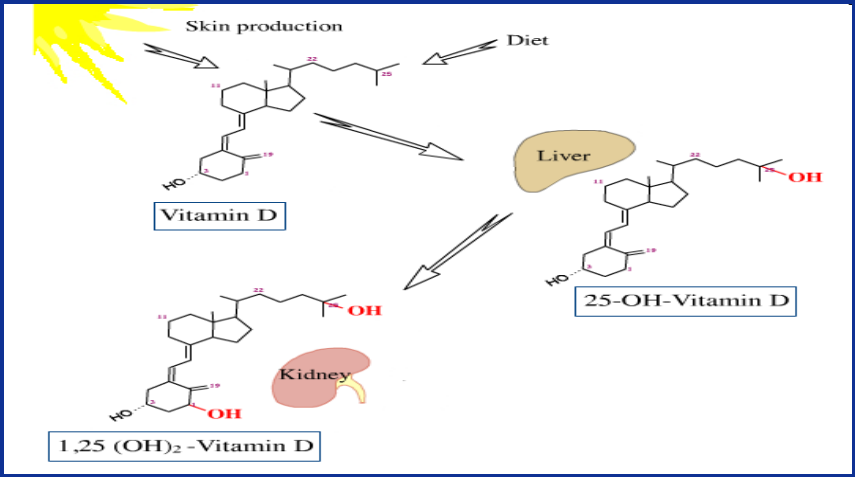
- Vitamins and traceelements

Agenda

- Vitamin D
- Folate
- Selenium
- Antioxidants (A,C,E)
- Conclusion

Vitamine D

Vitamin D



Is there a relation between vitamin D and Cancer?

- Animals studies have shown that Vitamin D can reduce the growth of malignant cells.
- Cellstudies have shown, that Vitamin D have influence on many processes in the body including more than 200 genes.

What is the optimal level of vitamin D?

- As high as possible, avoiding toxcicity? >50nmol/l, >80nmol/l? We don't know!

  Same level for all, or individual variation?

- What influence do the vitamin D receptor have?

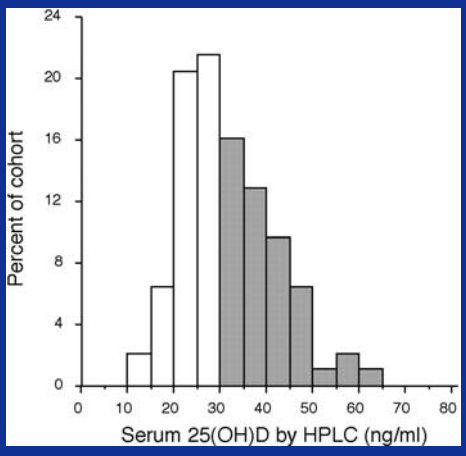
What supplement is necessary to reach the recommended level?

- In the Nordic Nutritional recommendation is it recommended to reach 7,5 mcg/day = 300 IU for adults, 10 mcg/d til >65 years or covered/ dark skin.

- If 80 nmol/l, ➔ 50 mcg/dag = 2000 IU

EXPOSURE?

93 young, living at Honolulu, 15+ hours of sunexposure/week

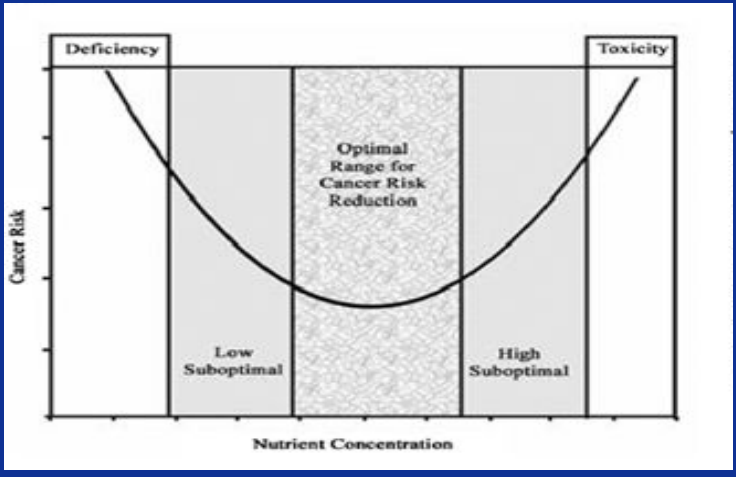


Binkley, N. et al. J Clin Endocrinol Metab 2007;92:2130-2135

Evidence from the past

- We have never seen cancer protective effects for a single micronutrinet when given in megadoses!
- High blood level of micronutrients is often a marker for a healthy life style.
- Sources are not unimportant; dietary supplements do not always have the expected effect!

Vitamin concentration and cancer risk



Serum Vitamin D & Colon Cancer

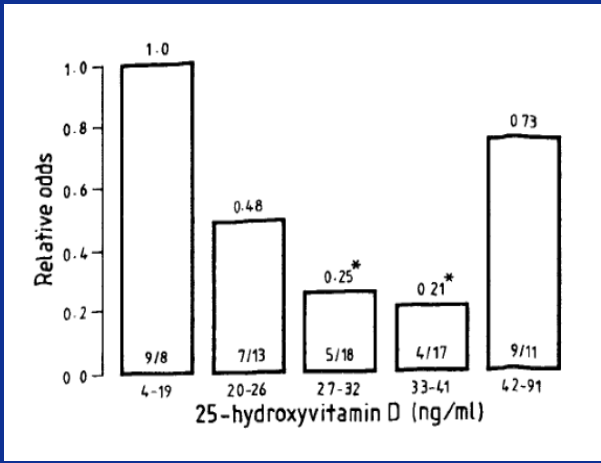
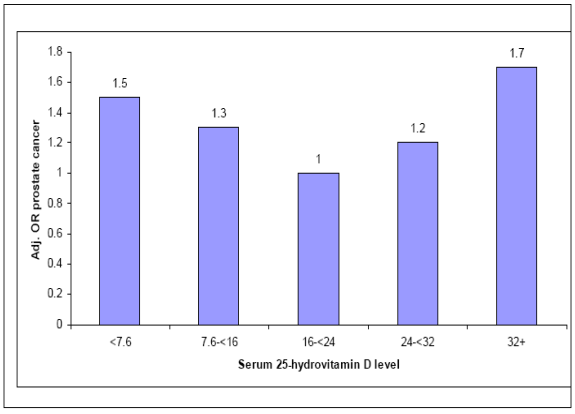


Figure 5.3 – *Caption in original article:* Risk of colon cancer by quintile of serum 25-hydroxyvitamin D. Numbers in columns = no of cases/no of controls."p2005. (Reprinted from The Lancet, 2(8673), Garland et al. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study.1176-8. Copyright 1989, with permission from Elsevier.")

Serum Vitamin D & Prostata Cancer



Vitamin D and breastcancer - Observational studies

- Dose-respons relativ risk for 1 unit per ng/mL 25-hydroxyvitamin D
- Pooled cohortestudies and nested case-control studies shows a RR = 0,994 (0,964-1,024)

Vitamin D and cancer?

- Some evidence for increased risk among persons with low blood levels.
- Low vitamin D $\Longleftrightarrow$ high BMI, low physical activity. Marker for an ”unhealthy lifestyle” ?
- Will supplementation with Vitamin D give the wanted effect?
- Can relatively small supplements pose a risk for some people?

Randomised trials on Vitamin D og cancer risk

Three studies:

1.Trivedi, 2003:

- 1600 IE, no colorectal or total cancer risk reduction

2.WHI, Wactawski-Wende, 2006:

- 36,282 women, 400 IU vit D3 (+1000 mg calcium) or placebo in 7 år. 322 cases of colorectal cancer, HR= 1.08 (0.86-1.34)

3.Lappe, 2007

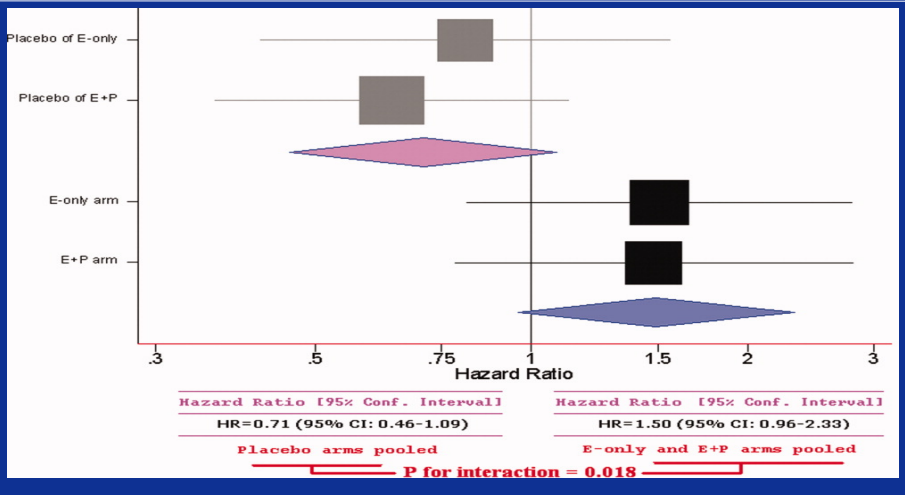
The New Eng Journal Medicine 2006; 354: 684-696

Calcium plus vitamin D Supplementation and the Risk of Colorectal Cancer

Table 2. Odds Ratios for Invasive Colorectal Cancer According to the Quartile of Serum 25-Hydroxyvitamin D Level at Baseline and Treatment Groups in a Nested Case–Control Study.*

Baseline Serum 25-Hydroxyvitamin D	Main-Effect Odds Ratio (95% CI)†	Calcium + Vitamin D	Placebo	Intervention Odds Ratio (95% CI)‡
		No. with Colorectal Cancer/ No. of Controls		
≥58.4 nmol/liter	1.00	33/48	27/45	1.15 (0.58–2.27)
42.4–58.3 nmol/liter	1.96 (1.18–3.24)	44/41	34/32	1.12 (0.59–2.12)
31.0–42.3 nmol/liter	1.95 (1.18–3.24)	35/32	45/41	0.99 (0.51–1.91)
<31.0 nmol/liter	2.53 (1.49–4.32)	46/39	42/28	0.75 (0.39–1.48)

Interaktion with HRT and risk of Colon Cancer

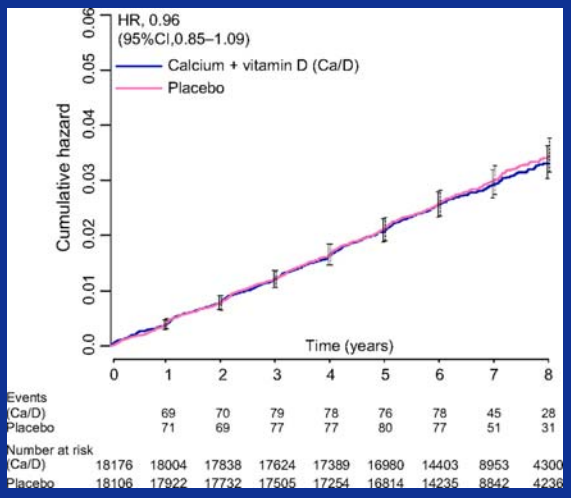


Breast cancer - WHI

- 400 IU, 1000mg calcium; Invasiv breast cancer, HR = 0,96 (0.85-1.09).
- Baseline vit D showed no association after correction for BMI and physical activity.
- High baseline vit D HR = 1.34 (1.01-1.78)
  Lowest baseline vit D HR = 0.79 (0.65-0.97)

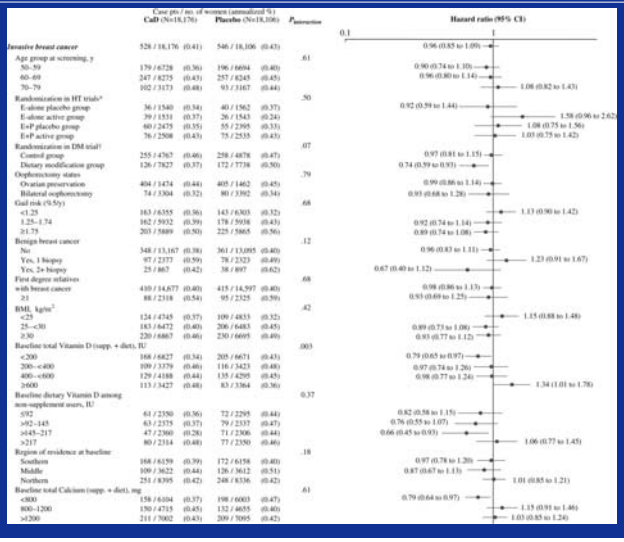
Chlebowski, 2008

Kaplan-Meier estimates of the cumulative hazard ratio for invasive breast cancer with supplemental calcium plus vitamin D (Ca/D) as compared with placebo



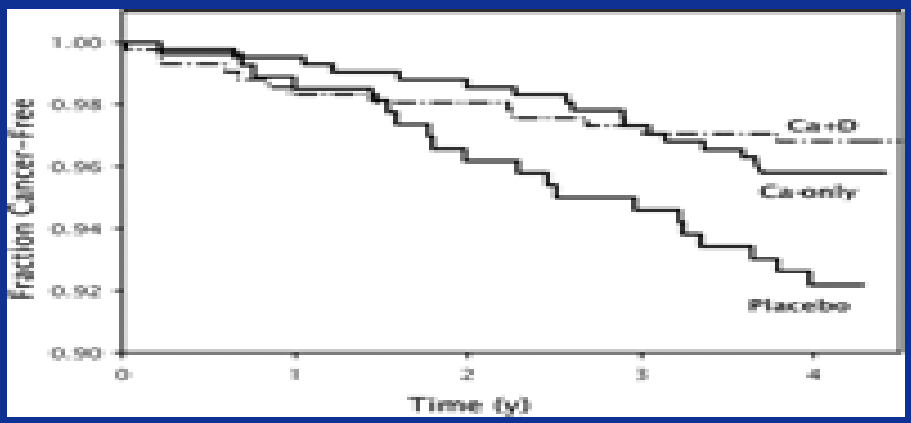
Chlebowski, R. T. et al. J. Natl. Cancer Inst. 2008 100:1581-1591; doi:10.1093/jnci/djn360

Estimated effects of supplemental calcium with vitamin D (CaD) on the risk of invasive breast cancer, according to selected baseline characteristics



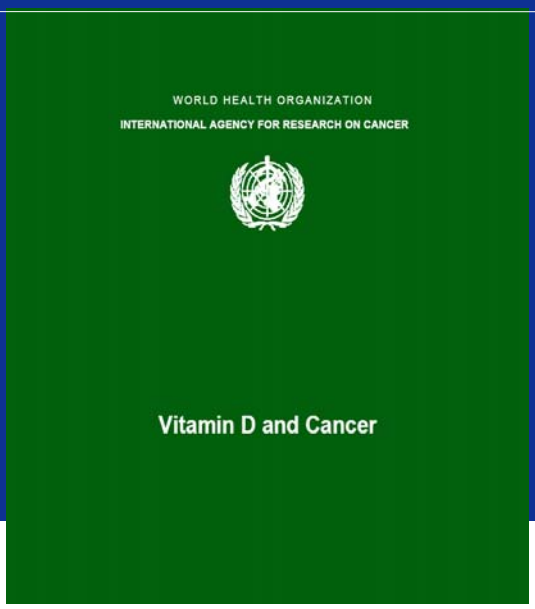
Chlebowski, R. T. et al. J. Natl. Cancer Inst. 2008 100:1581-1591; doi:10.1093/jnci/djn360

Secondary outcome total cancer incidence, 4 year trial,1179 women; obs correct intention to treat for vitamin D! no effect!



Lappe et al. 2007

WHO Rapport



IARC Conclusion

- Colorectal cancer: Observational studies shows invers ass.Obs causalitet due to confounding.
Randomised trials no effect demonstrated, obs dosis, interaction, duration.
- Breast cancer: weak invers association in observational studies.
Randomised trials no overall effect. Need for more studies.
- Prostata cancer: No effect of Vitamin D for incidence of prostatecancer.
- Data insufficient for all other cancer types.
- There is a lack of data on longterm effects of high doses of vitamin D for longer periods.
- There is a need for additional randomised trials.

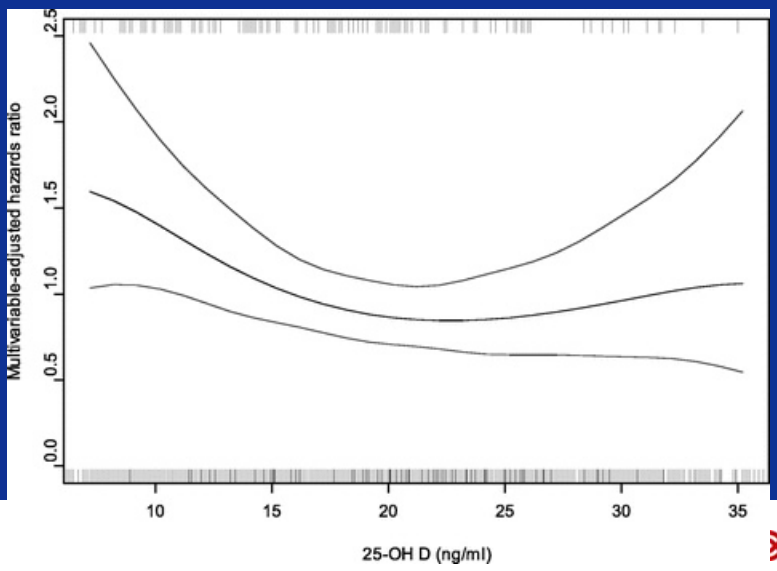
Conclusion?

Probably higher risk of colorectal cancer among persons with low blood levels

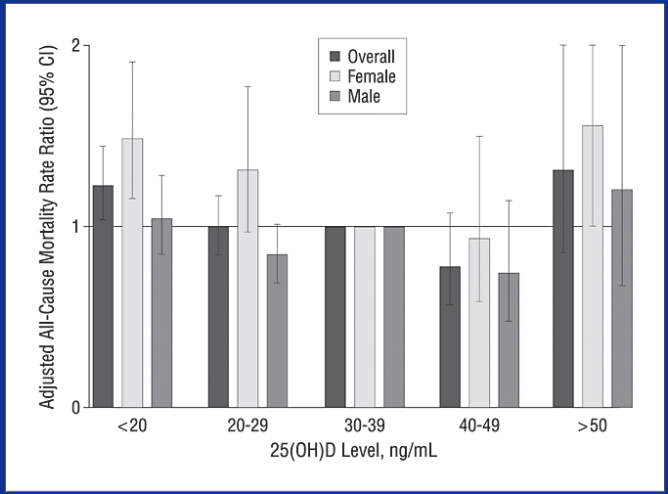
…… but

- We do not know the effect of supplementation
- We need to know the optimal level

Serum D vitamin og dødelighed

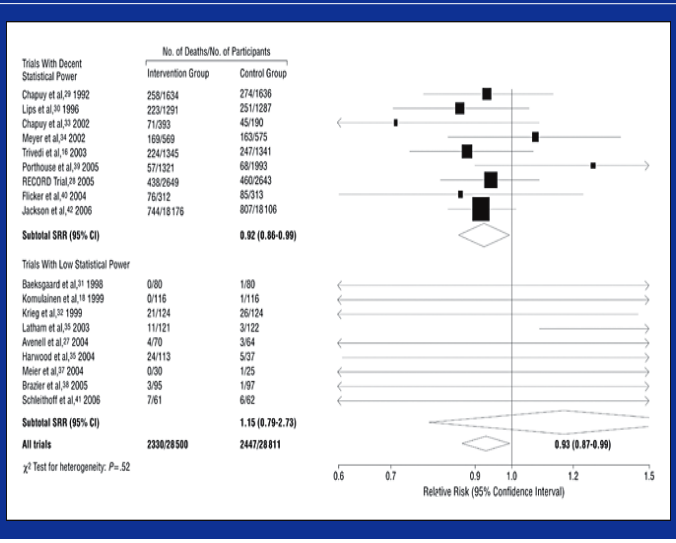


Associations between 25-hydroxyvitamin D (25[OH]D) levels and all-cause mortality in 13 331 participants of the Third National Health and Nutrition Examination Survey, overall and by sex



Melamed, M. L. et al. Arch Intern Med 2008;168:1629-1637

Meta-analysis of data on all-cause mortality in 18 randomized controlled trials with vitamin D

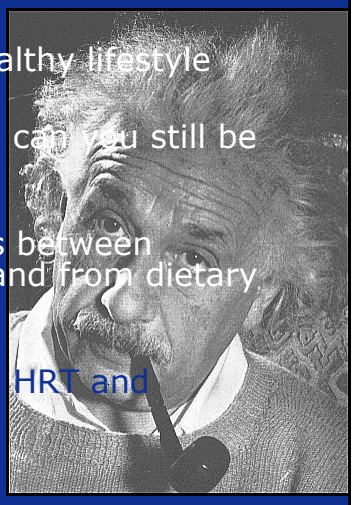


Trials With Decent Statistical Power	No. of Deaths/No. of Participants: Intervention Group	Control Group
Chapuy et al,[29] 1992	258/1634	274/1636
Lips et al,[30] 1996	223/1291	251/1287
Chapuy et al,[33] 2002	71/393	45/190
Meyer et al,[34] 2002	169/569	163/575
Trivedi et al,[16] 2003	224/1345	247/1341
Porthouse et al,[39] 2005	57/1321	68/1993
RECORD Trial,[28] 2005	438/2649	460/2643
Flicker et al,[40] 2004	76/312	85/313
Jackson et al,[42] 2006	744/18176	807/18106
Subtotal SRR (95% CI)		**0.92 (0.86-0.99)**
Trials With Low Statistical Power		
Baeksgaard et al,[31] 1998	0/80	1/80
Komulainen et al,[18] 1999	0/116	1/116
Krieg et al,[32] 1999	21/124	26/124
Latham et al,[35] 2003	11/121	3/122
Avenell et al,[27] 2004	4/70	3/64
Harwood et al,[36] 2004	24/113	5/37
Meier et al,[37] 2004	0/30	1/25
Brazier et al,[38] 2005	3/95	1/97
Schleithoff et al,[41] 2006	7/61	6/62
Subtotal SRR (95% CI)		**1.15 (0.79-2.73)**
All trials	**2330/28500**	**2447/28811**
χ^2 Test for heterogeneity: $P=.52$		

Autier, P. et al. Arch Intern Med 2007;167:1730-1737

We would like to know:

- Vitamin D – biomarker of a healthy lifestyle
- If the sun exposure is optimal, can you still be deficient?
- Are there biological differences between vitamin D from sun exposure and from dietary supplements?
- What does the interaction with HRT and lifestyle mean?



Folate/Folic acid

Folate and cancer

- Observational studies have shown protective effects aganst colorectal cancer (and breast cancer).
- Folate important for DNA replication og repair
- Lack of folate ➔ mutations
- Tumors upregulate folat receptors
- Anti-folate medicamina (metrotrexat) are effective against cancer

(Cole, JAMA, 2007)

Folic acid and colorectal adenomas

- Clinical trial, 1021 patients with adenomas randomised to 1mg/d folic acid, aspirin or placebo
- Colonoscopi after 3 and 5 years, number of adenomas, Advanced lesions (>25% villøse, high dysplasia, >1cm, number)

Cole, JAMA 2007

Folic acid and colorectal adenomas

- Result; After 5 years, no significant difference in the number of adenomas. Folic acid group had 67% significant more advanced lesions og 2,32 (1,23-4,35) times higher risk of 3 or more lesions
- The intervention group had significant more other cancers, especially prostata (24 cases against 9 cases in the controlgroup
- No interaction with BMI, alcohol or smoking

Folic acid and colorectal adenomas

Conclusion

- Not identified precurser lesions
- We know that 30% of the population at year 60 have adenomas in the colon!

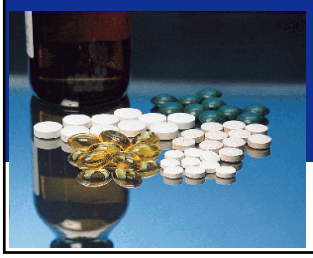
Antioxidants

Antioxidants

Vitamin E, C og A (β-caroten), selenium

Epidemiological studies have shown that a high intake in the DIET protect against cardiovascular diseases and some cancers

Interventionstudies have very seldom shown a protective effect of antioxidants as supplements



Cochrane review

Antioxidant supplements for prevention of gastro-intestinal cancers: a systematic review and meta-analysis

Bjelakovic G, Nikolova D, Simonetti RG, Gluud C

14 randomised trials (170,525) - supplement af β-caroten , vit, A, C, E og selenium in relation to esophageal, gastric, colorectal, pancreatic and livercancer – a total of 2100 cancere

(Lancet 2004; 364: 1219-28)

All Studies

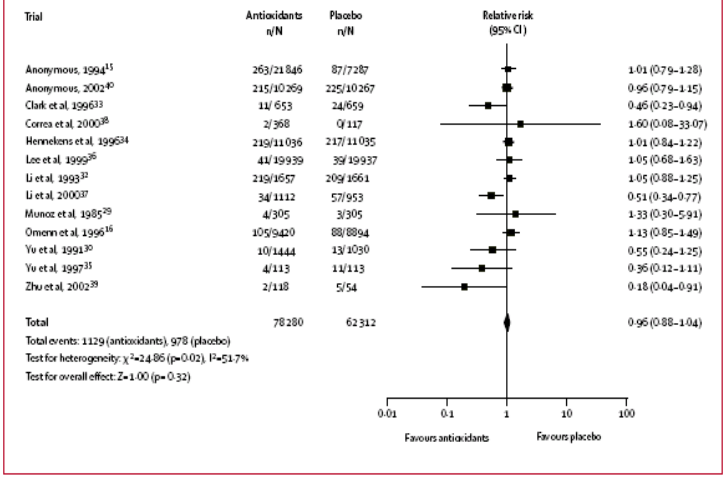


Figure 2: Intervention effect of all antioxidant supplements versus placebo on incidence of all gastrointestinal cancers combined
Relative risks analysed with fixed-effect model.

Antioxidant polyp prevention study

- 864 previous adenoma patients
- Intervention - 25 mg β-caroten/placebo
  vit. C (1000 mg) og vit. E (400 g)/placebo
- Colonoscopi after 1 and 4 years
- Information about lifestyle at baseline

Baron, JNCI 2003

Results - β-carotene

No alcohol/smoking:

RR = 0,56 (0,36-0,89)

One or more drinks/day and smoking:

RR = 2,07 (1,39-3,08)

Baron, JNCI 2003

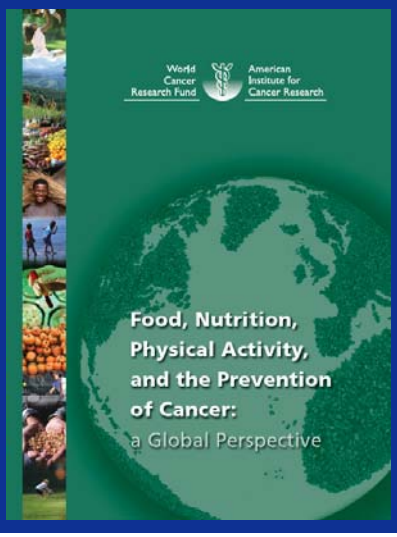
Conclusion: Antioxidants and cancer

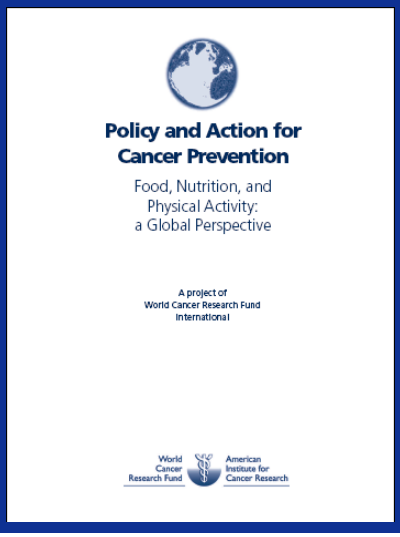
- Antioxidants given as supplements, might have potential negative effects
- Important mechanisms for protecting the cell can be disturbed by high doses of antioxidants.
- We don't know the optimal level of antioxidants.

Conclusion supplements

- There is no evidence for a beneficial effect of the intake of antioxidants and other vitamins as food supplemnts unless deficiency
- Vitamin E and β-caroten can have serious adverse effects in high doses
- We need more trials with folate?
- We need to define clearly the groups at risk for deficiency of vitamin D?
- Food enrichment, what is the consequences?

The WCRF reports 2007/2009





RECOMMENDATION 8

DIETARY SUPPLEMENTS

Aim to meet nutritional needs through diet alone[1]

PUBLIC HEALTH GOAL

Maximise the proportion of the population achieving nutritional adequacy without dietary supplements

PERSONAL RECOMMENDATION

Dietary supplements are not recommended for cancer prevention

[1] This may not always be feasible. In some situations of illness or dietary inadequacy, supplements may be valuable

Take home messages

- Remember the U shaped association between micronutrients and cancer risk.
- No documentation of benefical effects or provention of cancer from micronutrients taken as food supplements
- Possible harmful effects in relation to cancer, should be taken into consideration when discussing fortification with micronutrients