Institute of Food Research

Phytochemicals

Effective at Reducing Cancer Risk?

Ian Johnson

ESMO Symposium on Cancer & Nutrition

Zurich 2009

Presentation Overview

- **Epidemiological background**
- **Phytochemicals defined**
- **Mechanisms of action**
- **Phytochemicals in the human food chain**
  - glucosinolates as a case-study
- **Conclusions**

Evidence that a high intake of fruits and vegetables protects against cancer

WCRF Reports 1997 and 2007

- "Convincing" Evidence of Reduced Risk

  NONE

  Mouth, Pharynx, Oesophagus, Lung, Stomach, Colon, Rectum

- "Probable" Reduced Risk

  Mouth, Pharynx, Larynx, Oesophagus, Stomach, Lung

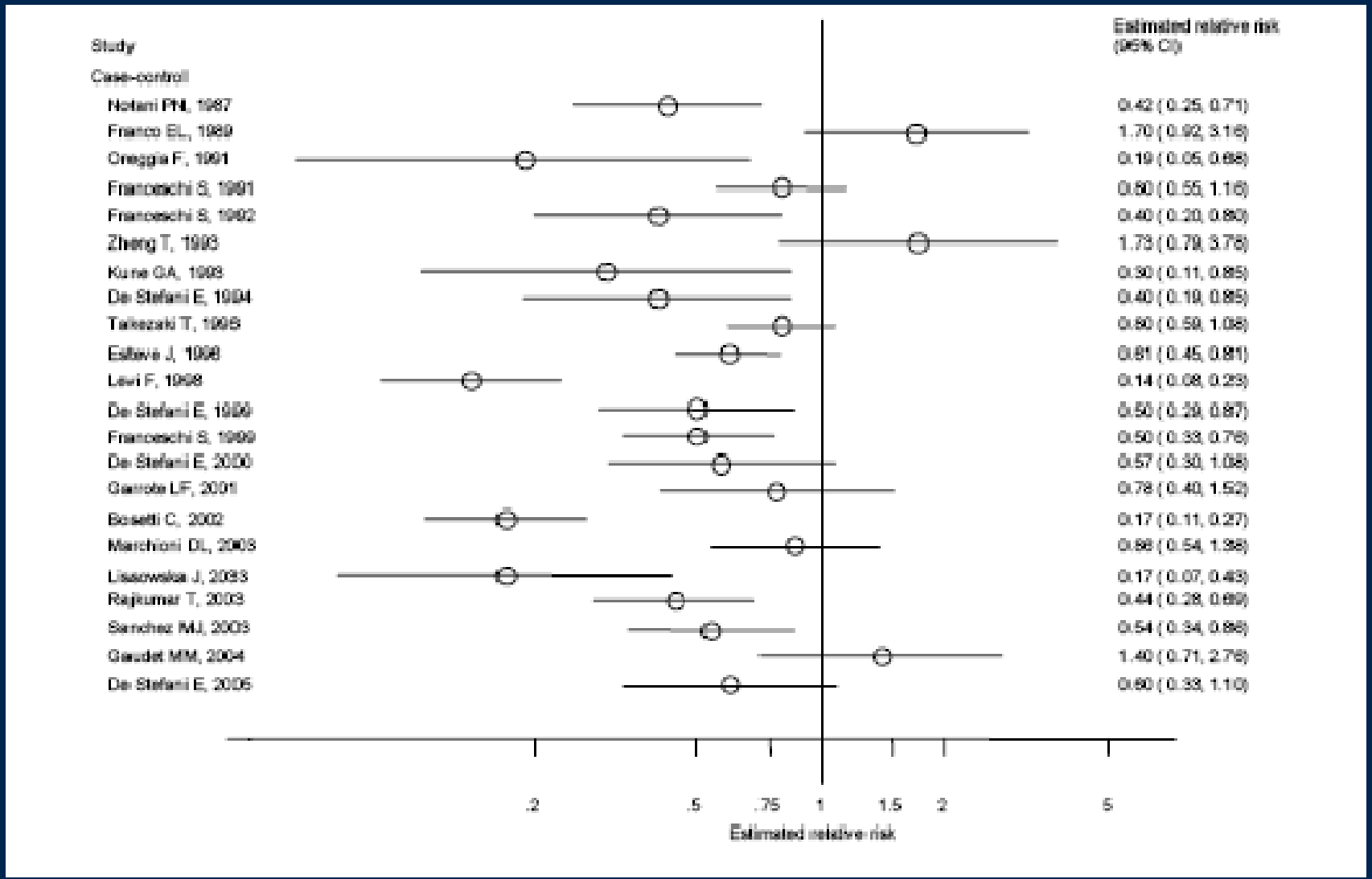
  Larynx, Pancreas, Breast, Bladder

- "Possible" Reduced Risk

  Nasopharynx, Cervix, Ovary, Endometrium, Thyroid, Liver, Prostate, Kidney, Mouth,pharynx,

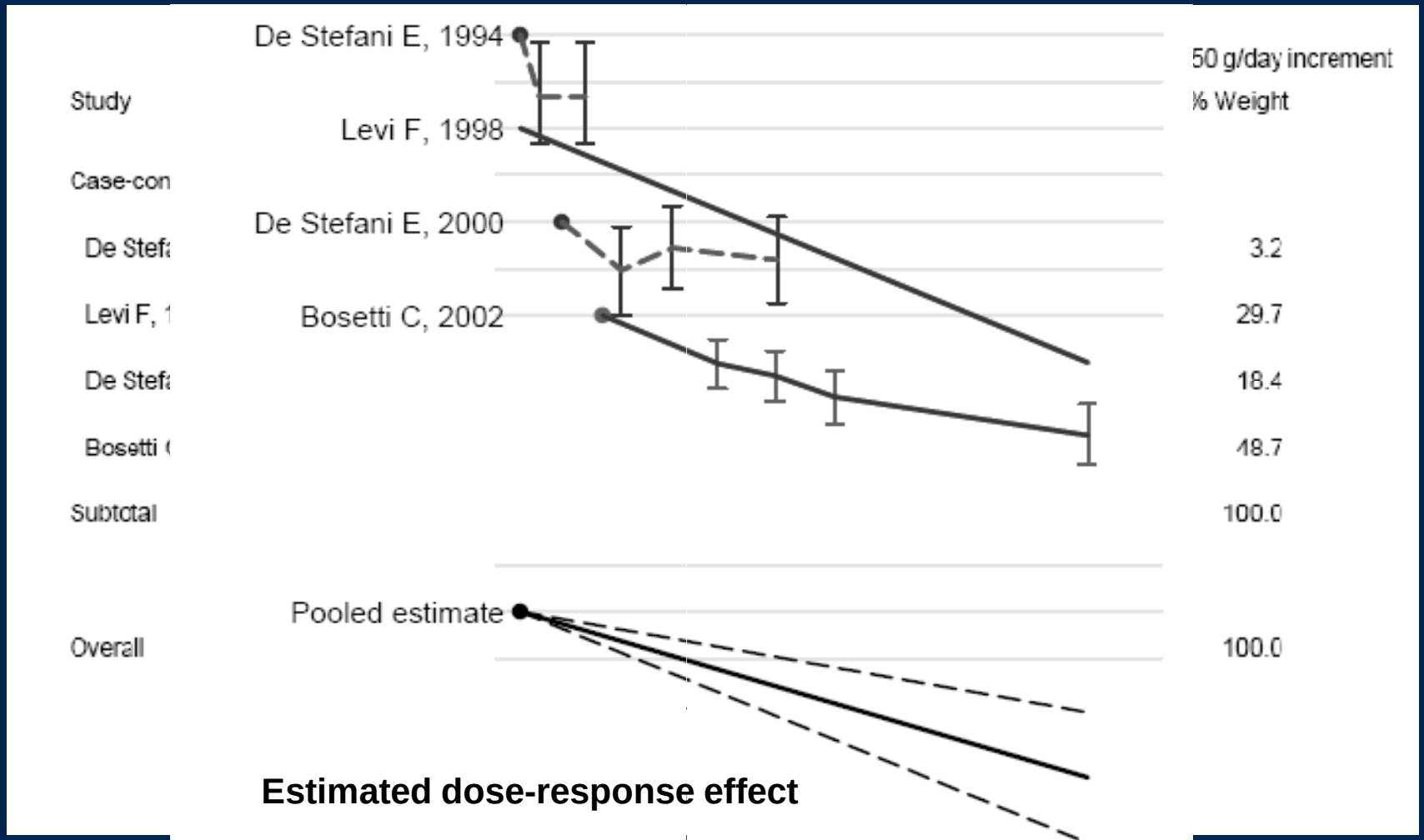
  Cervix, Ovary, Endometrium, Thyroid, Liver, Colon, Rectum, Pancreas, Prostate, Kidney,

An example: In case-control studies, risk of cancers of mouth, pharynx and larynx is lower in high consumers of non-starchy vegetables…



WCRF Report on Nutrition & Cancer 2008

An example: Where it can be measured, the risk appears to be inversely related to exposure…



Estimated dose-response effect

WCRF Report on Nutrition & Cancer 2008

Summary of Epidemiological Evidence

- Case-control studies indicate that in developed countries higher consumption of plant foods is associated with reduced risk of cancers of the upper GI tract and lung.
- Evidence from cohort studies is weaker – hence lower confidence in latest WCRF report.
- Protective effects of fruits and vegetables cannot be fully explained on the basis of their micro-nutrient content.
- These findings have driven a surge in research on the biological effects of phytochemicals.

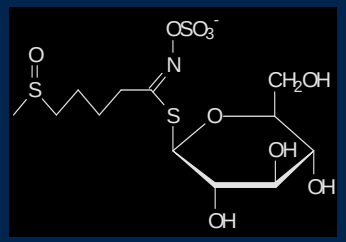
What are phytochemicals?

- **"Phytochemicals" are *secondary plant metabolites* that exert biological activity in mammalian systems, but for which there are no known deficiency disorders.**
- **Often function as natural pesticides in plant systems.**
- **Often referred to inaccurately in lay publications simply as "antioxidants".**
- ***In vitro* and animal studies provide evidence for a variety of potentially anticarcinogenic effects.**

There are thousands of secondary plant metabolites present in the human diet...

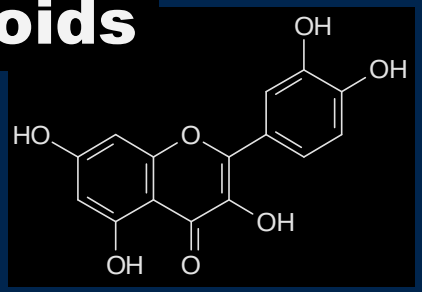
Two major groups of phytochemicals

Glucosinolates



- Found only in cruciferous plants
- Break down to release isothiocyanates

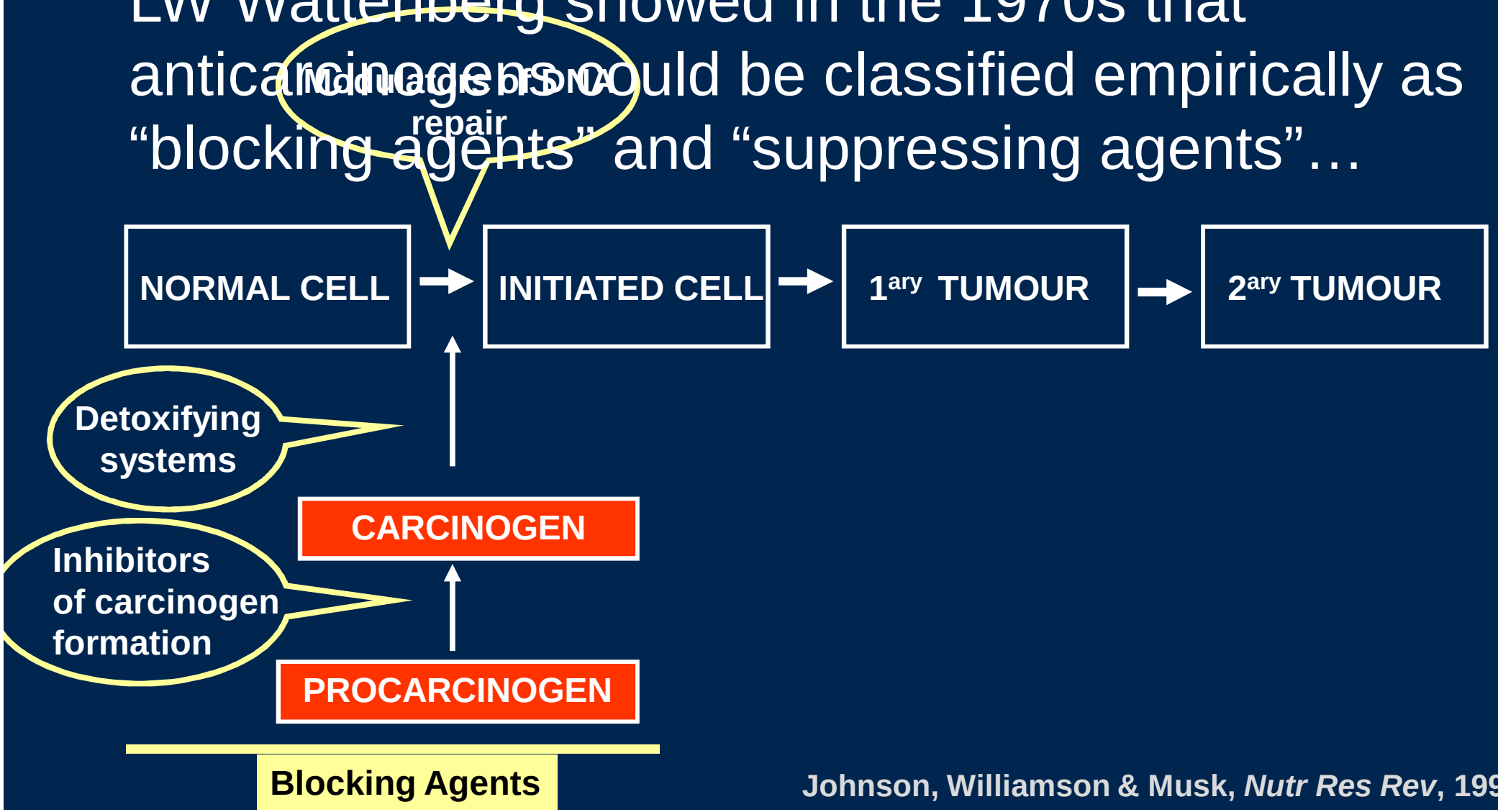
Flavonoids



- Occur as glycosides in coloured vegetables and fruits, tea and wine.

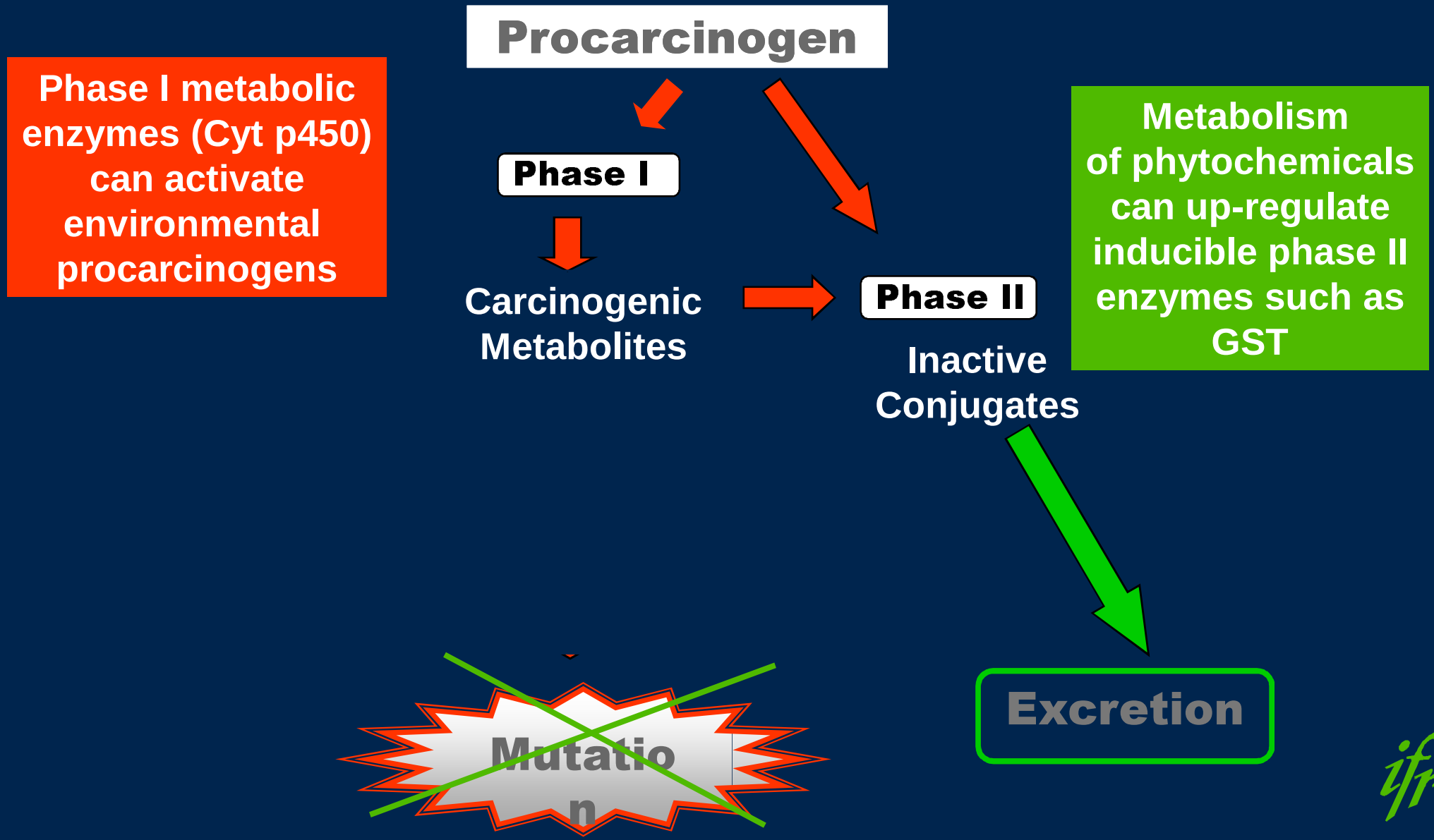
There are plausible mechanisms of for the inhibition carcinogenesis by phytochemicals…

LW Wattenberg showed in the 1970s that anticarcinogens could be classified empirically as "blocking agents" and "suppressing agents"…

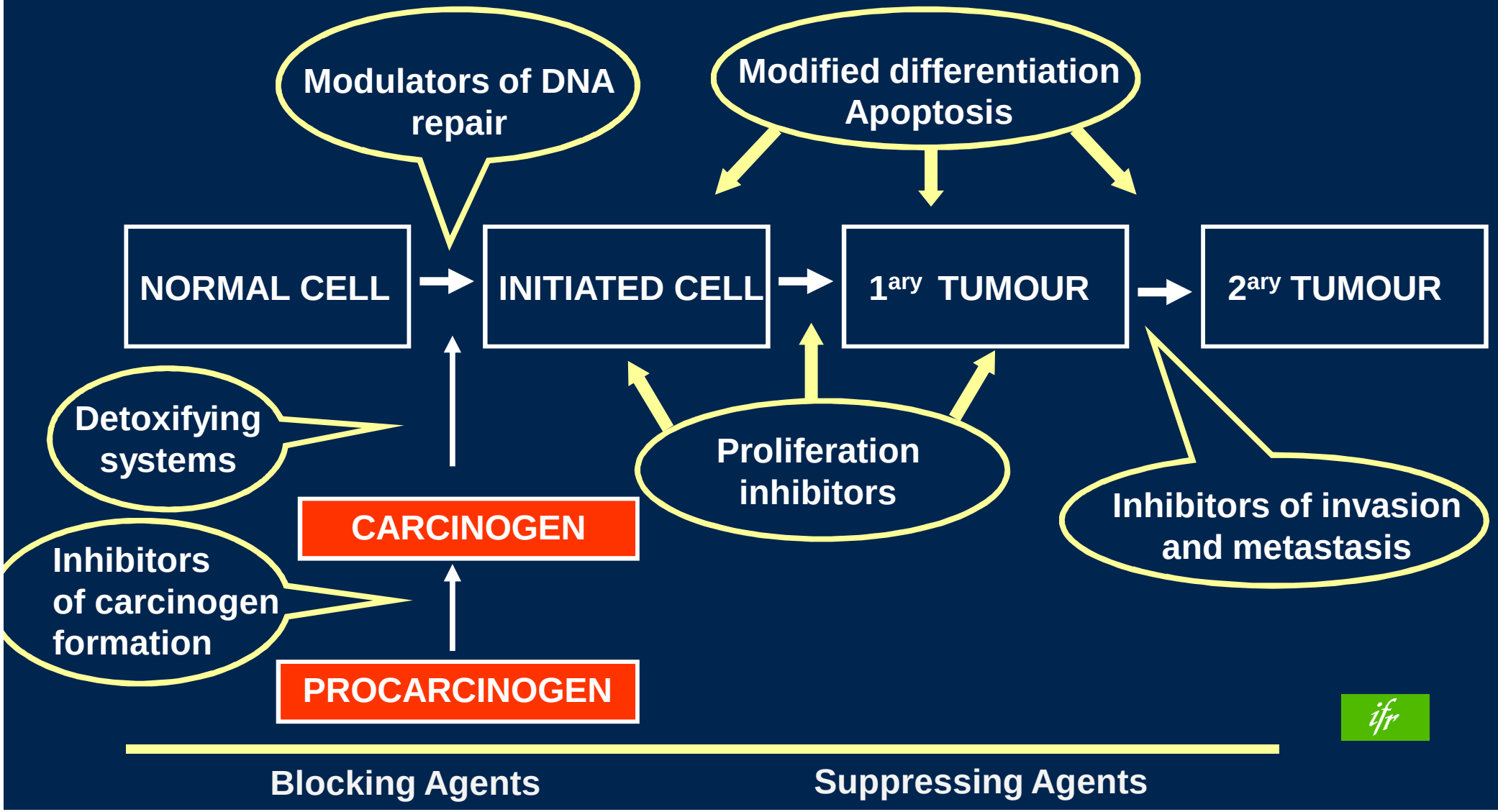


Johnson, Williamson & Musk, *Nutr Res Rev*, 1994.

Blocking agents often modulate carcinogen metabolism via phase II metabolism...



Suppressing agents act on the later stages of carcinogenesis...



Many potentially important suppressing mechanisms have been identified…

- **Suppression of inflammation**
  - Inhibition of inflammatory signalling via NFkB
  - Direct inhibition of COX-2
- **Inhibition of cell proliferation and induction of apoptosis**
  - Inhibitors of Wnt signals
  - Cell cycle modulators
  - Spindle inhibitors

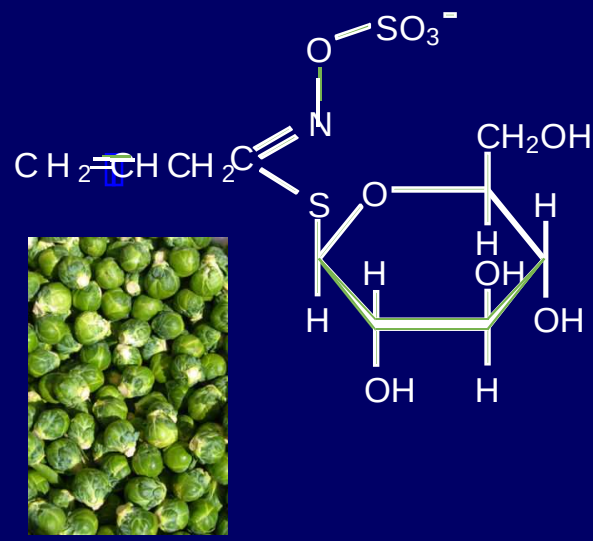
Multiple, interdependent, and probably synergystic effects…

Summary of mechanistic evidence

- A very large number of *in vitro* studies indicate that phytochemicals exert potentially anticarcinogenic effects.
- However, many have used un-metabolised parent compounds at concentrations that are unlikely to be achieved *in vivo*.
- Definitive mechanistic studies require (difficult) research with humans.
- The situation is complicated by the impact of genetic polymorphisms on phytochemical metabolism.

An example: Glucosinolates are broken down by myrosinase activity in the plant, or by bacteria in the colon, to release isothiocyanates….

Sinigrin



Glucose

Allyl Isothiocyanate

(*Myrosinase*)

Other Products

- **Thiocyanates**
- **Nitriles**

Similarly…

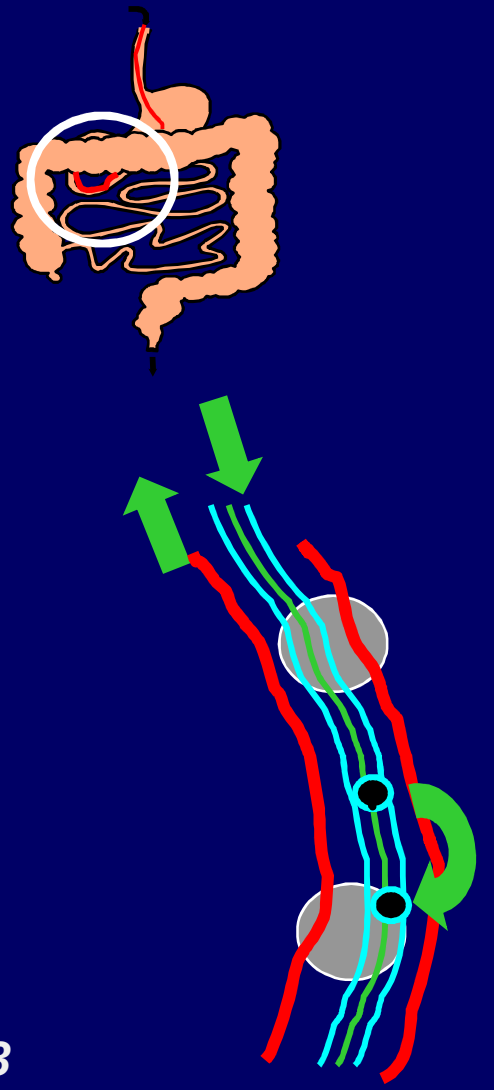
Glucoraphinin

Sulforaphane

Bioavailability is a potential limiting factor which has been studied only rarely in humans…

Methods…

- Six healthy volunteers
- Multiibore jejunal perfusion tube
- Segment isolated between balloons
  - Simultaneous perfusion & recovery
- Liquid extract of onions and broccoli, (containing sulforaphane and quercetin) perfused via central port and aspirated via proximal & distal ports
- Aspirate collected for analysis and compared with perfusate



Petri et al (2003) Drug Metabolism & Disposition 31, 805-813

Absorption and metabolism…

Results…

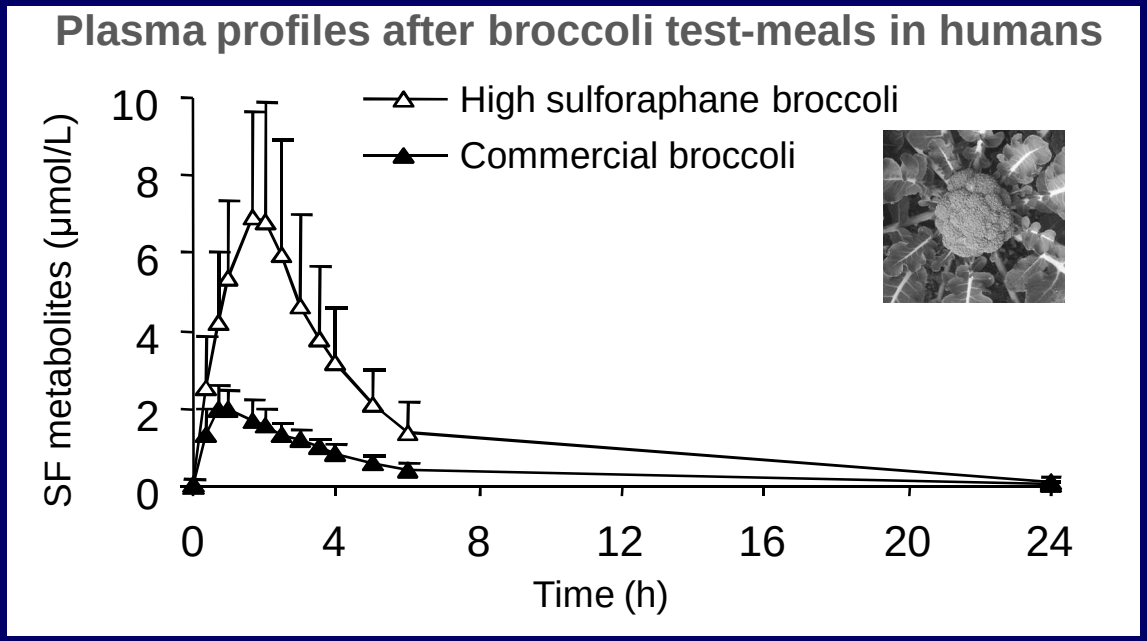
- *Sulforaphane (11 μM) and (57 μM) both rapidly disappeared from the luminal perfusate.*
- *About 60% reappeared in the lumen as sulforaphane-glutathione and quercetin-3' glucuronide respectively.*

Conclusions…

- *A large proportion of both Isothiocyanates and flavonoids are absorbed from food in the upper gut.*
- *Phase II metabolites are formed rapidly in the mucosa and re-secreted into the lumen.*
- *Blood-borne metabolites are rapidly excreted in urine.*

Petri et al (2003) Drug Metabolism & Disposition 31, 805-813

Isothiocyanates are present in the circulation only as phase II metabolites and for relatively short periods following a meal...



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Gasper et al. (2005) Am. J. Clin Nutr, 82:1283-91

Protective effects of exposure to isothiocyanates against lung cancer vary with genetic polymorphisms for glutathione s-transferase…

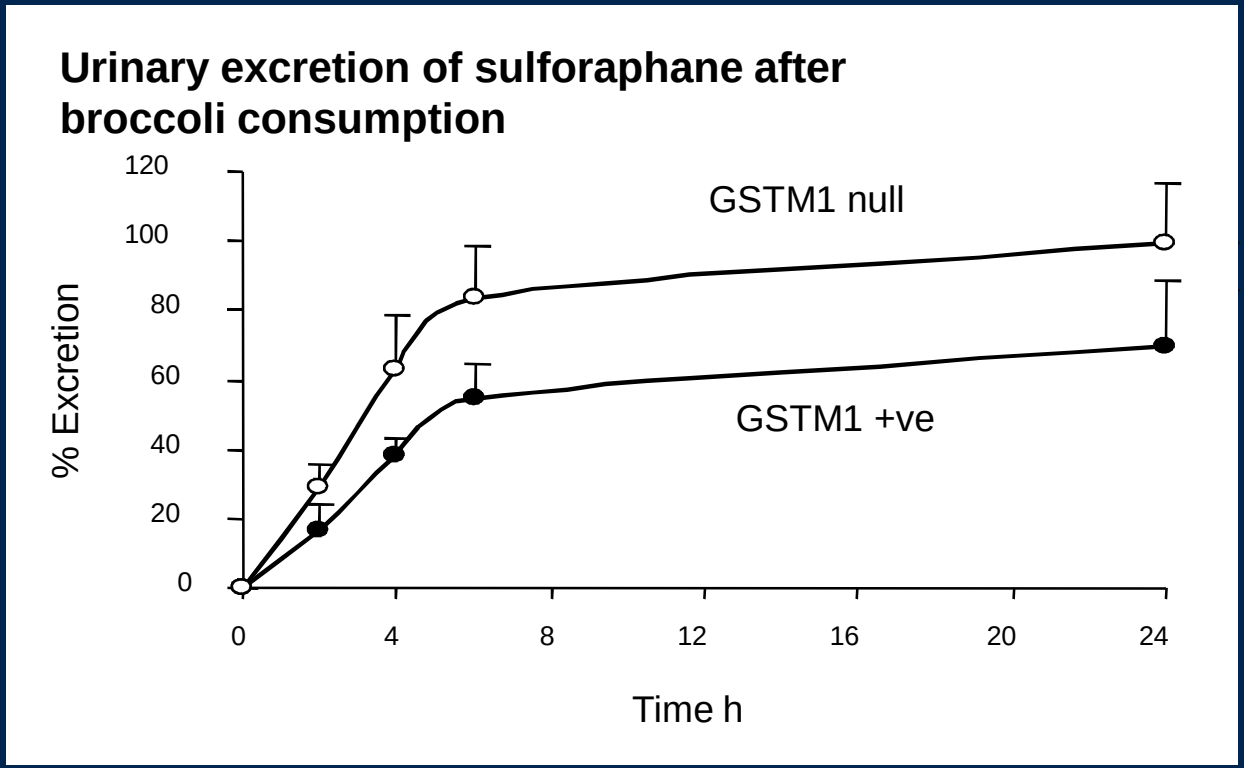
Sub-Group	RR (Zero Urine IST)	RR (Positive Urine IST)
All	1.0	0.65 (0.43-0.97)
GSTM1+ or *GSTT1*+	1.0	1.04 (0.60-1.67)
GSTM1 null	1.0	0.36 (0.20-0.63)
GSTT1 null	1.0	0.51 (0.30-0.86)
GSTM1 null & *GSTT1* null	1.0	0.28 (0.13-0.57)

London et al (2000), Lancet 356, 724

Similar effects observed in other studies…

- Lin et al *(1998) Cancer Epidemiol Biomarkers Prev 7, 647.*
- Spitz, MR *et al* (2000) *Cancer Epidemiol. Biomarkers Prev* 9, 1017.
- Zhao, B *et al* (2001) *Cancer Epidemiol. Biomarkers Prev* 10, 1063.
- Brennan, P *et al* (2005) *Lancet* 366, 1558.

Human feeding studies demonstrate that the urinary excretion pattern for sulforaphane metabolites depends on GST genotype…



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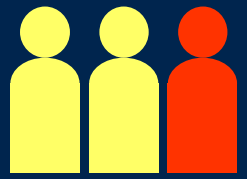
Gasper et al. (2005) American Journal of Clinical Nutrition, in press

The overall anticarcinogenic effects of phytochemicals will depend upon complex variables encountered at every step in the food chain…

High intakes may lead to
Toxic effects in some individuals.



Glucosinolate and myrosinase levels vary with cultivar, agronomy and storage.

It is technically feasible to produce vegetables high in phytochemicals.

Processing and cooking techniques modify intake and release of isothiocyantes, and must be optimised for maximum bioavailability

Individuals vary in their absorption, metabolism and response to ingested isothicyanates.

Specialised products and extracts…

Conclusions

- **Epidemiological evidence suggests that there are some protective effects of phytochemicals against cancers of GI tract and lung, and plausible biological mechanisms have been identified.**
- **Further studies with humans are required before chemoprevention using either modified plants or isolated compounds can be recommended.**
- **Meanwhile it is prudent to consume relatively large quantities of fruits and vegetables (ca. 400g/day) from a variety of sources.**