Biomarkers of Internal Dose

October 26, 2017

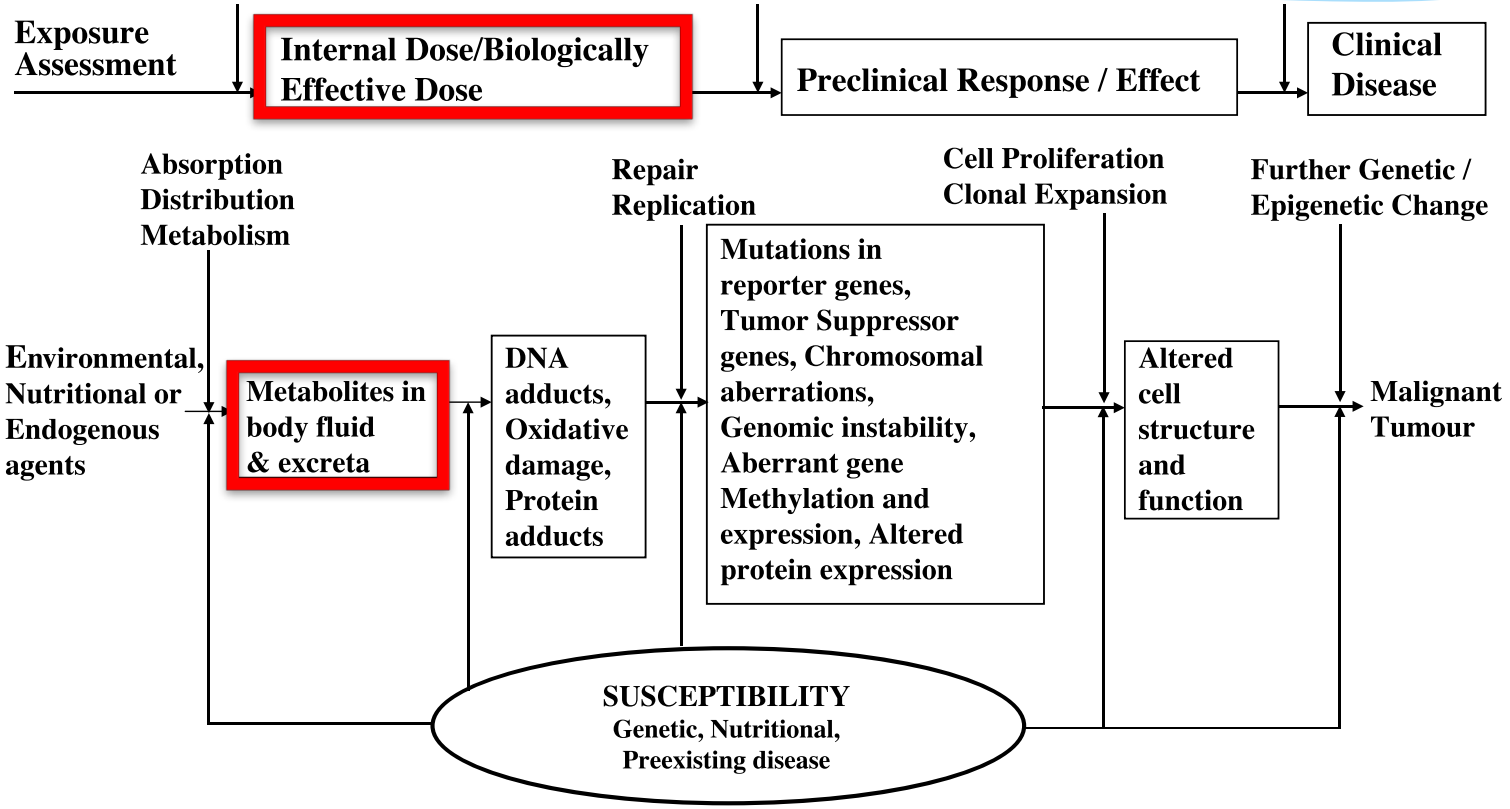
EPI 246

Biomarkers of Internal Dose

* Definition:

  Measurements of a parent compound or one of its metabolites in a biological specimen (e.g., serum or urine)

Primary Prevention and Clinical Interventions



Vineis & Perera *Cancer Epidemiol Biomarkers Prev* 2007

Overview

* Carcinogens
* Exposure assessment → internal dose
* Timing of exposure
* Case Study: Pooled analysis of carotenoids and breast cancer

What is a Carcinogen?

metabolic
dna damage

International Agency for Research on Cancer (IARC)

* Mission: to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer prevention and control
* IARC Monographs Program: international expert working groups evaluating the evidence of the carcinogenicity of specific exposures

IARC Categories

* Monographs evaluate agents, mixtures of agents, and exposure circumstances and the probability of carcinogenicity
  * Group 1: Carcinogenic to humans ddt
  * Group 2A: Probably carcinogenic to humans
  * Group 2B: Possibly carcinogenic to humans
  * Group 3: Not classifiable as to carcinogenicity in humans saflun hydrogenproxide
  * Group 4: Probably not carcinogenic to humans

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 240

26 October 2015

IARC Monographs evaluate consumption of red meat and processed meat

Lyon, France, 26 October 2015 – The International Agency for Research on Cancer (IARC), the cancer agency of the World Health Organization, has evaluated the carcinogenicity of the consumption of red meat and processed meat.

Red meat

After thoroughly reviewing the accumulated scientific literature, a Working Group of 22 experts from 10 countries convened by the IARC Monographs Programme classified the consumption of red meat as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* that the consumption of red meat causes cancer in humans and *strong* mechanistic evidence supporting a carcinogenic effect.

This association was observed mainly for colorectal cancer, but associations were also seen for pancreatic cancer and prostate cancer.

Processed meat

Processed meat was classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in humans that the consumption of processed meat causes colorectal cancer.

Sources of Carcinogens

occupationl
enviromenta
air pollustion
diet
tobacco
bateria

Sources of Preventive Agents

Traditional Exposure Assessment

* Ecological studies: comparison of high to low exposure populations
* Summing exposure from numerous sources (e.g., air, water)
* Linking exposure levels in environment to residential data (e.g., chlorinated by-products)
* Work exposures (e.g., dioxin)

Advantages of Biomarkers of Carcinogens or Preventive Agents

* Internal dose reflects exposure by all routes
  * Inhalation, ingestion, dermal absorption
* Internal dose is a factor of
  * Level of exposure in environment (air, water, food…)
  * Individual exposure (food or water consumed, absorption from gut or lung, metabolism, etc.)
  * Others… e.g., presence of bacteria in gut

Aflatoxin: Diet vs. Biomarker

Dietary aflatoxin level by urinary aflatoxin marker status in 267 controls					
	Percentiles and mean dietary intake (µg/month)				
	N	P25	P50	P75	Mean
No	158	6.2	8.0	10.9	10.8
Yes[a]	109	5.7	7.9	11.2	10.9
AFB_1-N^7-gua neg.	78	6.0	8.1	13.1	11.5
AFB_1-N^7-gua pos.	31	4.8	7.0	9.5	9.1

[a] Presence of AFB_1, AFP_1, AFM_1, or AFB_1-N^7-gua.

Qian et al, *CEBP* 1994

Aflatoxin: Diet x HCC

Risk of hepatocellular carcinoma by estimates of dietary aflatoxin B_1 exposure in cohort subjects			
Dietary aflatoxin B_1 exposure (µg/yr)	Total person-years	No. of cases	Age- and smoking-adjusted RR (95% CL)
Low (<71)	21,833	14	1.0
Medium (71-113)	23,547	25	1.6 (0.8, 3.1)
High (113+)	24,013	16	0.9 (0.4, 1.9)

Qian et al, *CEBP* 1994

Timing of Interest vs. Measurement

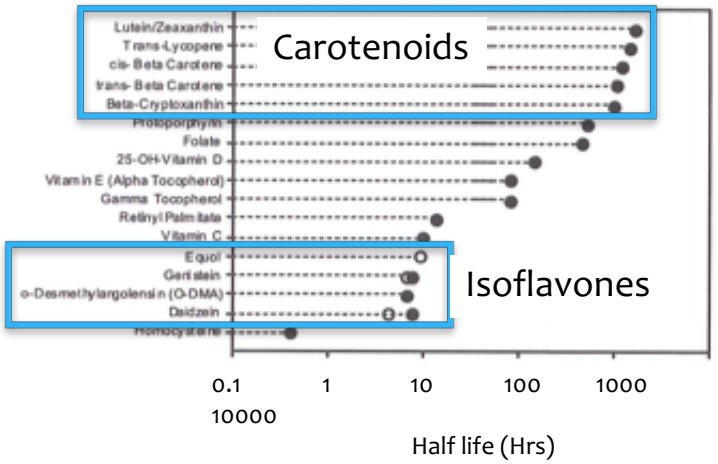
* Past or long-term exposure is most relevant for carcinogenesis
* Recent exposure biomarkers may be useful if biomarker (usually repeated measures) is superior to traditional methods of assessment and exposure is fairly constant over time

Timing of Exposure

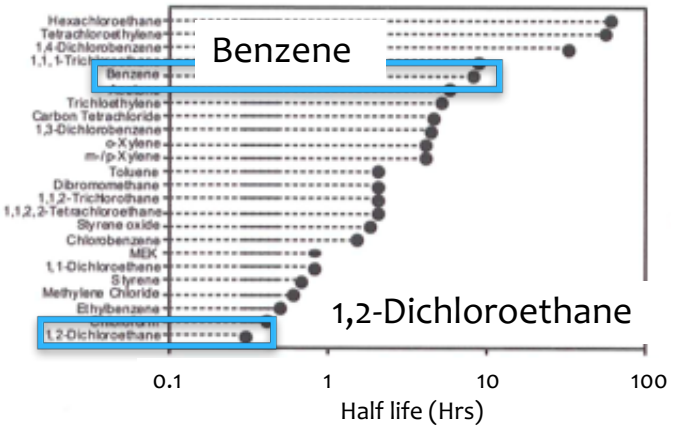
prognostic biomarker

* What time period does the biomarker reflect
  * Half-life can vary from <1 hour to more than 10 years

Macro- & Micro-nutrients



Solvents



IARC, *Molecular Epidemiology: Principles and Practices*, 2012

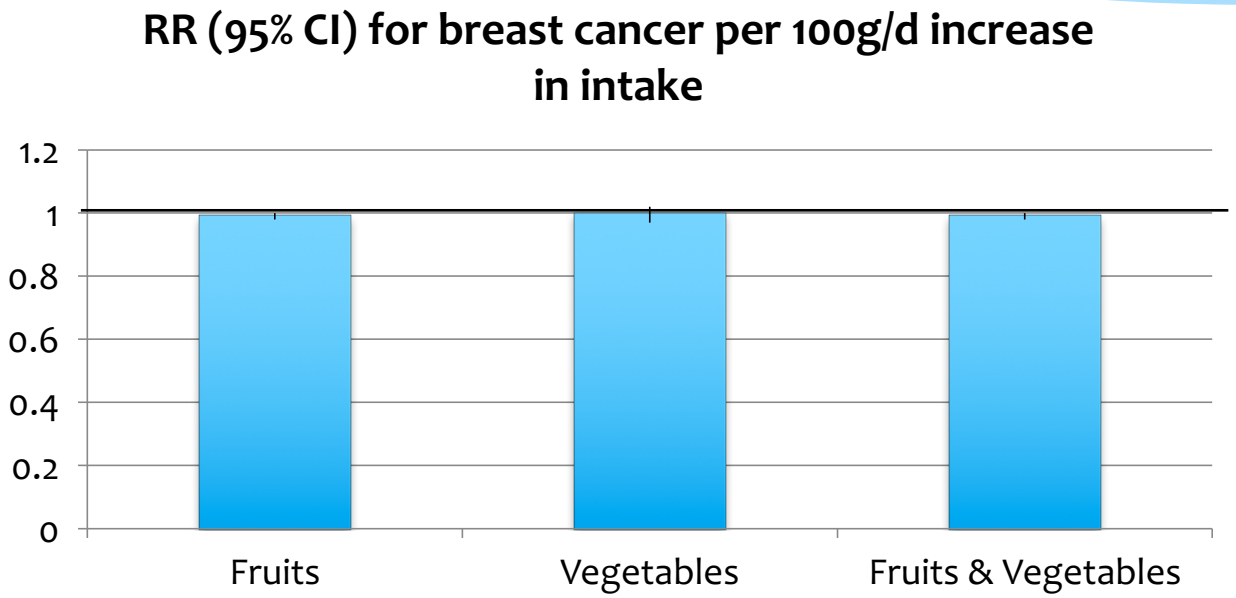
Case Study

Pooled Analysis of Plasma Carotenoids and Breast Cancer

Carotenoids are the pigments that give fruits and vegetables such as carrots, cantaloupe, sweet potato, and kale their vibrant orange, yellow, and green colors.

Eliassen et al, *JNCI* 2012

Fruit & Vegetable Intake



Smith-Warner et al, *JAMA* 2001

Correlations Between Diet, Plasma, Breast Adipose Tissue

Diet and Plasma Correlations (~1000 NHS breast cancer controls)				
α-carotene	β-carotene	β-cryptoxanthin	Lutein/zeaxanthin	Lycopene
0.35	0.29	0.36	0.23	0.14

Serum and Breast Tissue Correlations (Yeum, 1998)				
α-carotene	β-carotene	Cryptoxanthin	Lutein/zeaxanthin	Lycopene
0.55	0.87	0.44	0.64	0.59

Motivation

	Columbia (1998)	Umea (2001)	CLUE I (2002)	CLUE II (2002)	NHS (2005)	WHS (2005)	NYUWHS (2006)
α-carotene	1.8	0.7	0.69	0.84	0.64	1.06	0.50
β-carotene	1.1	0.8	0.41	0.62	0.73	1.36	0.45
β-cryptoxanthin	0.6	0.9	0.98	0.70	0.95	0.82	0.60
Lutein	--	1.0	0.77	0.40	--	--	0.48
Zeaxanthin	--	0.8	--	--	--	--	0.89
Lutein/zeaxanthin	0.9	--	--	--	0.74	0.78	--
Lycopene	0.5	1.0	0.55	0.80	1.01	0.93	0.67
Total carotenoids	--	--	0.55	0.61	0.76	--	0.43

RR for top vs. bottom quartile or quintile

Pooled Cohorts

Study	Author, year	Cases	Controls
Columbia	Dorgan, 1998	105	209
Umea	Hulten, 2001	201	389
CLUE I	Sato, 2002	244	244
CLUE II	Sato, 2002	115	115
NHS	Tamimi, 2005	962	962
WHS	Sesso, 2005	508	508
NYUWHS	Toniolo, 2006	269	269
SWHS	Dorjgochoo, 2009	365	725
MEC	Epplein, 2009	286	535
TOTAL		**3,055**	**3,956**

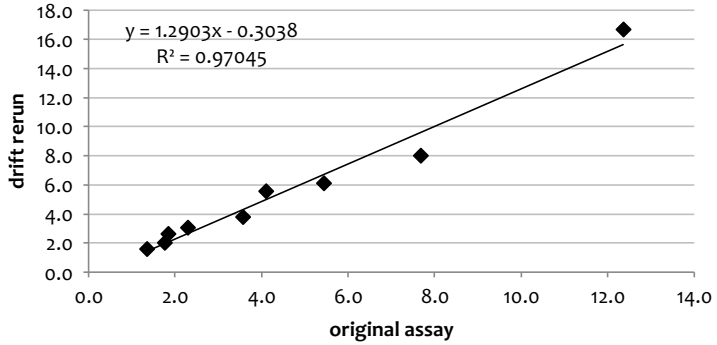
Carotenoids in NHS & WHS

Median (10^{th}-90^{th})	NHS	WHS
Carotenoid	**Controls**	**Controls**
α-carotene	5.8 (2.5-13.3)	5.9 (1.9-16.8)
β-carotene	24.0 (9.7-62.0)	19.0 (7.2-52.0)
β-cryptoxanthin	6.4 (2.7-12.8)	8.9 (2.8-21.7)
Lutein/Zeaxanthin	17.3 (4.7-29.7)	16.7 (8.8-30.0)
Lycopene	40.9 (20.8-68.7)	9.6 (5.1-16.4)
Total carotenoids	99.5 (55.0-171.4)	64.1 (34.8-124.5)

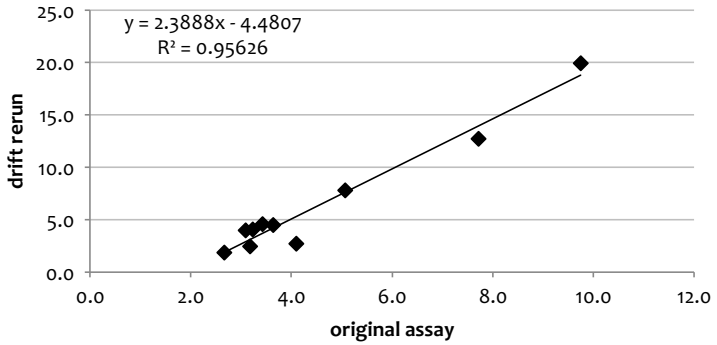
Recalibration Methods

* Samples from ~20 controls from each cohort assayed in Hannia Campos' lab (HSPH) by HPLC
  * Selected according to α-carotene and total carotenoids distributions
* Regression recalibration with original lab value and rerun Campos value
  * drift_value = α + β(original_value) + ε
  * Slope and intercept applied to original data

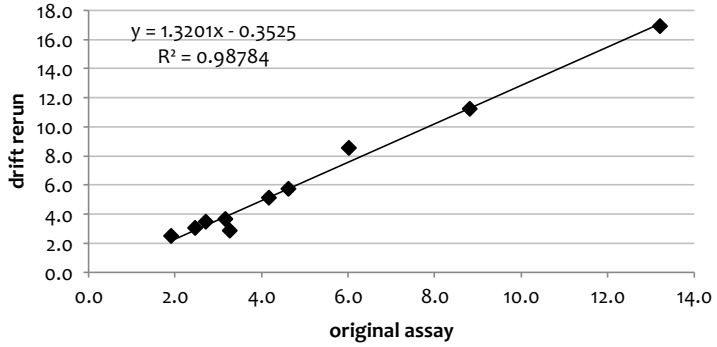
α-carotene: NHS lab12



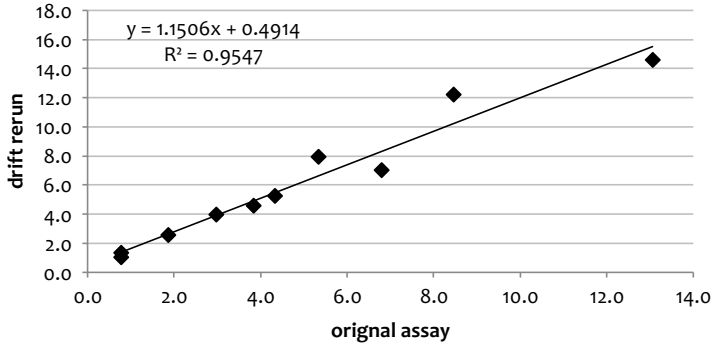
α-carotene: NHS lab63



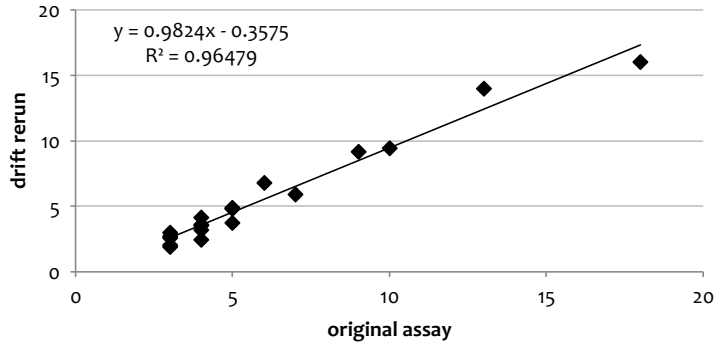
α-carotene: NHS lab151



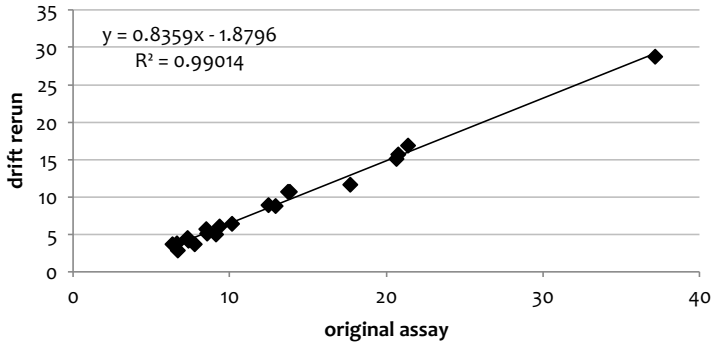
α-carotene: NHS lab264



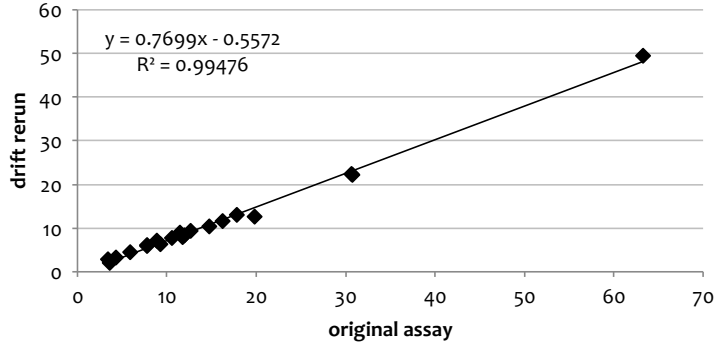
α-carotene: Columbia



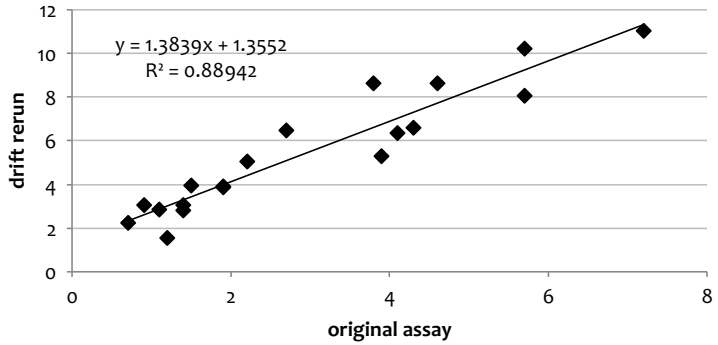
α-carotene: Umea



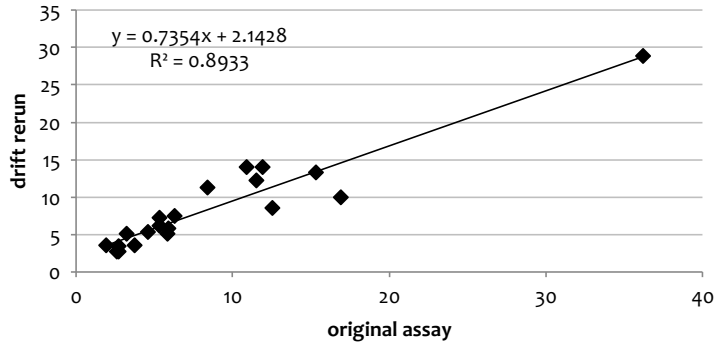
α-carotene: NYUWHS



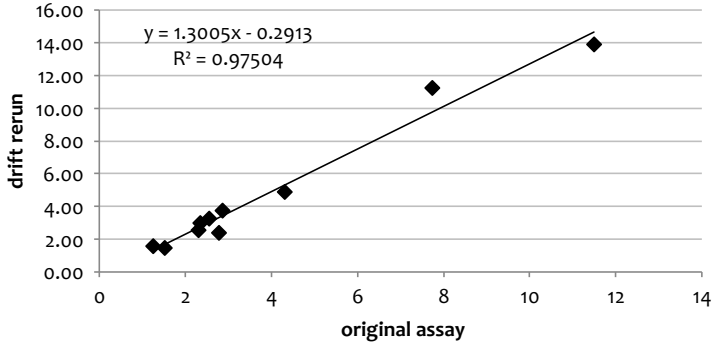
α-carotene: CLUE



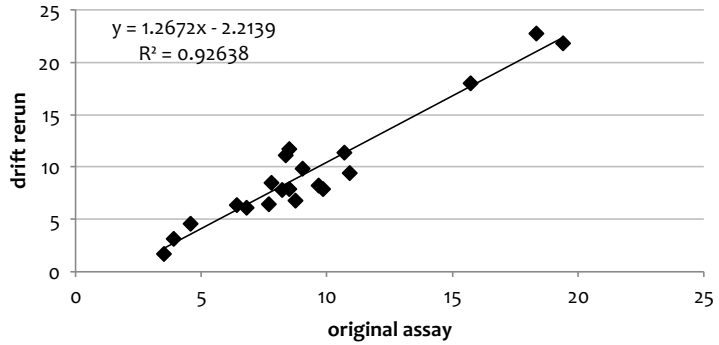
α-carotene: WHS



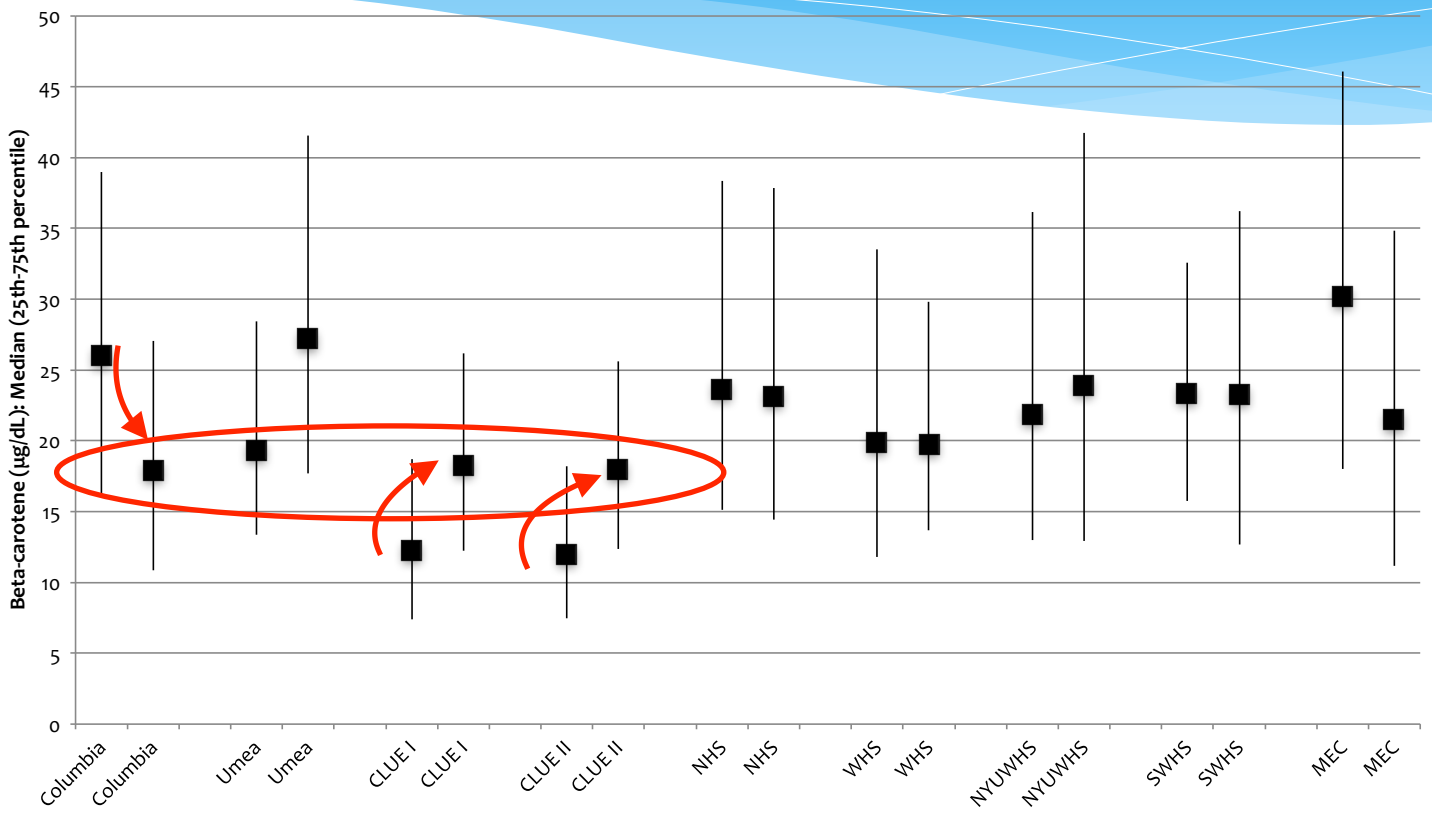
α-carotene: Shanghai



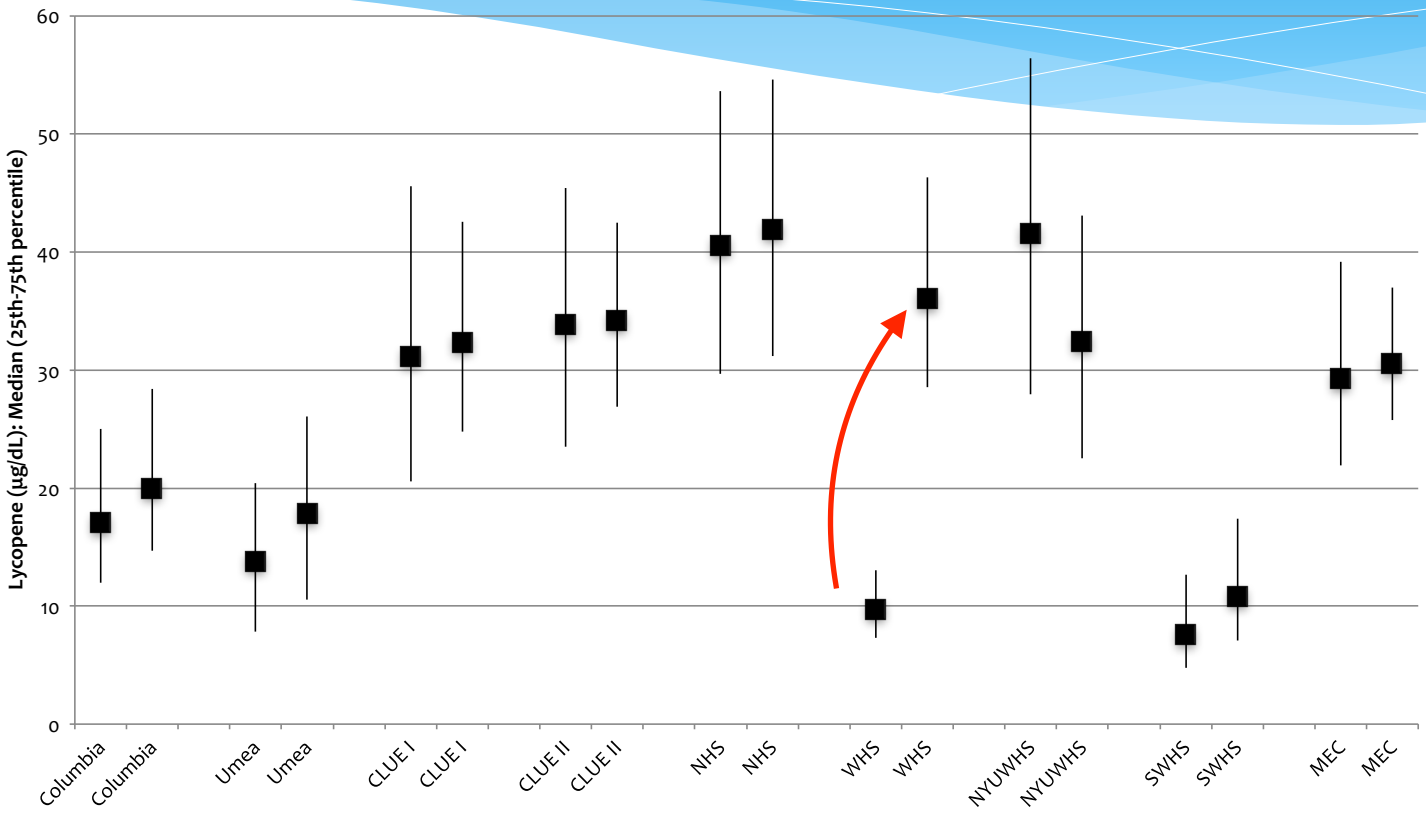
α-carotene: MEC



Original & Recalibrated β-carotene by Cohort



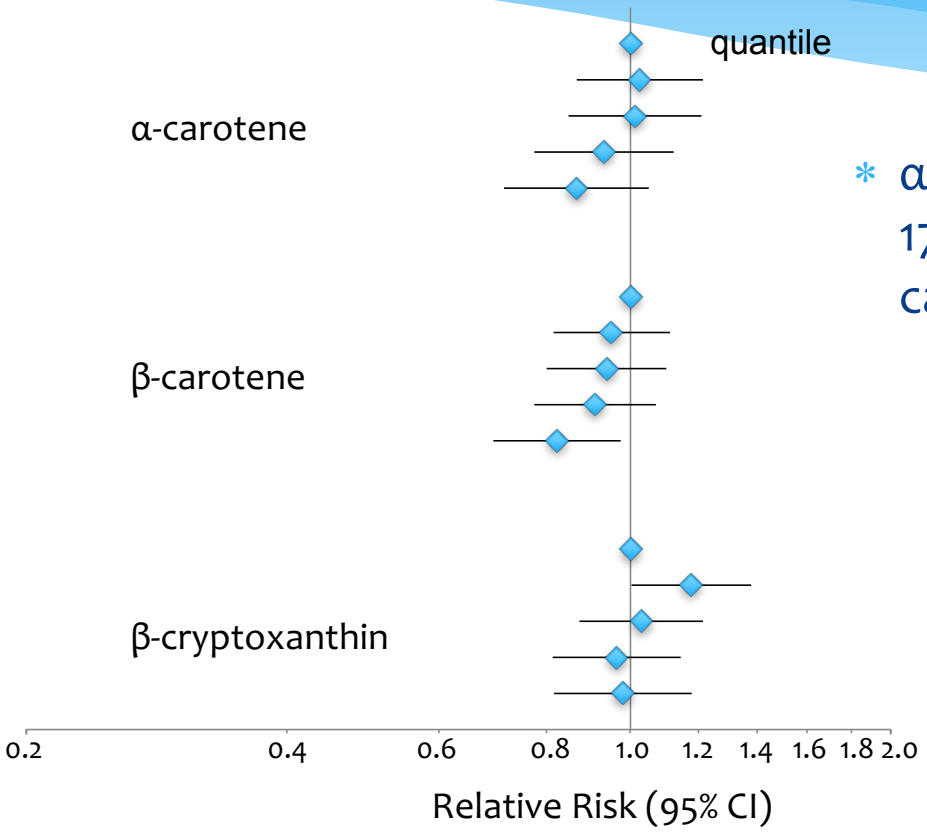
Original & Recalibrated Lycopene by Cohort



Characteristics of Cases and Controls

Characteristic	Cases (N=3,055)	Controls (N=3,956)
Age (y), mean (SD)	56.5 (9.2)	56.7 (9.4)
BMI (kg/m^2), mean (SD)	25.3 (4.5)	25.4 (4.6)
Nulliparous, %	9.0	8.1
Age at first birth (y), mean (SD)	24.9 (4.5)	24.4 (4.2)
Postmenopausal, %	66.5	67.5
Hormone use among postmenopausal, %	37.2	33.0
Family history of breast cancer, %	13.9	8.7
Time from blood to diagnosis (y), mean (SD)	4.3 (3.6)	--

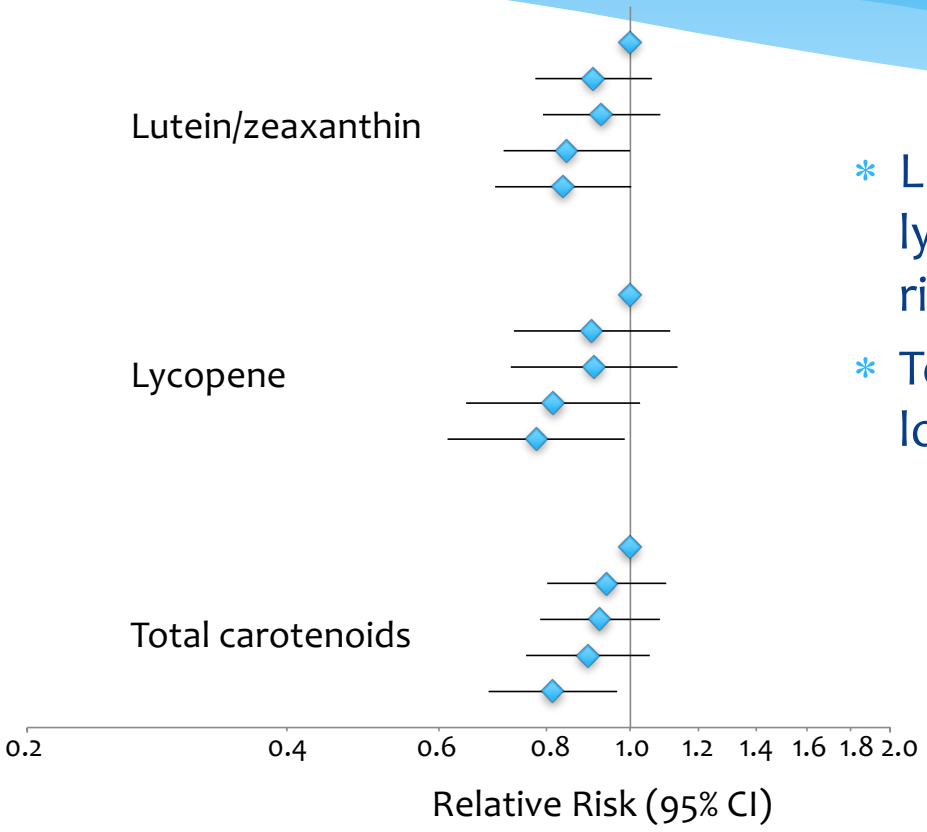
Results



* α- and β-carotene: 13-17% lower risk of breast cancer

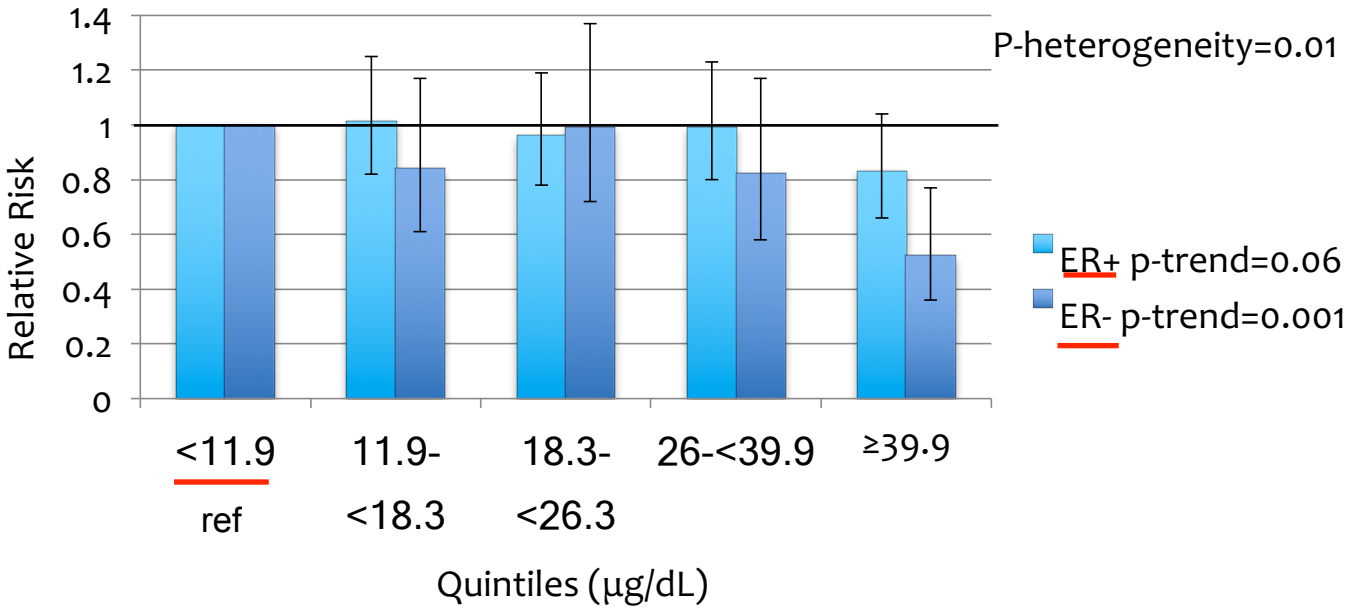
Eliassen, et al. *J Natl Cancer Inst* 2012

Results



* Lutein/zeaxanthin, lycopene: 16-22% lower risk of breast cancer
* Total carotenoids: 19% lower risk

ER+ vs. ER-: β-carotene



Strengths & Limitations

* Strengths:
  * Pooled raw data from >80% of published literature
  * Re-assayed blood samples for recalibration
    * Population vs. laboratory differences
  * Large numbers for subset analyses
* Limitations:
  * Potential for residual confounding
  * Poor track record of β-carotene supplements

Residual confounding is the distortion that remains after controlling for confounding in the design and/or analysis of a study.

how to choose confounder??

Summary: Internal Dose

* Biomarkers can provide data on:
  * Low levels of exposure
  * Ubiquitous exposure
  * Occupational exposures to specific compounds
  * Possible mechanisms of association between exposure and disease
  * Integration of intake and individual variation in absorption

Summary: Internal Dose

* Biomarkers are not perfect
  * Latency not addressed
  * Recent vs. lifetime exposure
  * Measurement error

Papers for Discussion

* Ross RK, Yuan J-M, Yu MC, Wogan GN, Qian GS, Tu JT, Groopman JD, Gao YT, Henderson BE. Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. *Lancet* 1992;339(8799):943–946.
* Yuan J-M, Knezevich AD, Wang R, Gao YT, Hecht SS, Stepanov I. Urinary levels of the tobacco-specific carcinogen N'-nitrosonornicotine and its glucuronide are strongly associated with esophageal cancer risk in smokers. *Carcinogenesis* 2011;32(9):1366–1371.