An End to Breast Cancer by 2020?

Sharif B. Mohr, PhD, MPH;
Edward D. Gorham, PhD, MPH
Cedric F. Garland, DrPH, MPH;

University of California San Diego
Department of Family and Preventive Medicine, La Jolla, California

June 12, 2013
Commonwealth Club
595 Market Street
San Francisco, California 6/12/2013 v5

cgarland@ucsd.edu 941051

Research by Drs. Frank Garland, Cedric Garland, Edward Gorham and their colleagues encouraged research by other scientists, including Dr. Bill Grant

Thanks to Dr. Frank Garland, Epidemiologist, 1950-2010, to whom this lecture is dedicated.

Thanks to:

William B. Grant, Ph.D.
SUNARC and the
Commonwealth Club

Carole Baggerly,
Grassroots Health

cgarland@ucsd.edu 941053

A Quick End to Breast Cancer?

The problem: How breast cancer arises

- Scientists are asked to help – 1974

The solution:

- Scientists find the cause – 1990
- A simple means of preventing the disease exists, yet virtually no one has acted on the science
- Needless cases and deaths continue, largely unabated
- Rescue action would be easy

US science focused on point for humanity was stimulated by Sputnik, in the past century, 1957

DINOMIT - Evolutionary theory of breast cancer (Darwin-Garland-Gorham)

- D-coupling – Loss of tight junctions due to low vitamin D
- Initiation – Genetic variation, mainly from infidelity of reproduction of DNA not mainly carcinogens
- Natural selection – Competition for growth and aggression
- Overgrowth – Palpable mass and invasion
- Metastasis – Remote colonization
- Involution and transition to scar

And a JFK speech . . .

"We choose to go to the moon. We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win . . .." Rice University, 1962

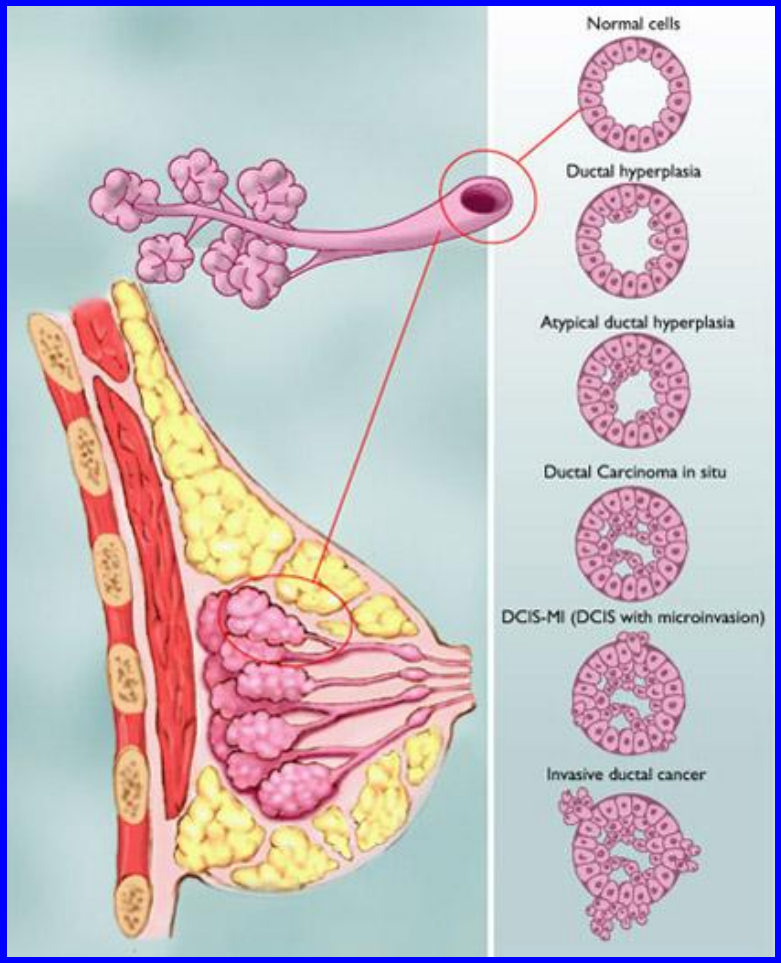
Angelina Jolie's Decision

Breast cancer

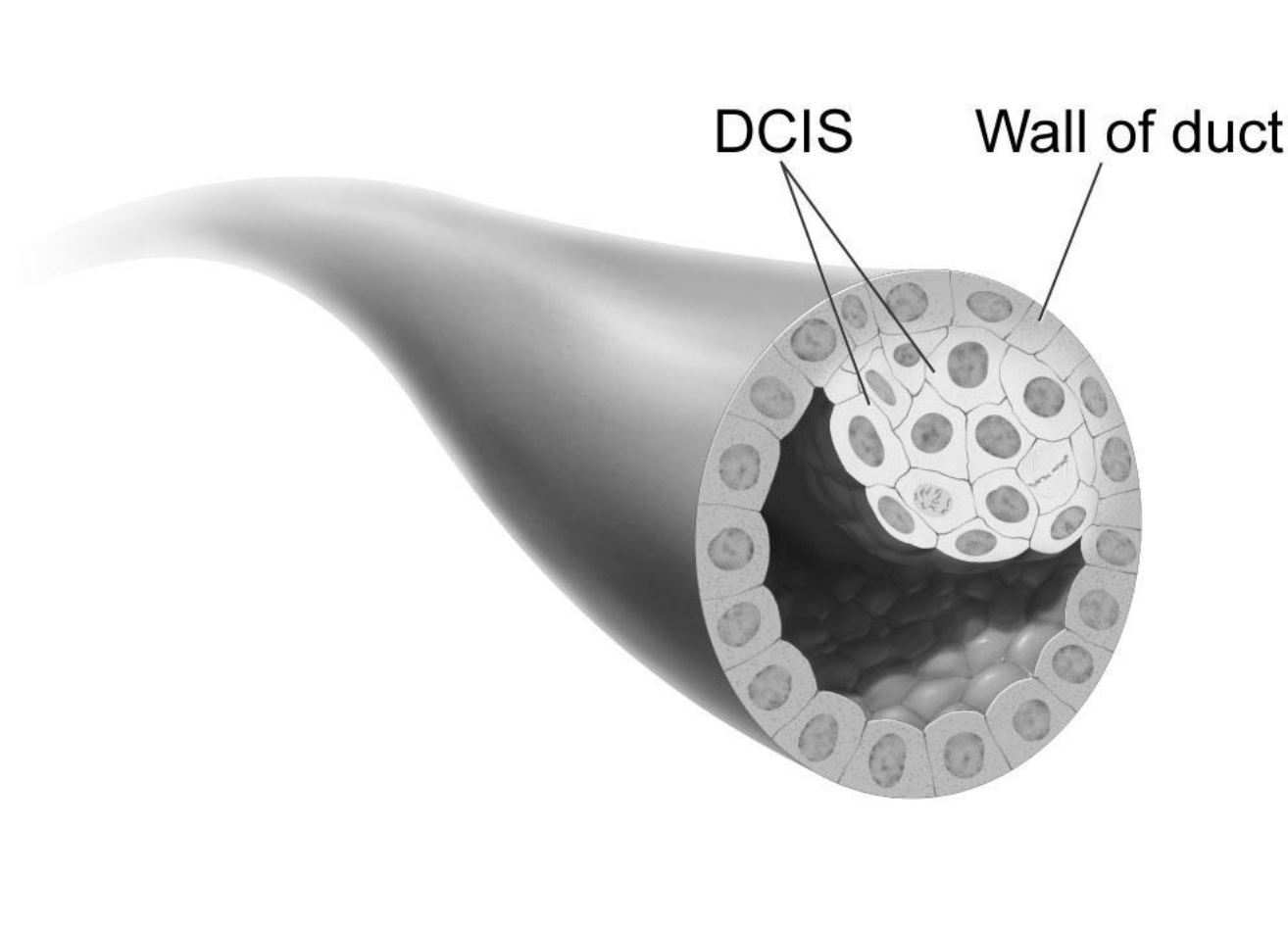
- Problem
- Solution
- Action

The problem

Cancer arises in terminal units

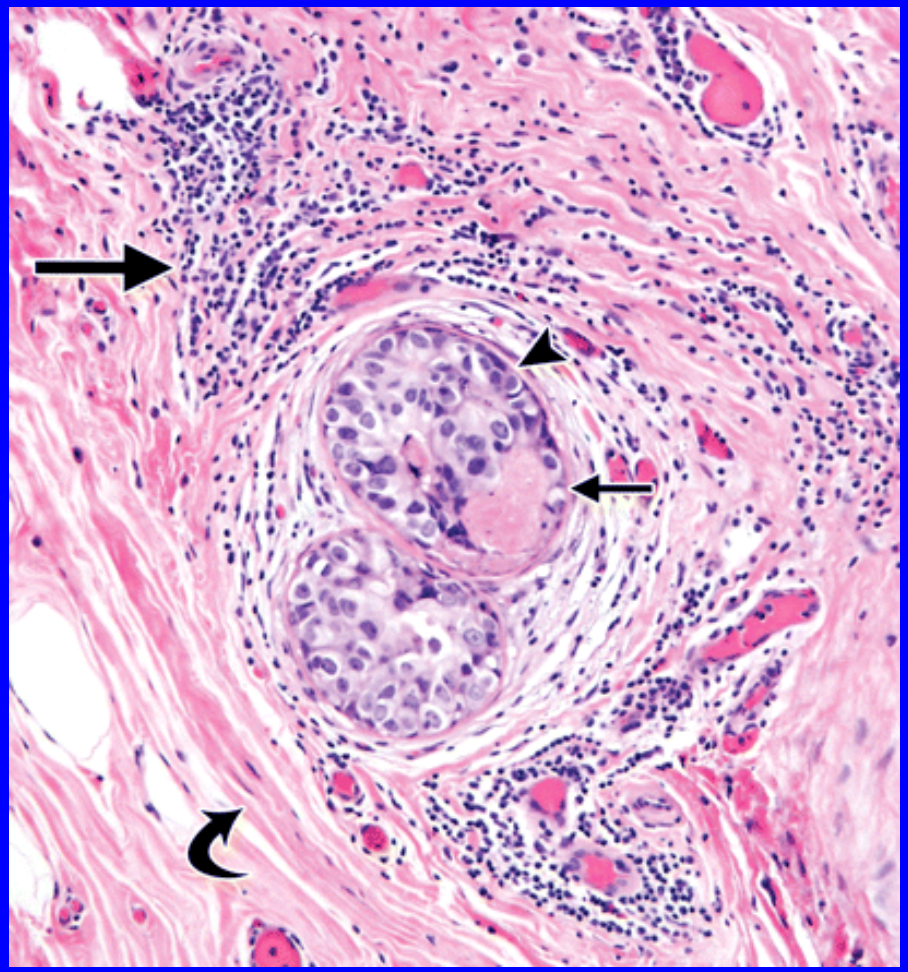


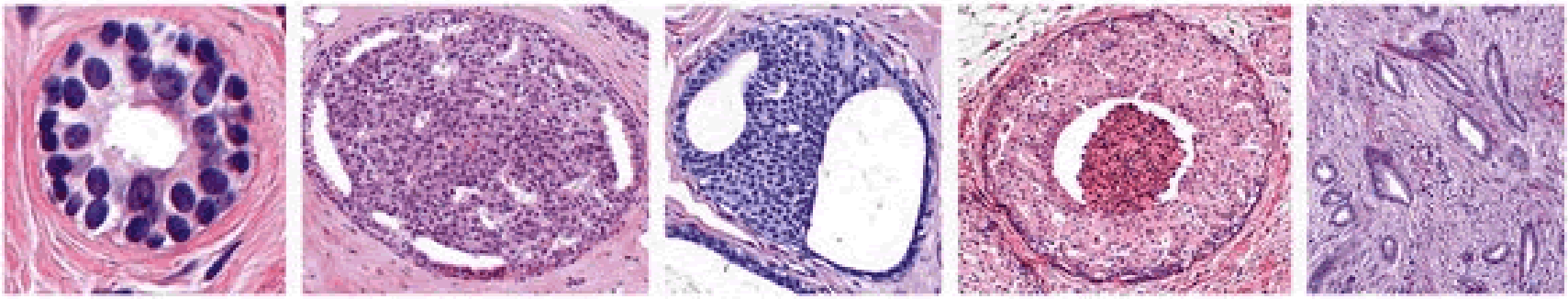
How it begins



Ductal carcinoma in situ

Source: Radiographics 2010;30:1673-87





Normal Ductal Lumen | Benign Proliferative Changes | Atypical Hyperplasia | Ductal Carcinoma in Situ | Invasive Carcinoma

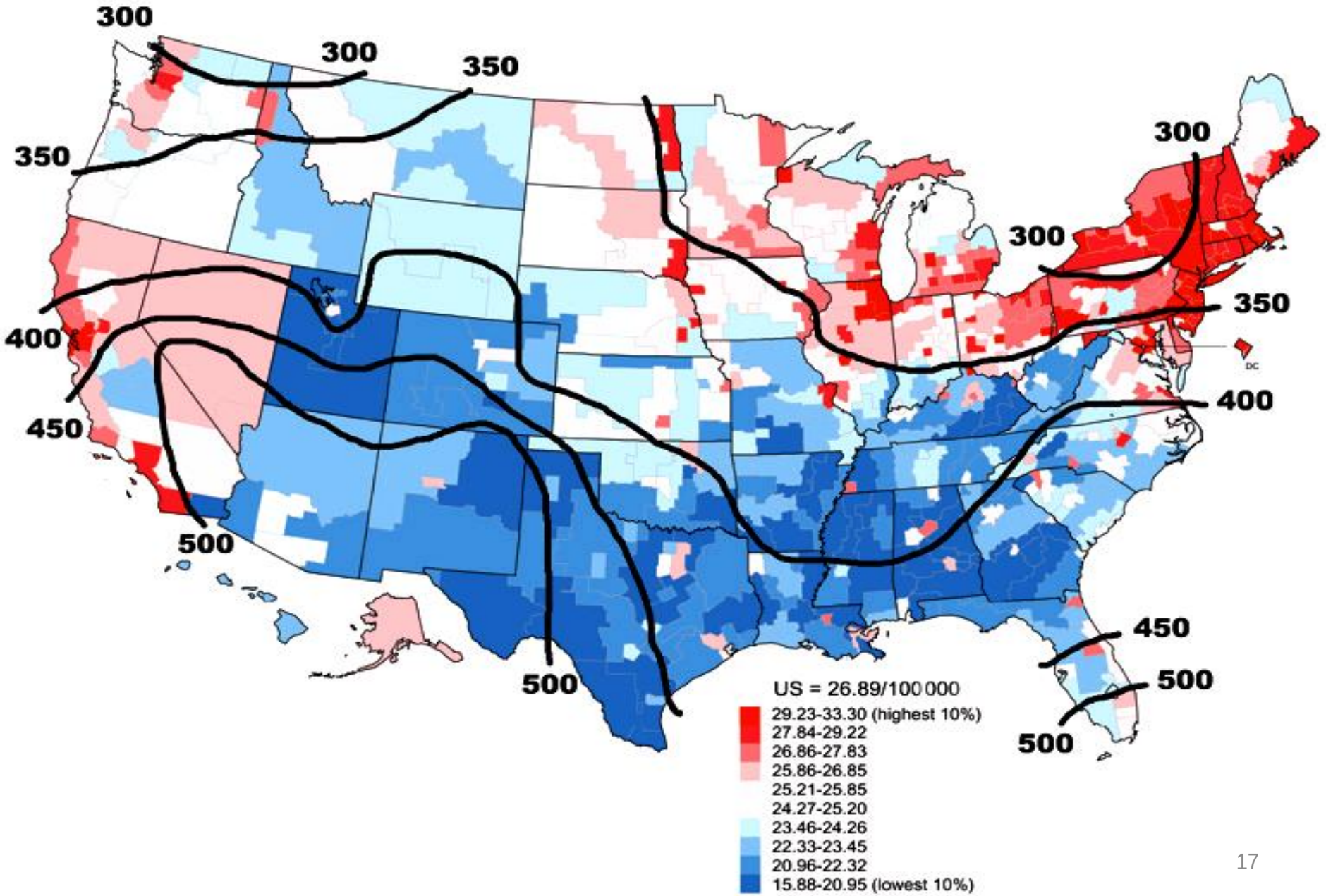
Accumulation of genetic and epigenetic changes

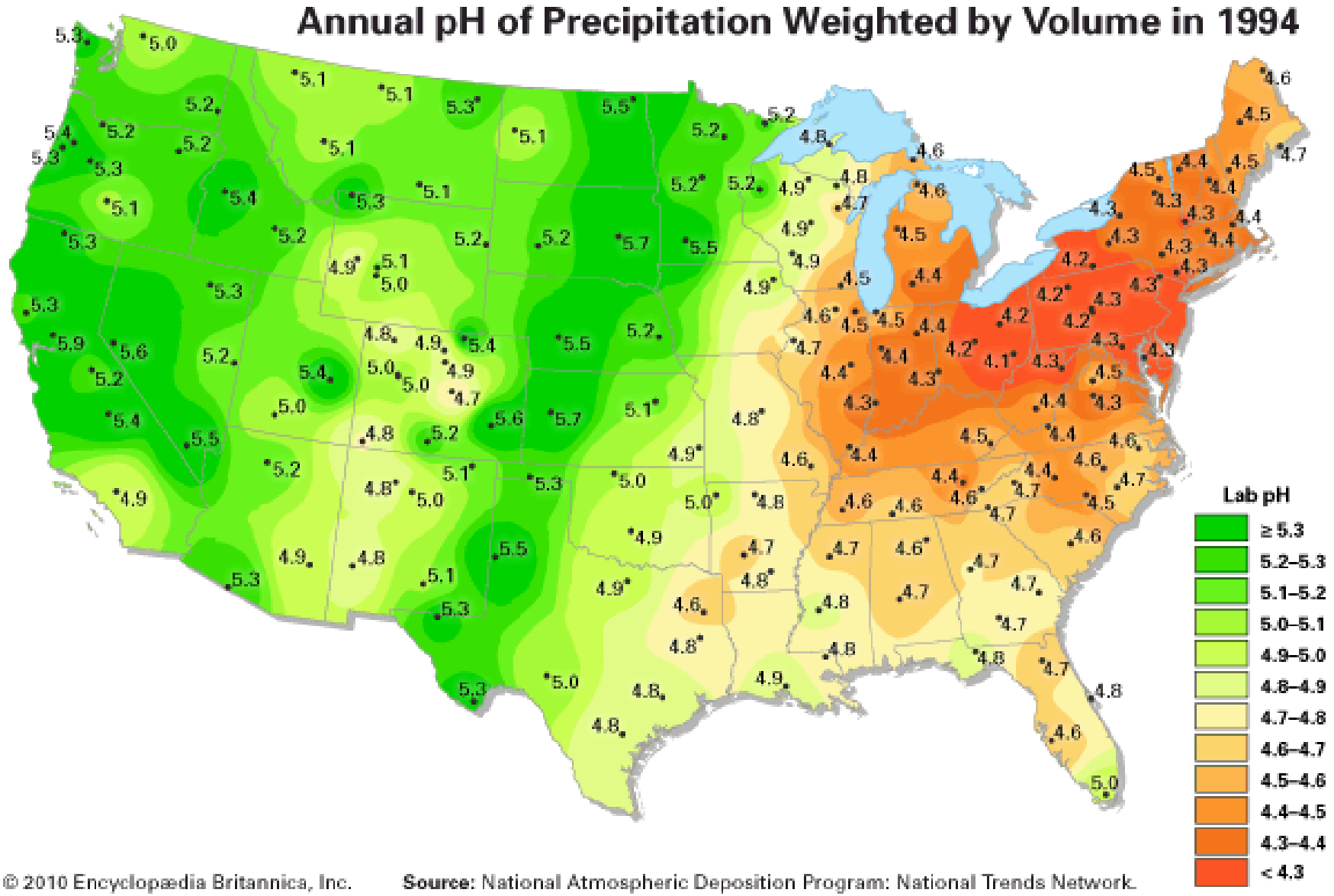
- Abnormal response to growth factors (e.g., estrogen receptor)
- Abnormal oncogene expression (e.g., *HER2/neu*)
- Tissue invasion (gain of function by malignant cells vs. loss of function of normal cells)
- Loss of tumor-suppressor function (e.g., p53)
- Stromal changes (e.g., angiogenesis)
- Failure to respond to normal signals for apoptosis
- Genetic instability (e.g., loss of heterozygosity)
- Clinical phenotype of tumor determined

- Breast cancer is the most common cause of cancer death in women
  - Most common invasive cancer in women in the US, with an estimated 230,500 cases and 39,500 deaths per year [32]
  - -- Approximately 450,000 deaths per year in world [3]
  - -- Breast cancer incidence and mortality rates are higher in areas with low levels of solar ultraviolet B irradiance [4,5]

Scientists are asked to help

Breast Cancer Mortality Rates, USA



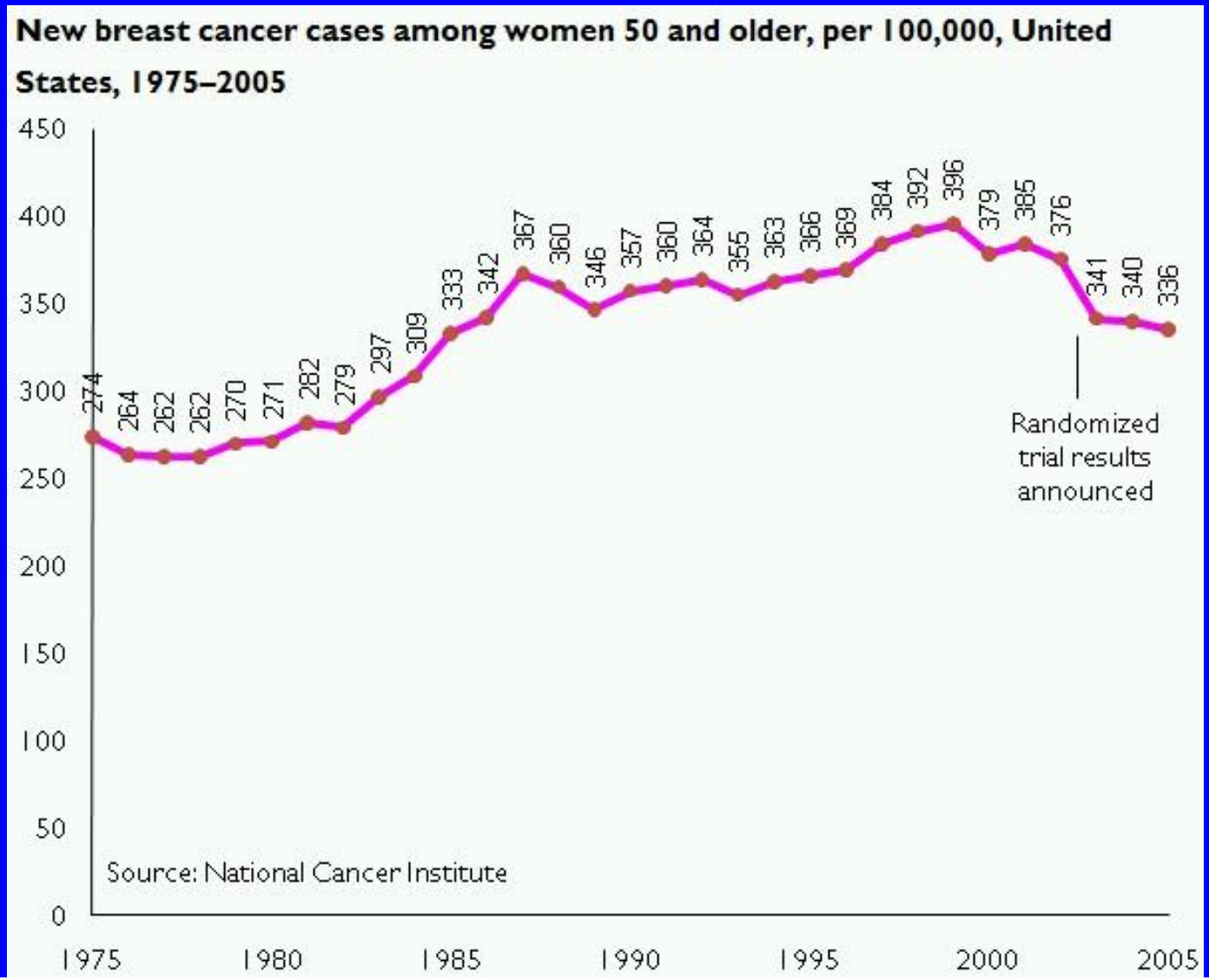

Annual pH of Precipitation Weighted by Volume in 1994
Lab pH
≥ 5.3
5.2–5.3
5.1–5.2
5.0–5.1
4.9–5.0
4.8–4.9
4.7–4.8
4.6–4.7
4.5–4.6
4.4–4.5
4.3–4.4
< 4.3
© 2010 Encyclopædia Britannica, Inc.
Source: National Atmospheric Deposition Program: National Trends Network.

Sun

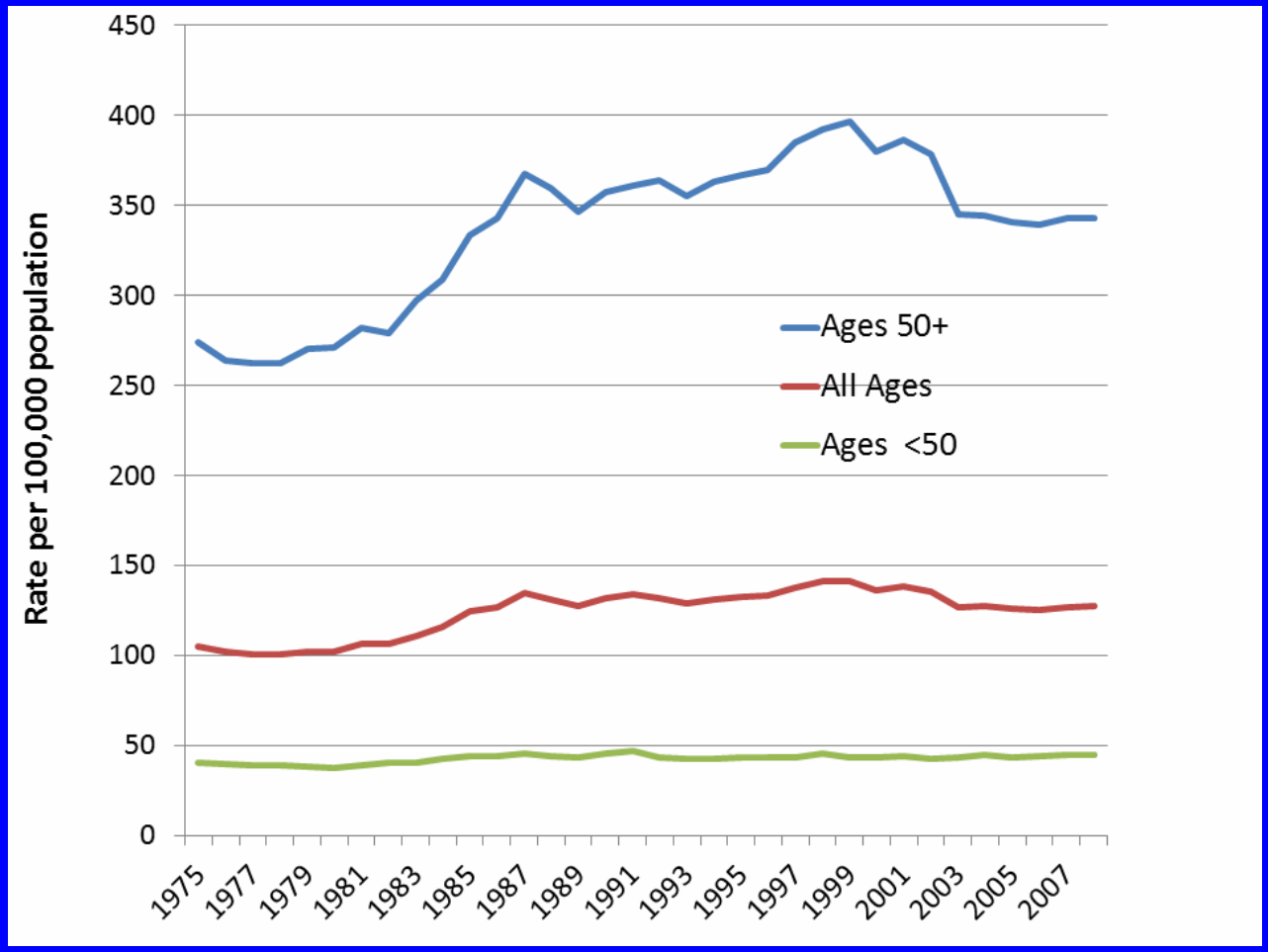
DINOMIT - Evolutionary theory of breast cancer (Darwin Garland-Gorham)

- D-coupling – Loss of tight junctions due to low vitamin D
- Initiation – Genetic variation, mainly from infidelity of reproduction of DNA and mainly not carcinogens
- Natural selection – Competition for growth and aggression
- Overgrowth – Palpable mass and invasion
- Metastasis – Remote colonization
- Involution and Transition to scar

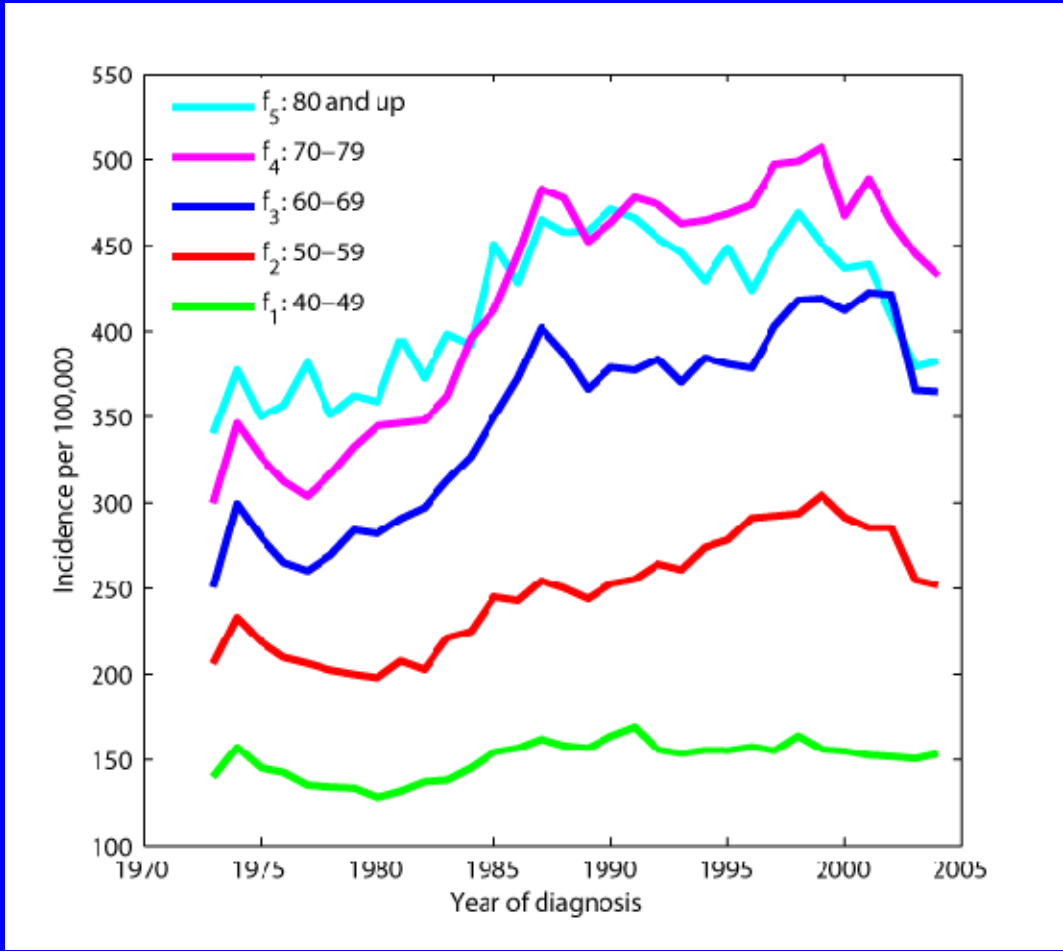
Postmenopausal breast cancer incidence rates



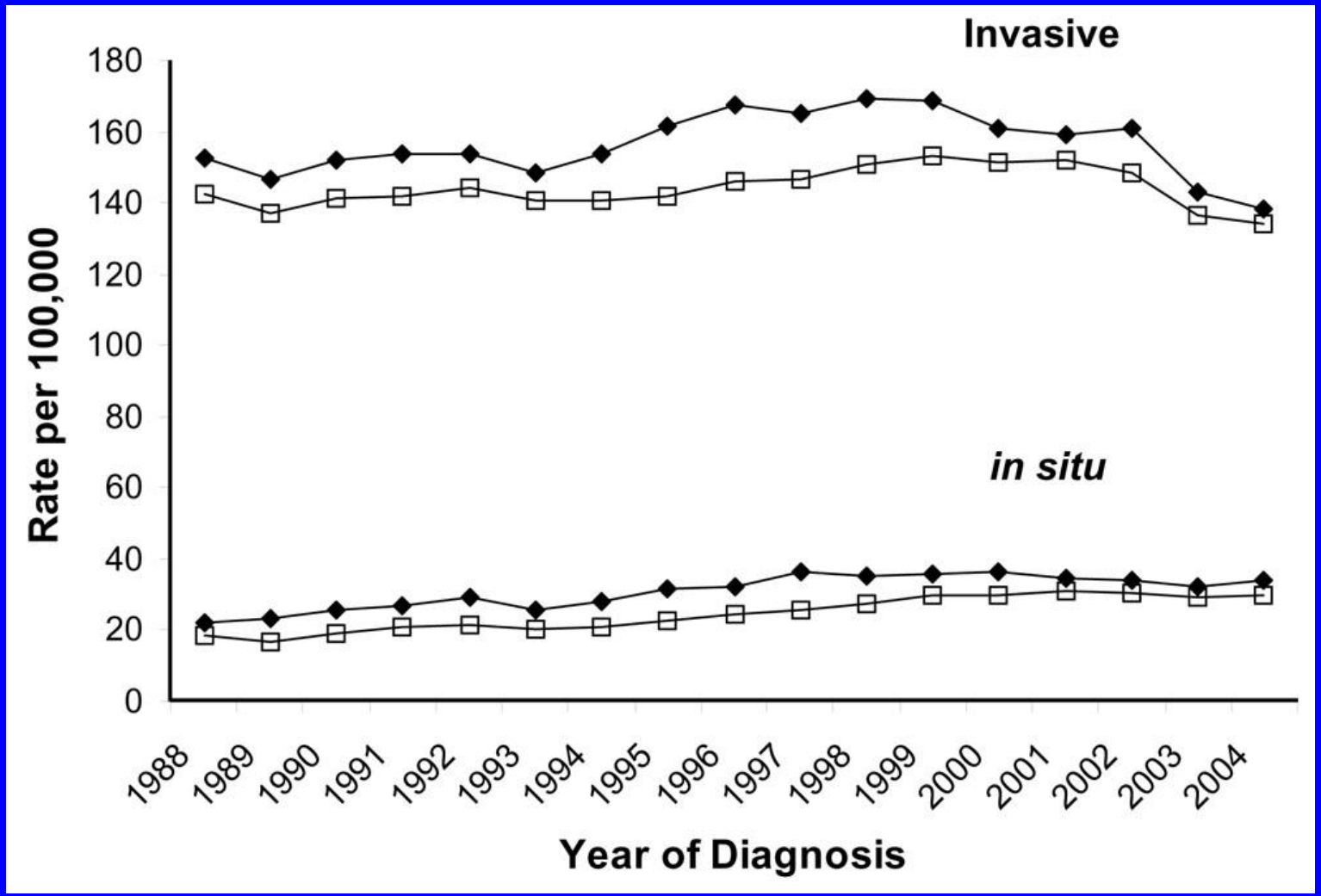
Incidence rates of breast cancer, 1975-present



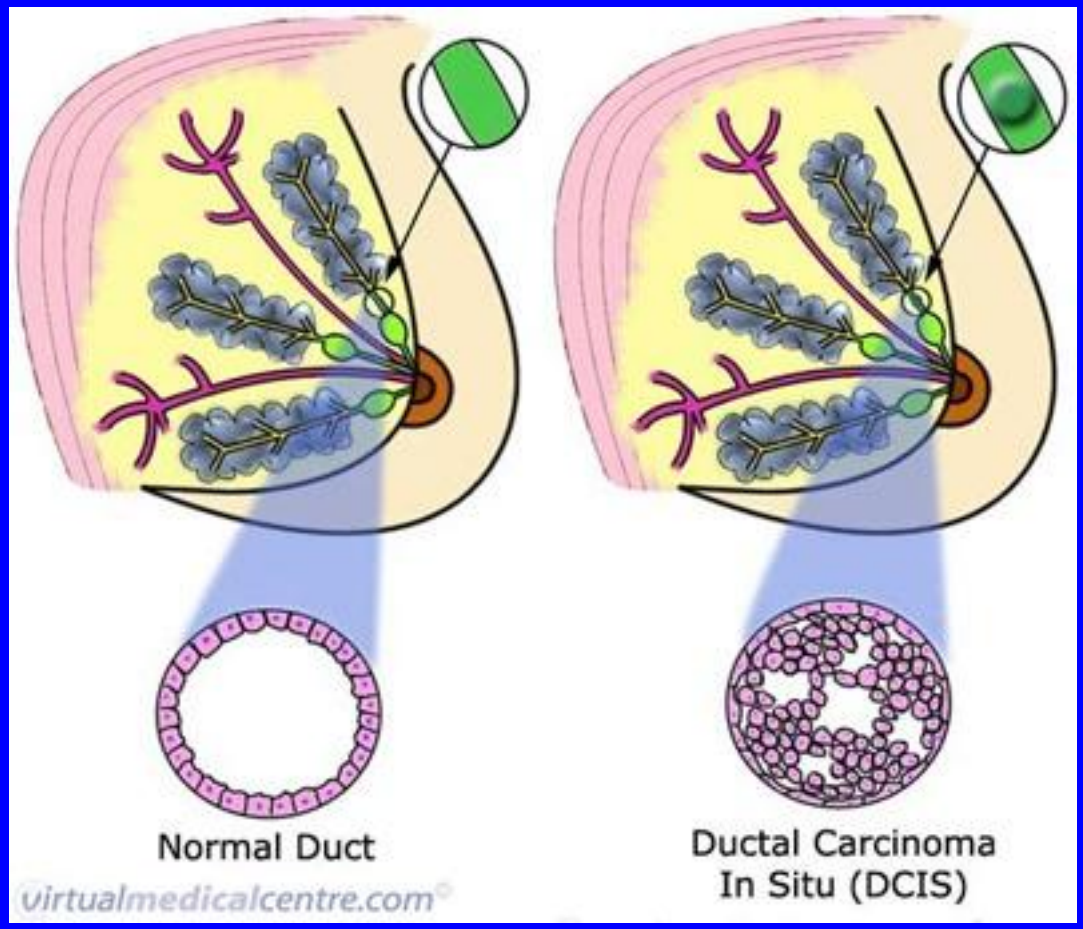
Breast cancer incidence rate trends by age



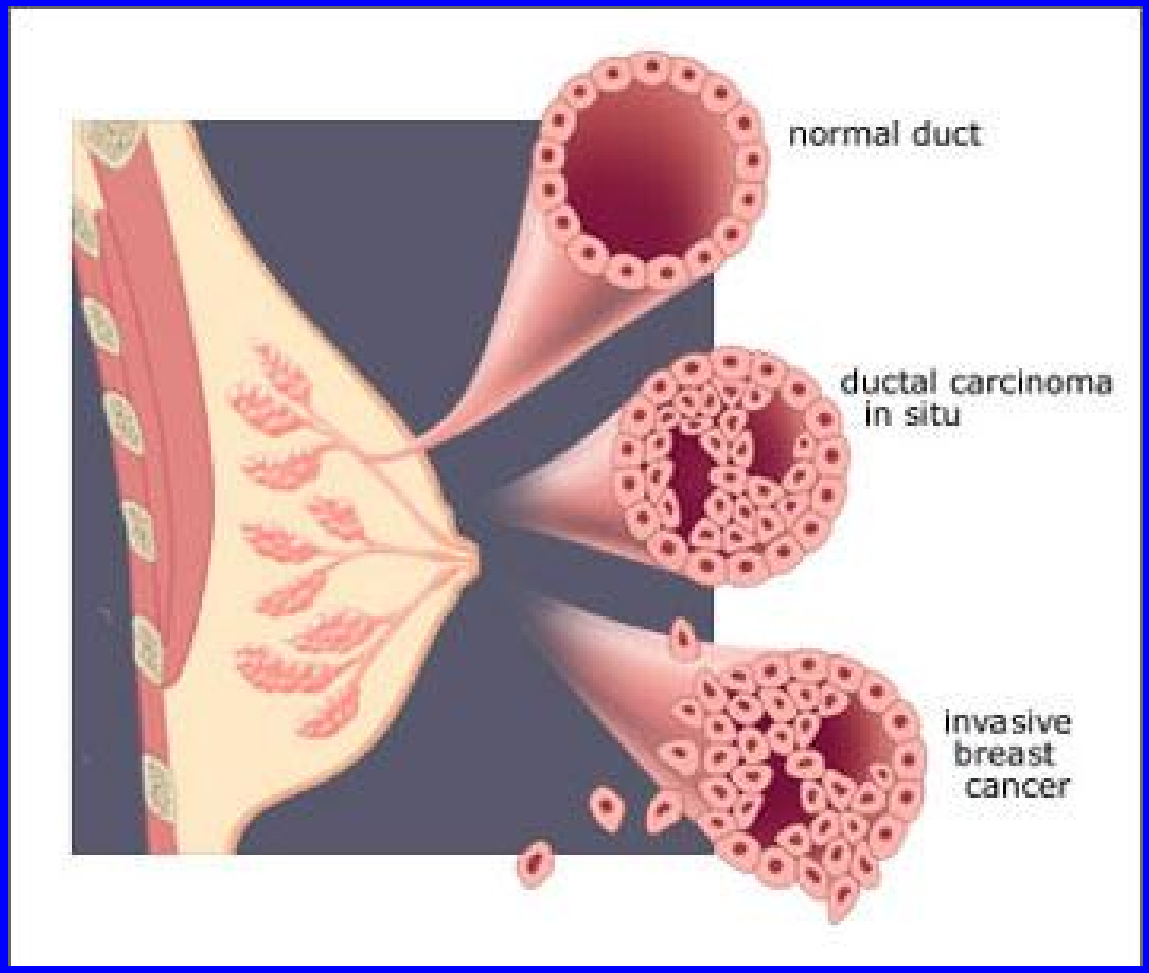
Breast cancer incidence rates, all ages



Low vitamin D causes ducts to fill

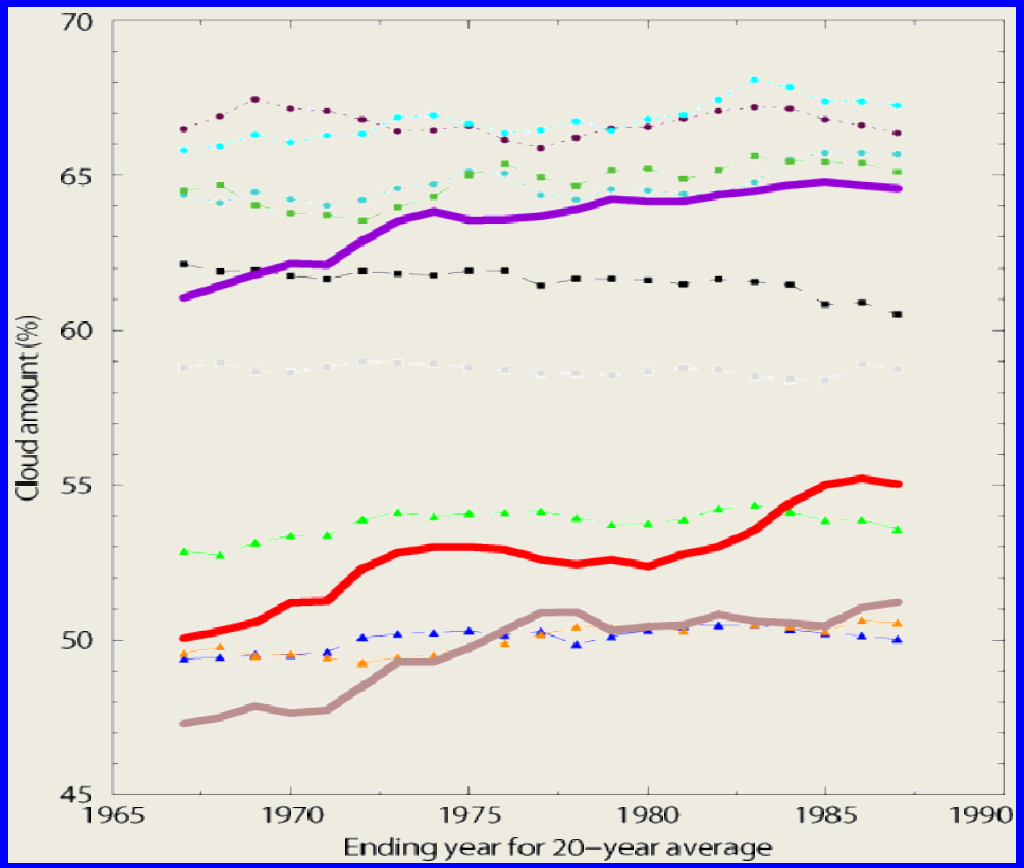


Low vitamin D causes overgrowth and invasion



Cloudiness (% overcast)

Sources: Karl T, Steurer P. Geophysical Research Letter 1990;17:1925-28, NASA /ISCCP(Rossow W, Schiffer R. Bulletin Am Meteorol Soc 1999;80:2261-87.



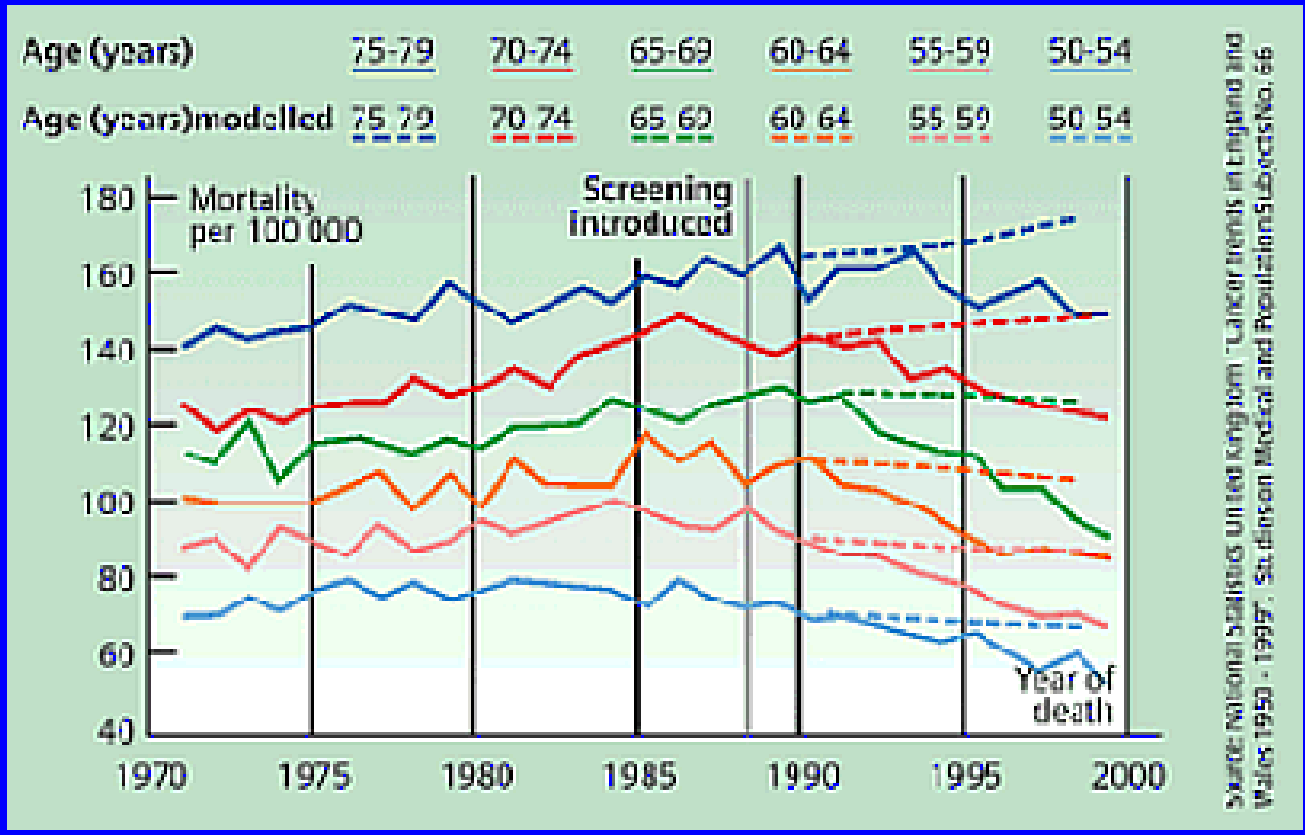
Is it hereditary?

Heredity plays a role, mostly in cancer families

- Is mammo-graphy the answer?

Do mammograms help?

Benefits of mammography in UK Source: Siemens.com



Types of Epidemiological Studies That Have Been Done for Breast Cancer

__Ecological studies (countries)

__Case-control studies (individual patients and matched controls)

__ Nested case-control studies (of individuals from a cohort of people with stored samples of serum)

__Cohort studies (long-term)

__Meta-analysis

__Randomized controlled clinical trial

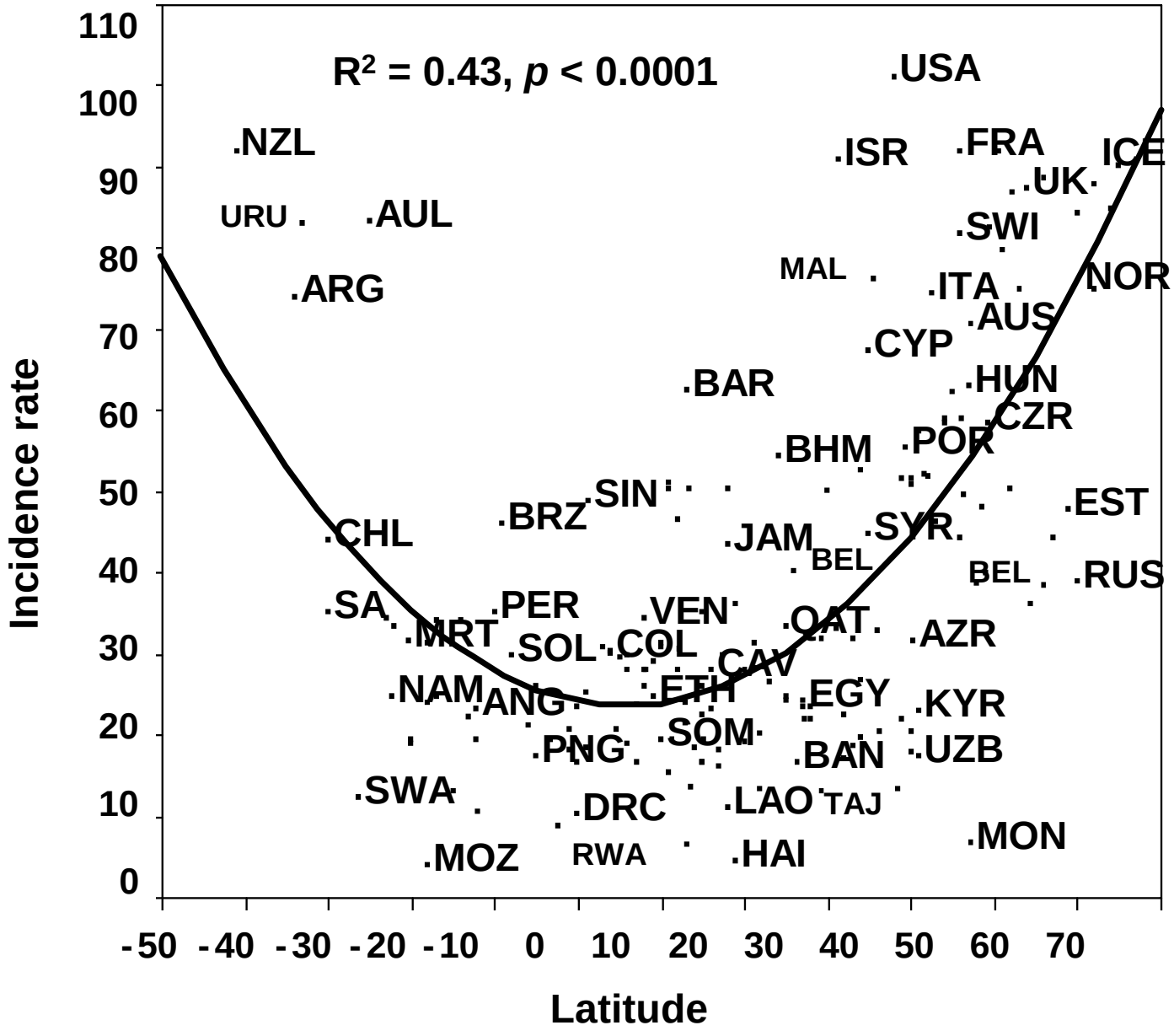
The solution

- The first recognition of the importance of vitamin D in the promotion of human health was made indirectly by Hippocrates in ancient Greece, who wrote that living on the south face of a hill, the side that receives the most sunlight, was the healthiest place one could live.

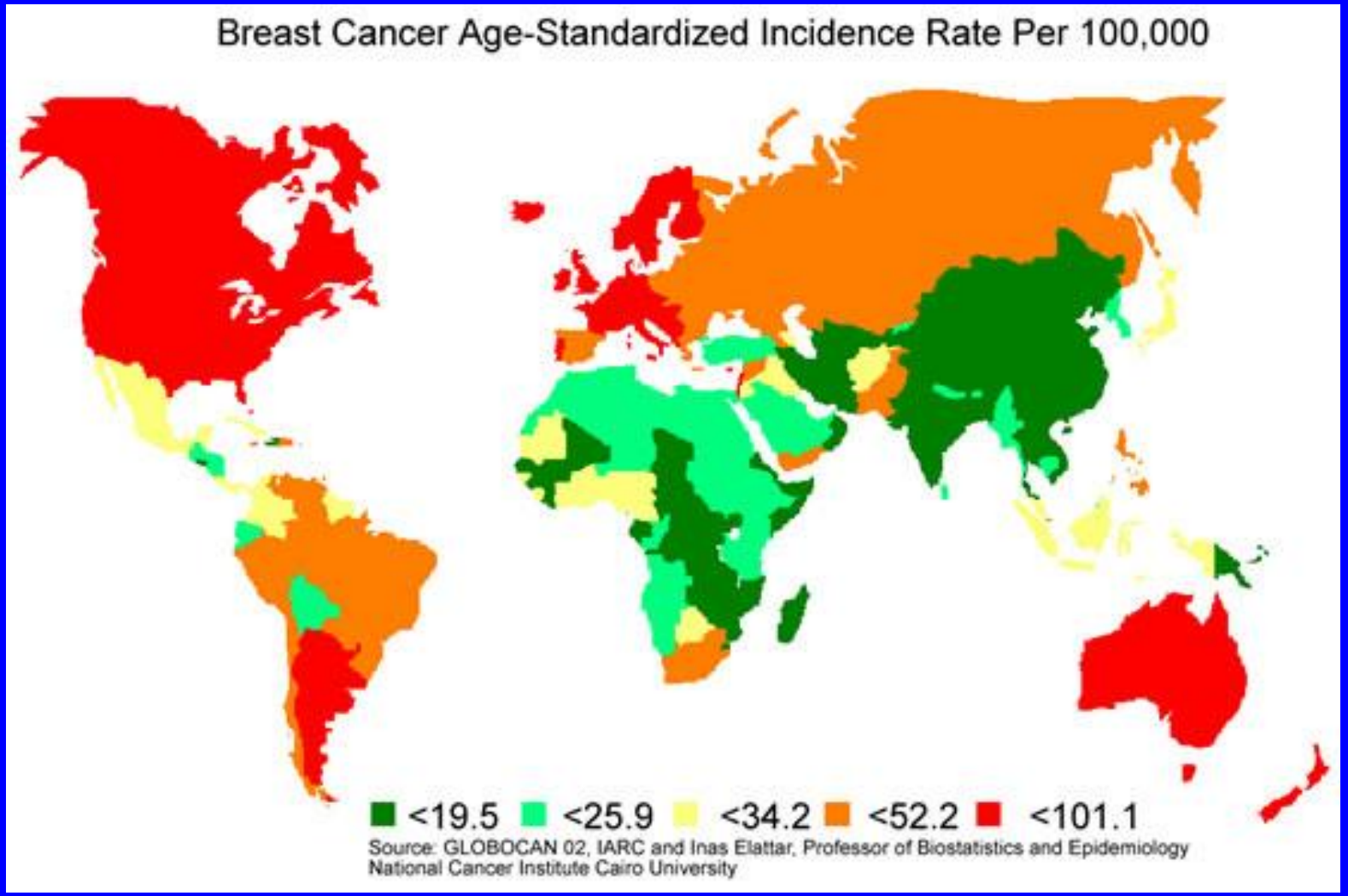
Is lower solar irradiance is associated with lower rates of breast cancer?

Source: Mohr S, Gorham E, Alcaraz J, et al. Ultraviolet B irradiance, modeled serum 25-hydroxyvitamin D, and breast cancer mortality: an ecological analysis. Manuscript in preparation, 2012.

Age-adjusted Breast Cancer Incidence Rates by Latitude, 174 countries, IARC, GloboCan, 2002



Breast cancer by latitudes



Solar ultraviolet B irradiance and other covariates in association with age-standardized breast cancer mortality rates, 107 countries

Covariate	Regression coefficient	Standard error	*t*	*p*
Solar UVB irradiance, Watts/m^2	-0.46	0.22	-2.10	0.04
Per capita alcohol consumption (no. of drinks per person per year)	0.01	0.01	1.56	0.12
Proportion of female population overweight (BMI > 25)	0.02	0.03	0.86	0.39
Per capita cigarette consumption (no. of cigarettes per person per year)	0.001	0.001	1.43	0.15

Solar ultraviolet B irradiance and other covariates in association with age-standardized breast cancer mortality rates, 107 countries, 2002, continued

Covariate	Regression coefficient	Standard error	*t*	*p*
Total fertility rate per 1000 women	1.53	0.45	3.37	0.001
Per capita health expenditure, dollars/yr	0.001	0.001	1.43	0.16
Intercept	10.0	3.19	3.10	0.002

$R^2 = 0.34$, $p < 0.0001$

- Limitations cont.
  - No data on type of clothing worn

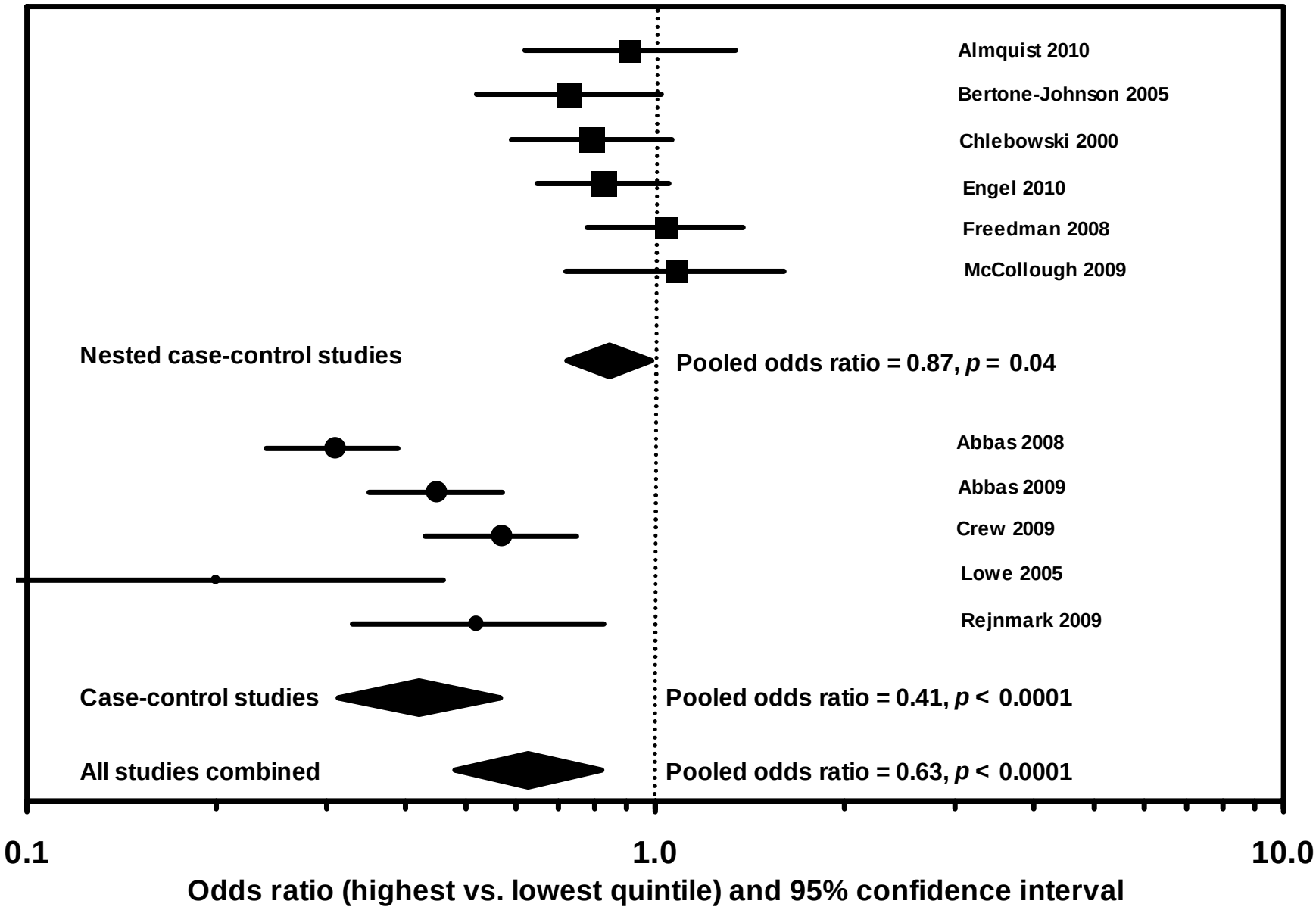
The Next Step

ANTICANCER RESEARCH *31*: 2939-2948 (2011)

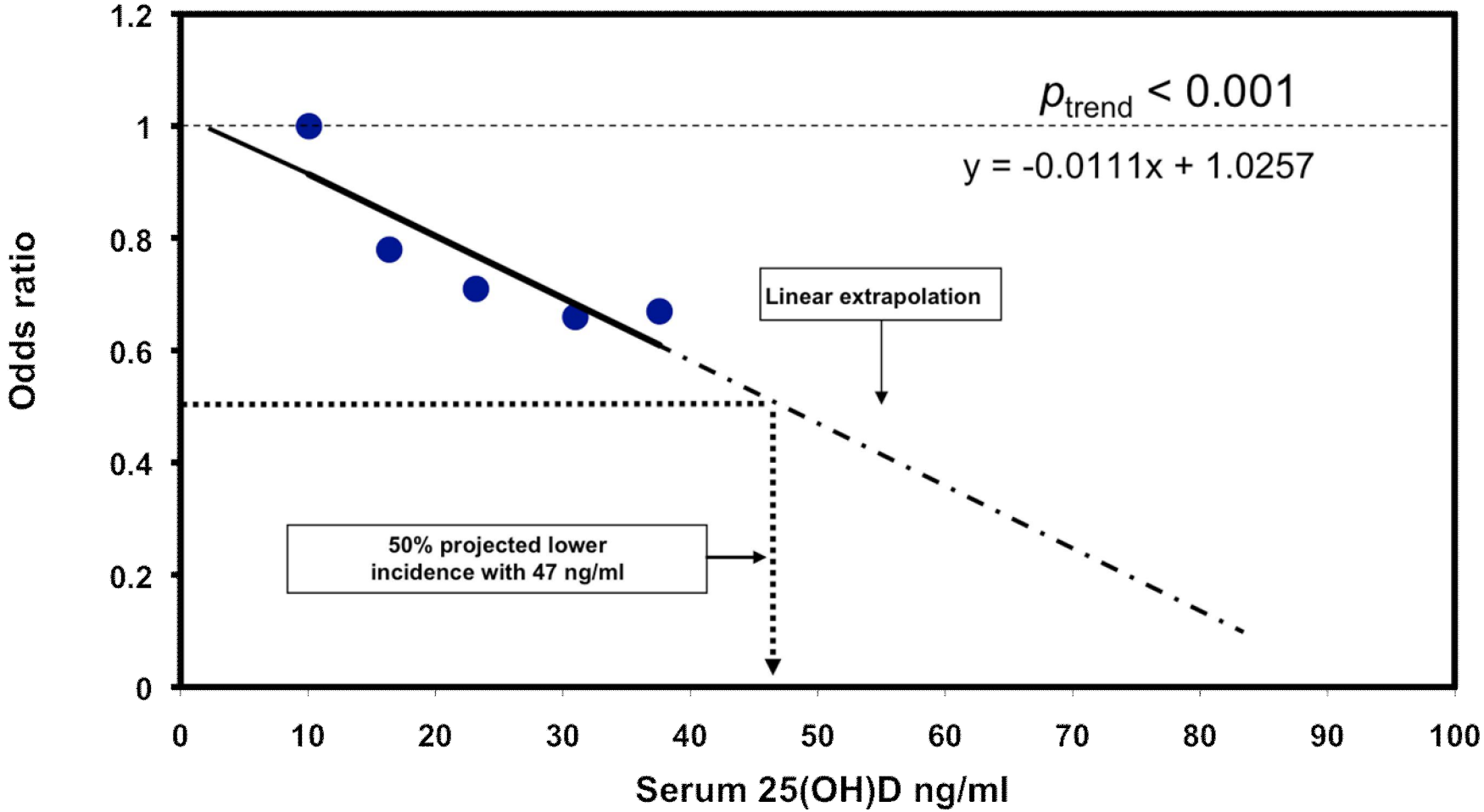
Serum 25-Hydroxyvitamin D and Prevention of Breast Cancer: Pooled Analysis

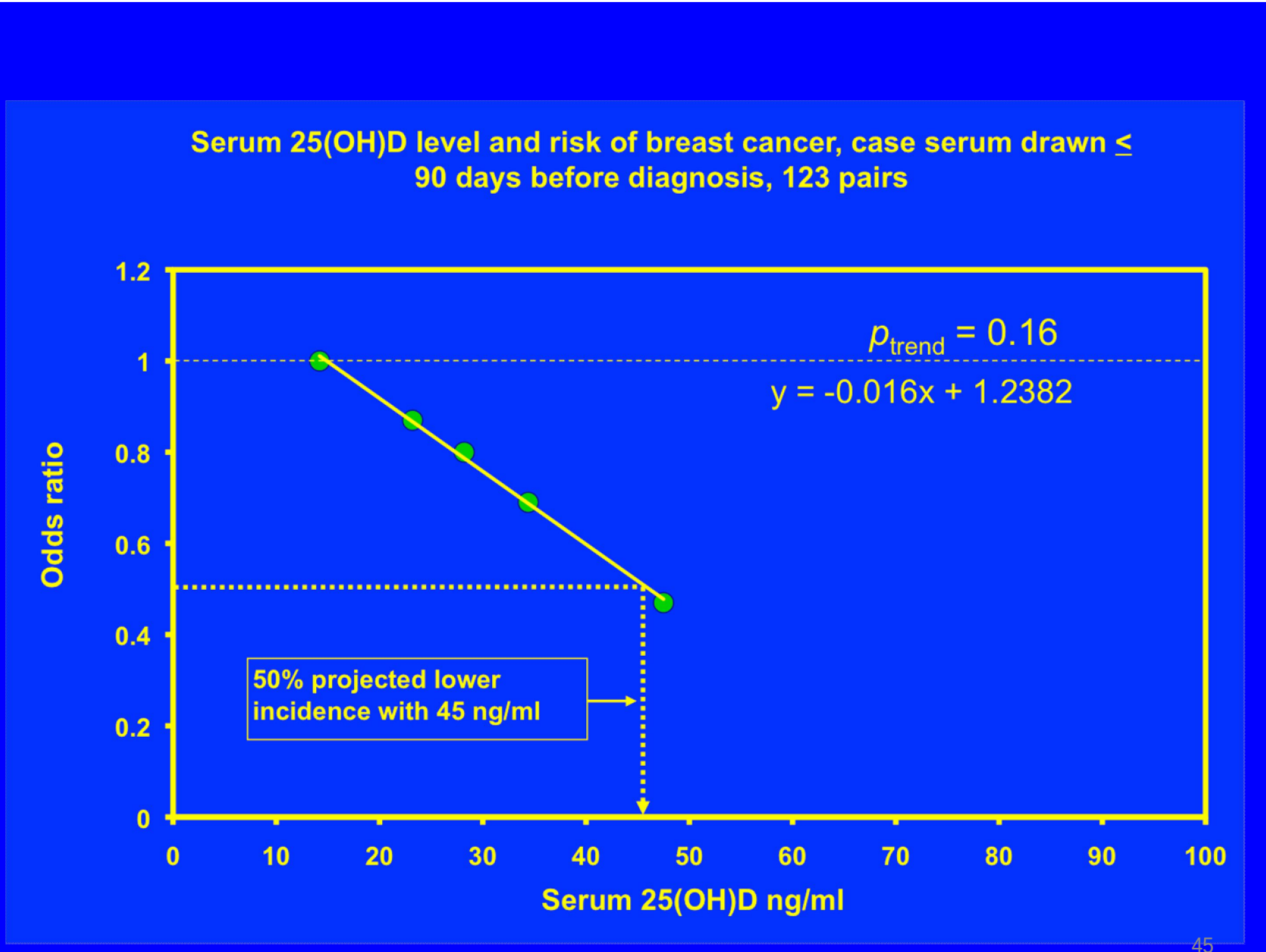
SHARIF B. MOHR[1], EDWARD D. GORHAM[1,2], JOHN E. ALCARAZ[3], CHRISTOPHER J. KANE[4], CAROLINE A. MACERA[2,3], J. KELLOGG PARSONS[4], DEBORAH L. WINGARD[1] and CEDRIC F. GARLAND[1,2]

[1]Division of Epidemiology, Department of Family and Preventive Medicine, and
[4]Department of Surgery, School of Medicine, University of California San Diego, La Jolla CA, U.S.A.;
[2]Naval Health Research Center, San Diego, CA, U.S.A.;
[3]Department of Epidemiology and Biostatistics, Graduate School of Public Health, San Diego State University, San Diego CA, U.S.A.

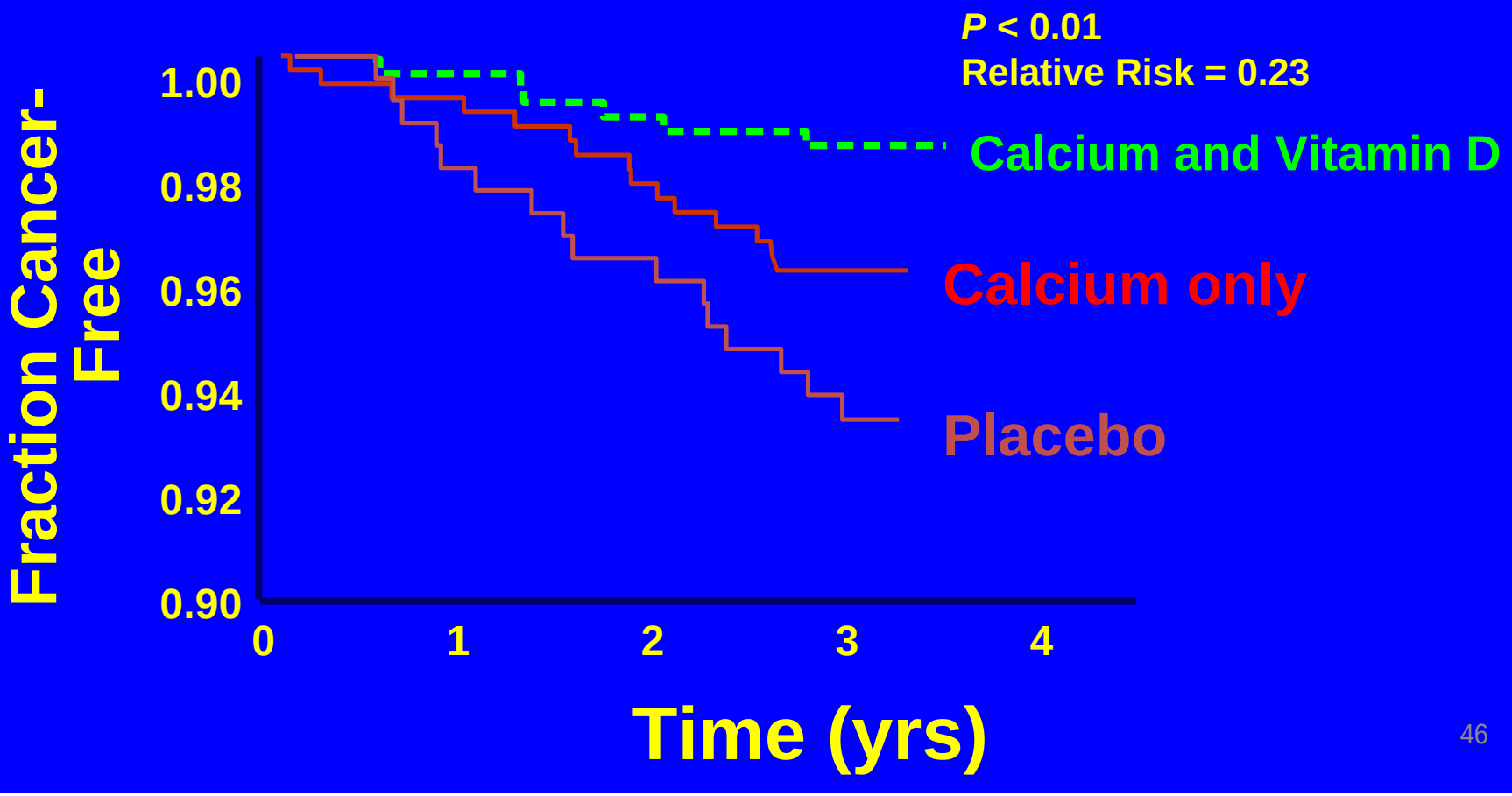

Almquist 2010
Bertone-Johnson 2005
Chlebowski 2000
Engel 2010
Freedman 2008
McCollough 2009
Nested case-control studies
Pooled odds ratio = 0.87, p = 0.04
Abbas 2008
Abbas 2009
Crew 2009
Lowe 2005
Rejnmark 2009
Case-control studies
Pooled odds ratio = 0.41, p < 0.0001
All studies combined
Pooled odds ratio = 0.63, p < 0.0001
0.1
1.0
10.0
Odds ratio (highest vs. lowest quintile) and 95% confidence interval

Pooled analysis of studies of serum 25(OH)D level and risk of breast cancer
Source: Mohr et al. *Anticancer Research* 2011

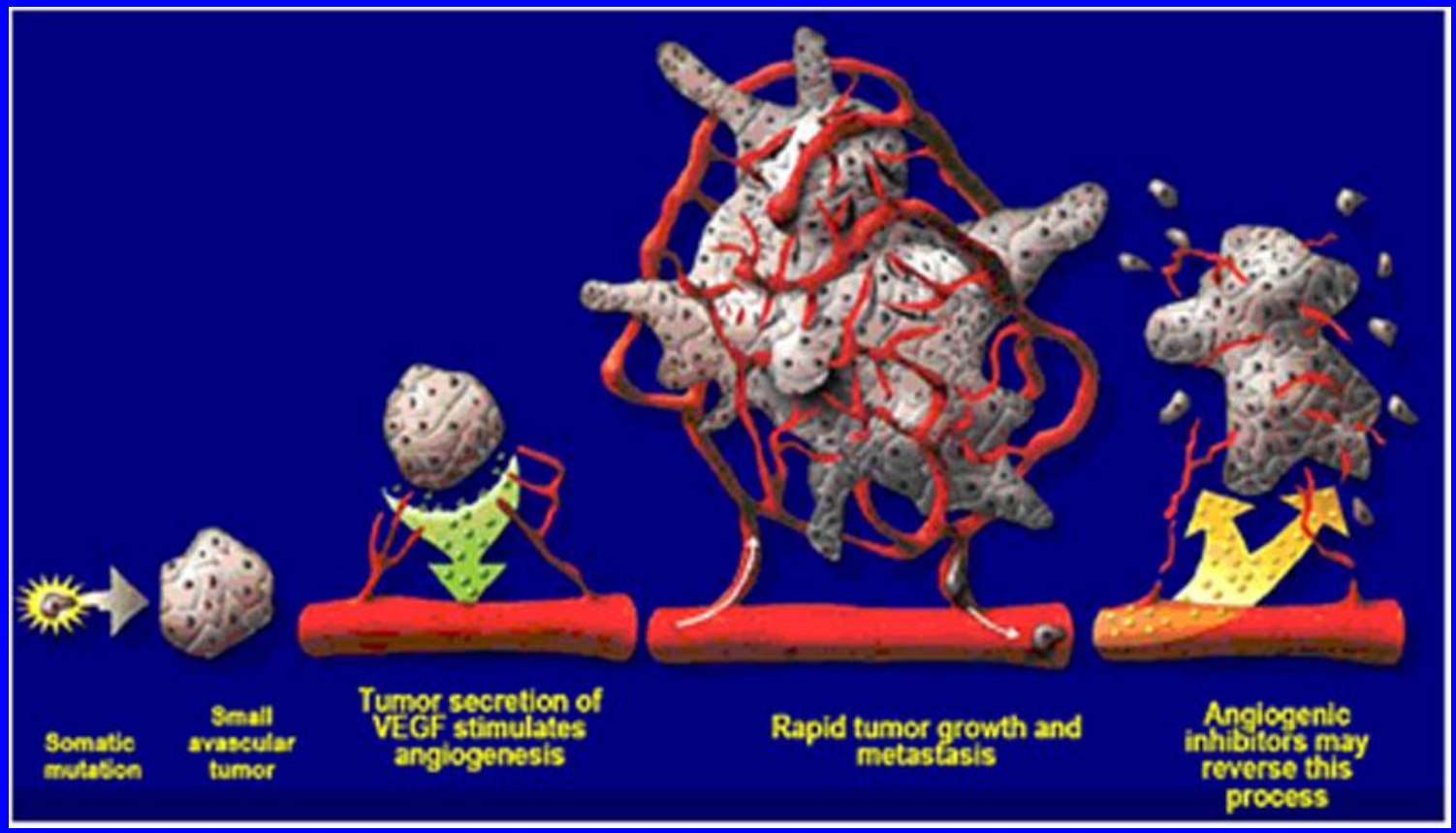



Serum 25(OH)D level and risk of breast cancer, case serum drawn ≤ 90 days before diagnosis, 123 pairs
p_{trend} = 0.16
y = -0.016x + 1.2382
50% projected lower incidence with 45 ng/ml
Odds ratio
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
100
Serum 25(OH)D ng/ml

Randomized controlled trial performed (RCT) by Lappe et al, 2007, results shown below. An earlier trial of lower dose of vitamin D was inconclusive.

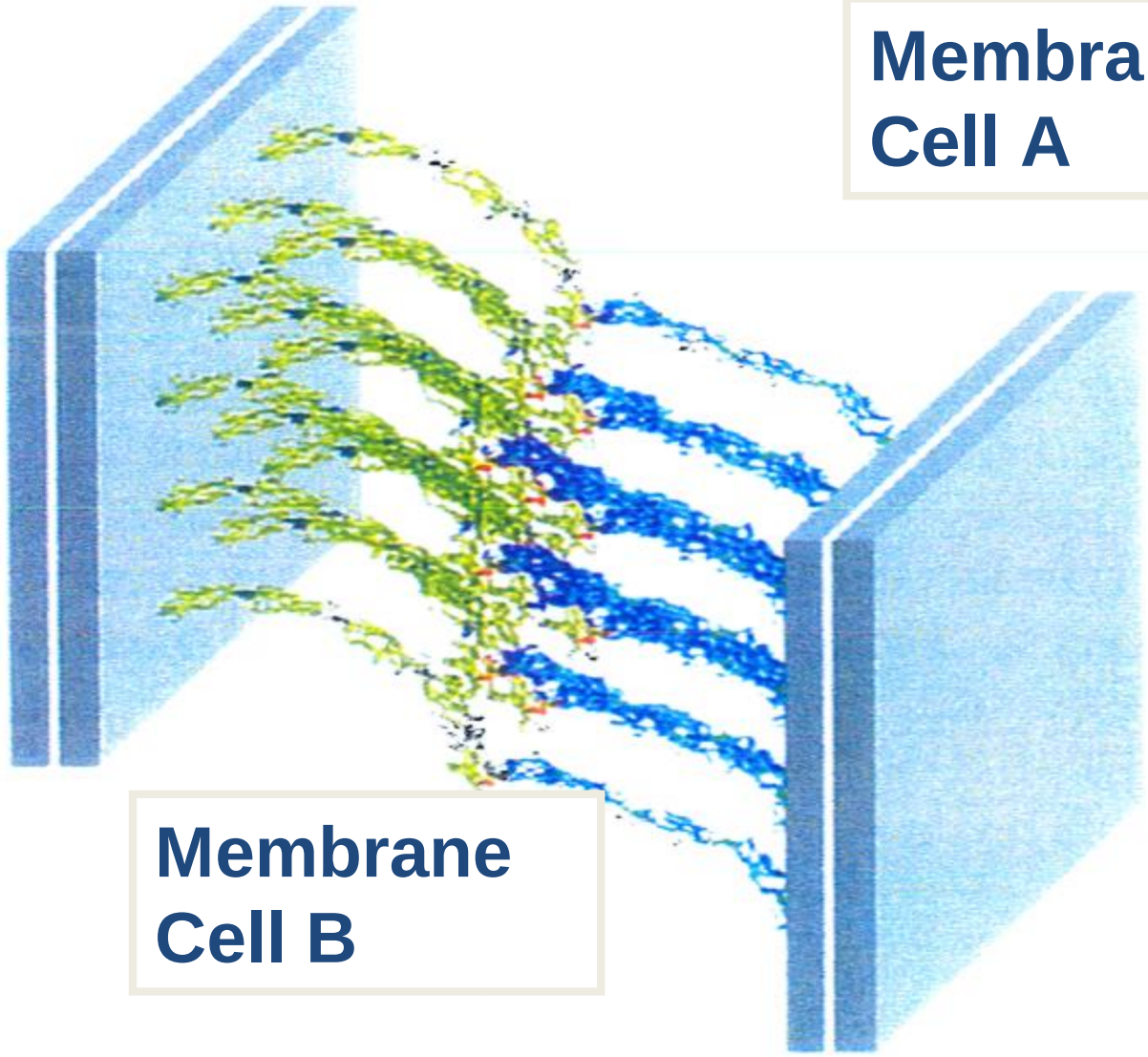


- Vitamin D metabolites may the greatest effect in preventing the last doubling before likely clinical detection of the tumor
  - Possibly due to inhibition of blood vessel recruitment (neoangiogenesis)[44,45]
  - The most commonly observed doubling time is 3 months, although it can occur in as little as 1.2 months [46,47]



- Biological Plausibility
  - Laboratory studies have demonstrated anticarcinogenic properties of Vitamin D metabolites, especially $1,25(OH)_2D$
    - Inhibit angiogenesis [44]
    - Induce apoptosis [45]
    - Inhibit cell proliferation [45]
    - Promote differentiation [49-51]
      - Up-regulate e-cadherin
      - Up-regulate tight junctions

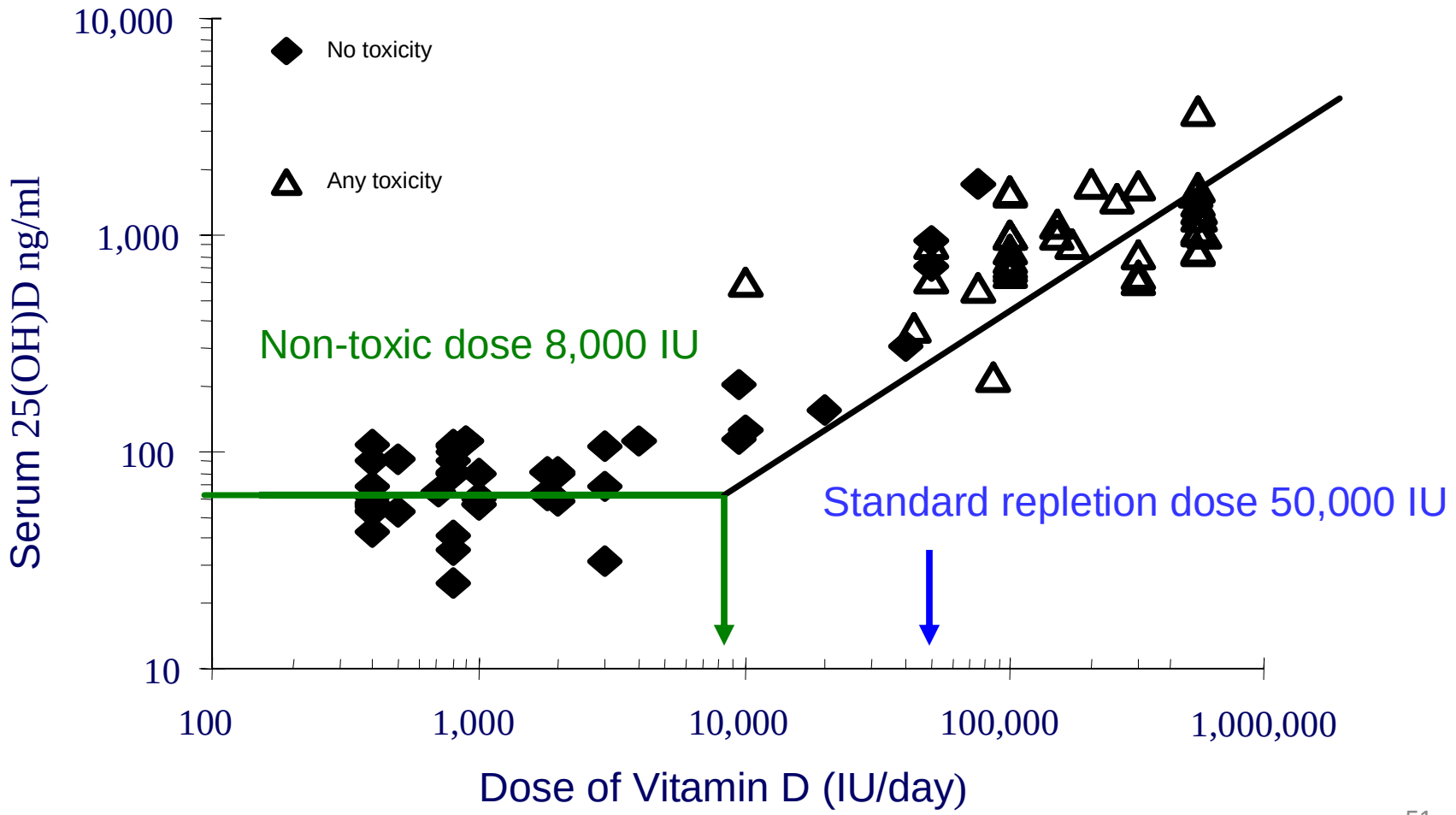
Tight junctions binding cells



- In the meantime, supplementation of vitamin D_3 in high risk populations should be started
  - 4000 IU/day is safe at ages 9 years and older according to National Academy of Sciences, and would boost population 25(OH)D levels to 40 – 60 ng/ml, well below the lowest adverse effect level of 150 ng/ml [57-59]

Cancer and Vitamin D

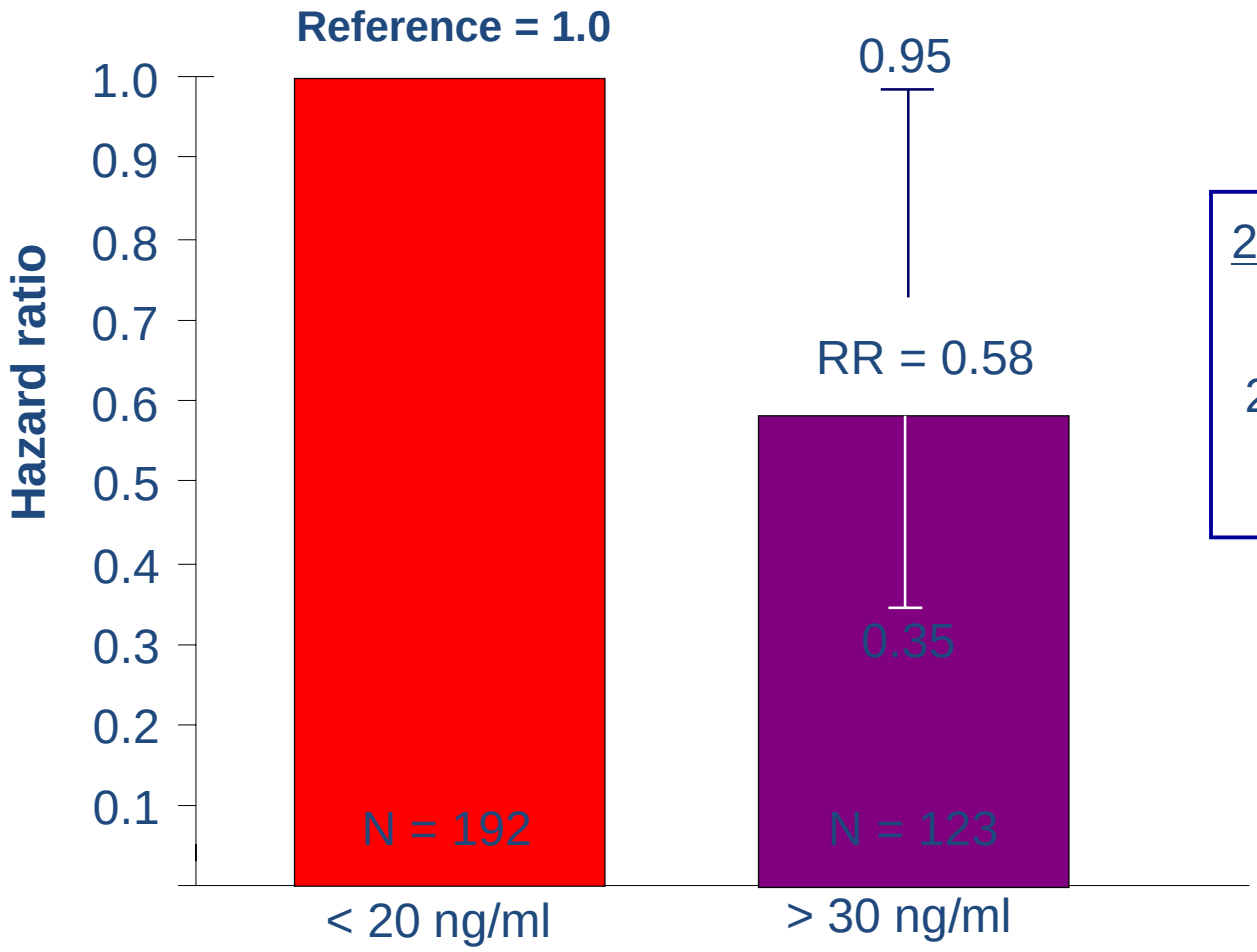
Vitamin D Dosage and Toxicity Studies



Source: Vieth R. Vitamin D and cancer mini-symposium: the risk of additional vitamin D. Ann Epidemiol. 2009 19(7):441-5.

- Vitamin D supplementation would be a cheap, effective, and safe intervention
- Raising population serum 25(OH)D concentrations through supplementation has the potential to save hundreds of thousands of lives around the globe

Hazard of death, 512 women with breast cancer, by 25(OH)D level at diagnosis, median follow-up 11.6 years, Toronto, Canada



p = 0.02

25 (OH)D at dx (ng/ml)	
< 20	N= 192
20 - 29.9	N= 197
> 30	N= 123

Hazard ratio and 95% confidence intervals for overall survival by 25(OH)D serum level at diagnosis, Toronto, Canada (latitude 43^0 40 N')

*8

ANTICANCER RESEARCH *31*: 2939-2948 (2011)

Serum 25-Hydroxyvitamin D and Prevention of Breast Cancer: Pooled Analysis

SHARIF B. MOHR[1], EDWARD D. GORHAM[1,2], JOHN E. ALCARAZ[3], CHRISTOPHER J. KANE[4], CAROLINE A. MACERA[2,3], J. KELLOGG PARSONS[4], DEBORAH L. WINGARD[1] and CEDRIC F. GARLAND[1,2]

[1]Division of Epidemiology, Department of Family and Preventive Medicine, and
[4]Department of Surgery, School of Medicine, University of California San Diego, La Jolla CA, U.S.A.;
[2]Naval Health Research Center, San Diego, CA, U.S.A.;
[3]Department of Epidemiology and Biostatistics, Graduate School of Public Health, San Diego State University, San Diego CA, U.S.A.

Table I. *Case–control and nested case–control studies of serum 25-hydroxyvitamin D metabolites and risk of cancer of the breast, ICD-CM Code 174, according to PubMed search, 1966-2010.*

Author(s) (ref)	Year	Study design	Country	Matching criteria	Number of cases/controls	Quantile cut-points for 25(OH)D ng/ml	Relative risk	95% Confidence interval	
								Lower	Upper
Engel *et al.* (22)	2010	NCC	France	Age, menopausal status, age at menopause, center and year of blood draw	636/1272	<19.8	1.00	-	-
						19.8-27	0.87	0.68	1.1
						>27	0.80	0.62	1.0
Almquist *et al.* (29)	2010	NCC	Sweden	Age, date of blood collection, menopausal status	764/764	18.1†	1.00	-	-
						24.8	0.84	0.6	1.2
						29.5	0.84	0.6	1.2
						37.4	0.93	0.7	1.3
Abbas *et al.* (16)	2009	CC	Germany	Age, study region	289/595	<12	1.00	-	-
						12-18	0.68	0.4	1.1
						18-24	0.59	0.4	0.9
						>24	0.45	0.3	0.7
Crew *et al.* (21)	2009	CC	USA	Age	1026/1075	<20	1.00	-	-
						20-29	0.80	0.6	1.0
						30-39	0.83	0.6	1.1
						>40	0.56	0.4	0.8
Rejnmark *et al.* (28)	2009	NCC	Denmark	Age, menopausal status, season of blood draw	142/420	<24	1.00	-	-
						24-33.6	0.94	0.6	1.5
						>33.7	0.52	0.3	0.9

Table I. *Case–control and nested case–control studies of serum 25-hydroxyvitamin D metabolites and risk of cancer of the breast, ICD-CM Code 174, according to PubMed search, 1966-2010.*

Author(s) (ref)	Year	Study design	Country	Matching criteria	Number of cases/controls	Quantile cut-points for 25(OH)D ng/ml	Relative risk	95% Confidence interval	
								Lower	Upper
Engel *et al.* (22)	2010	NCC	France	Age, menopausal status, age at menopause, center and year of blood draw	636/1272	<19.8	1.00	-	-
						19.8-27	0.87	0.68	1.1
						>27	0.80	0.62	1.0
Almquist *et al.* (29)	2010	NCC	Sweden	Age, date of blood collection, menopausal status	764/764	18.1†	1.00	-	-
						24.8	0.84	0.6	1.2
						29.5	0.84	0.6	1.2
						37.4	0.93	0.7	1.3
Abbas *et al.* (16)	2009	CC	Germany	Age, study region	289/595	<12	1.00	-	-
						12-18	0.68	0.4	1.1
						18-24	0.59	0.4	0.9
						>24	0.45	0.3	0.7
Crew *et al.* (21)	2009	CC	USA	Age	1026/1075	<20	1.00	-	-
						20-29	0.80	0.6	1.0
						30-39	0.83	0.6	1.1
						>40	0.56	0.4	0.8
Rejnmark *et al.* (28)	2009	NCC	Denmark	Age, menopausal status, season of blood draw	142/420	<24	1.00	-	-
						24-33.6	0.94	0.6	1.5
						>33.7	0.52	0.3	0.9

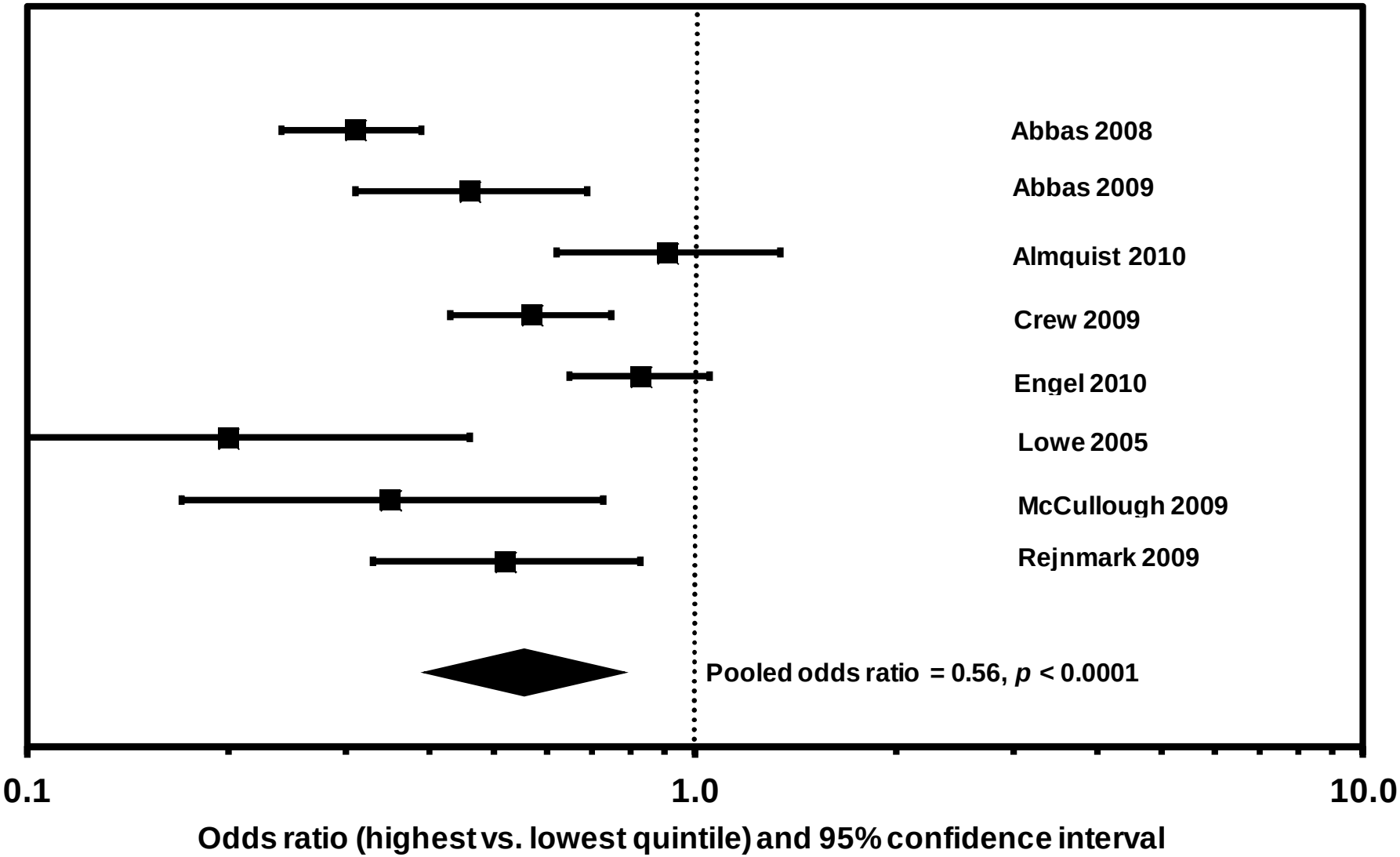
McCullough *et al.* (27)	2009	NCC	USA	Age, race, date of blood draw	516/516	<14.7	1.00	-	-
						14.7-19.1	1.29	0.9	1.9
						19.9-24.3	1.14	0.8	1.7
						24.3-29.2	1.44	1.0	2.2
						>29.2	1.09	0.7	1.7
Abbas *et al.* (17)	2008	CC	Germany	Age, study region	1394/1365	<12	1.00	-	-
						12-18	0.57	0.5	0.7
						18-24	0.49	0.4	0.6
						24-30	0.43	0.3	0.6
						>30	0.31	0.2	0.4
Chlebowski *et al.* (19)	2008	NCC	USA	Age, latitude of clinic, race, date of blood draw	895/898	9.44†	1.00	-	-
						15.4	0.96	0.7	1.3
						19.7	1.08	0.8	1.4
						24.4	0.93	0.7	1.4
						32.8	1	0.6	1.3
Freedman *et al.* (23)	2008	NCC	USA	Age, year of entry	1005/1005	<18.3	1.00	-	-
						18.3-23.4	1.02	0.75	1.4
						23.5-28.2	1.36	0.99	1.9
						28.3-33.6	1.13	0.82	1.6
						>33.7	1.04	0.75	1.5
Bertone-Johnson *et al.* (18)	2005	NCC	USA	Age, date of blood draw, time of blood draw, PMH use, menopausal status, fasting status	701/701	<22†	1.00	-	-
						25.8	0.95	0.7	1.4
						31.7	0.74	0.5	1.1
						37.6	0.77	0.5	1.1
						41.7	0.73	0.5	1.1
Lowe *et al.* (26)	2005	CC	UK	Age, date of blood draw, menopausal status	179/179	<20	1.00	-	-
						20-40	0.34	0.2	0.6
						40-60	0.31	0.2	0.6
						>60	0.20	0.1	0.5

CC, Case–control; NCC, nested case–control; †median values, cut-off points were not provided.

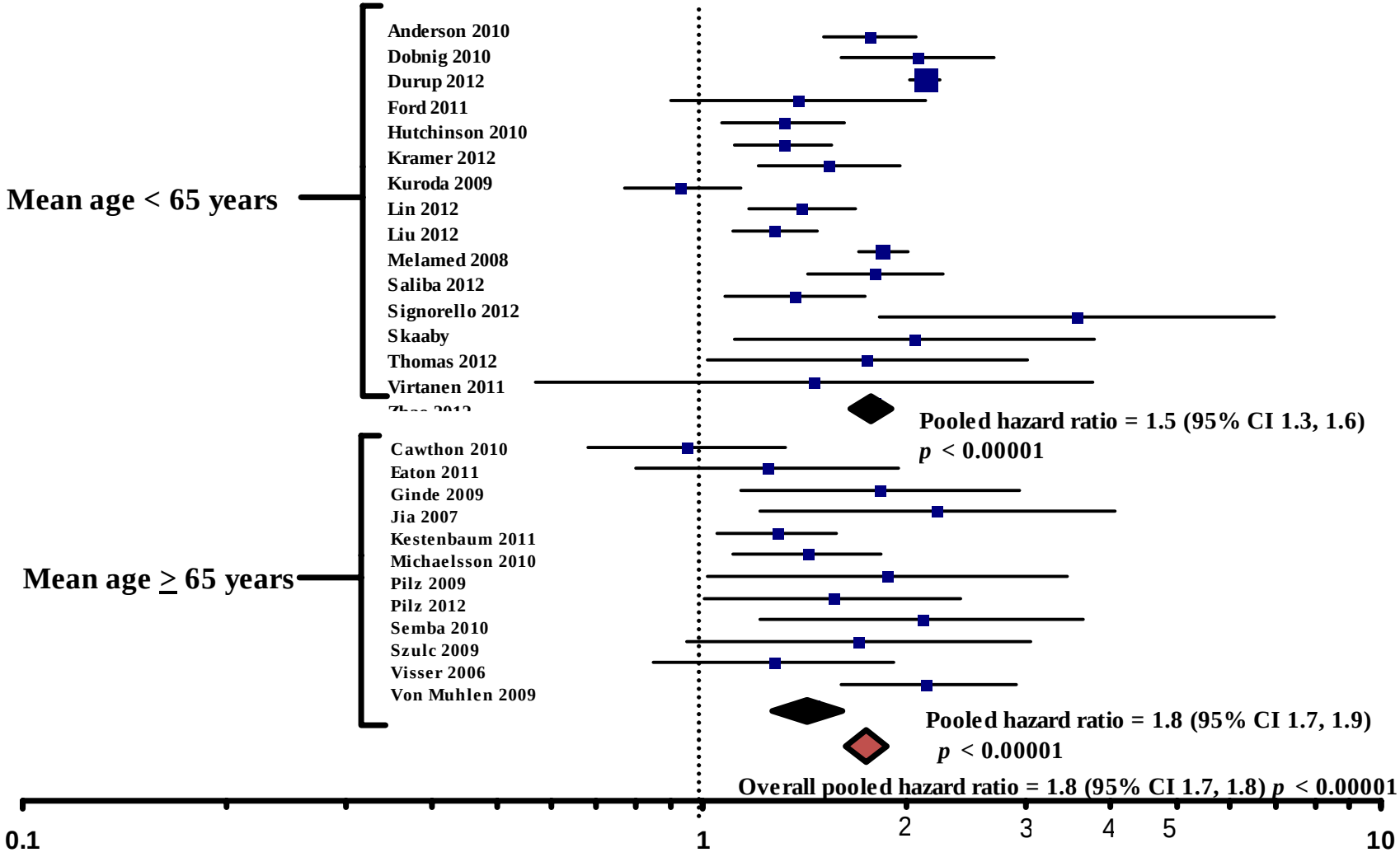
McCullough *et al.* (27)	2009	NCC	USA	Age, race, date of blood draw	516/516	<14.7	1.00	-	-
						14.7-19.1	1.29	0.9	1.9
						19.9-24.3	1.14	0.8	1.7
						24.3-29.2	1.44	1.0	2.2
						>29.2	1.09	0.7	1.7
Abbas *et al.* (17)	2008	CC	Germany	Age, study region	1394/1365	<12	1.00	-	-
						12-18	0.57	0.5	0.7
						18-24	0.49	0.4	0.6
						24-30	0.43	0.3	0.6
						>30	0.31	0.2	0.4
Chlebowski *et al.* (19)	2008	NCC	USA	Age, latitude of clinic, race, date of blood draw	895/898	9.44†	1.00	-	-
						15.4	0.96	0.7	1.3
						19.7	1.08	0.8	1.4
						24.4	0.93	0.7	1.4
						32.8	1	0.6	1.3
Freedman *et al.* (23)	2008	NCC	USA	Age, year of entry	1005/1005	<18.3	1.00	-	-
						18.3-23.4	1.02	0.75	1.4
						23.5-28.2	1.36	0.99	1.9
						28.3-33.6	1.13	0.82	1.6
						>33.7	1.04	0.75	1.5
Bertone-Johnson *et al.* (18)	2005	NCC	USA	Age, date of blood draw, time of blood draw, PMH use, menopausal status, fasting status	701/701	<22†	1.00	-	-
						25.8	0.95	0.7	1.4
						31.7	0.74	0.5	1.1
						37.6	0.77	0.5	1.1
						41.7	0.73	0.5	1.1
Lowe *et al.* (26)	2005	CC	UK	Age, date of blood draw, menopausal status	179/179	<20	1.00	-	-
						20-40	0.34	0.2	0.6
						40-60	0.31	0.2	0.6
						>60	0.20	0.1	0.5

CC, Case–control; NCC, nested case–control; †median values, cut-off points were not provided.

Figure 3. Pooled odds ratios of breast cancer risk according to serum 25-hydroxyvitamin D, 1966-2010, comparing highest vs lowest quintile, studies based on populations residing at >37 degrees N latitude

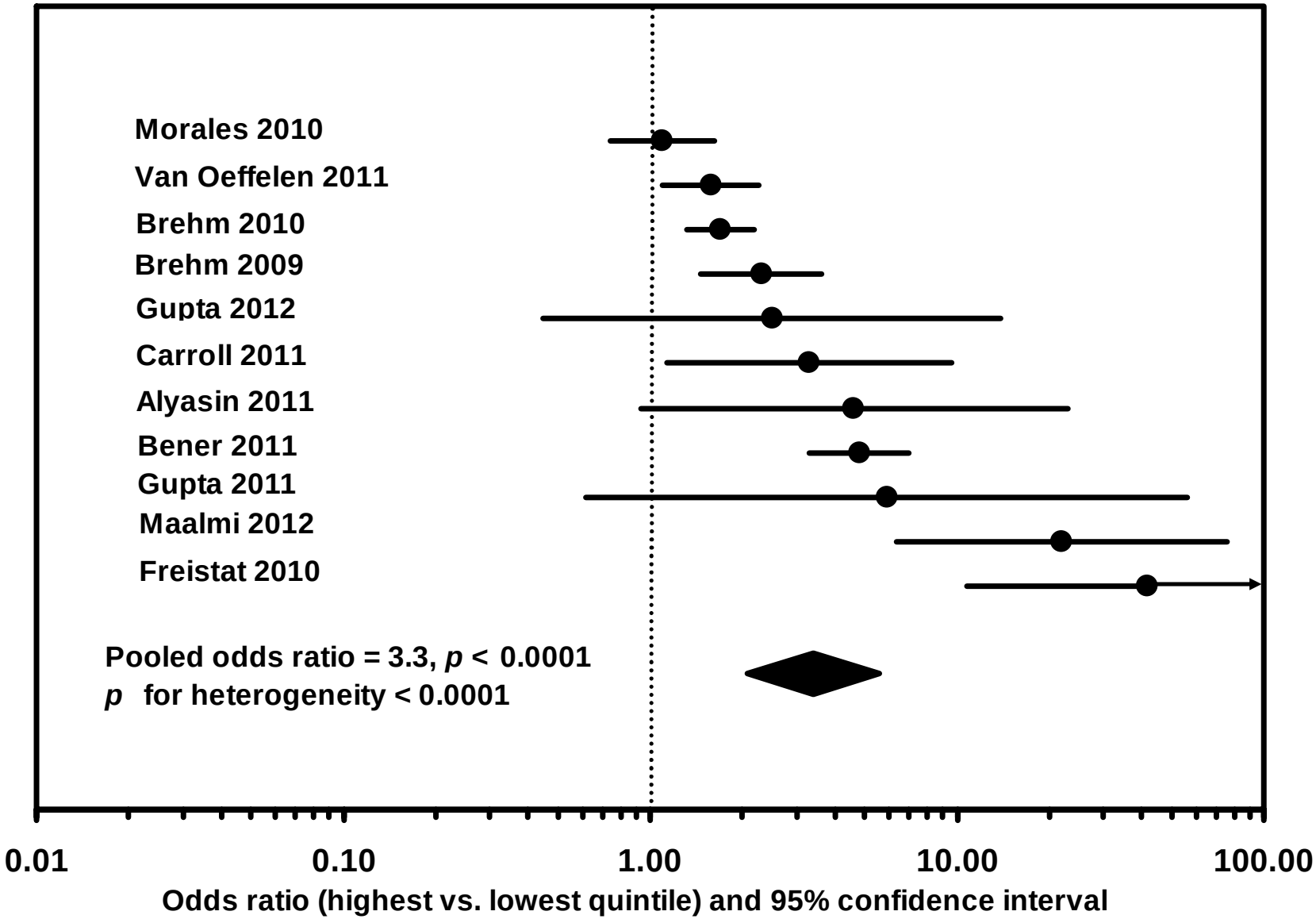


25(OH)D and all cause mortality



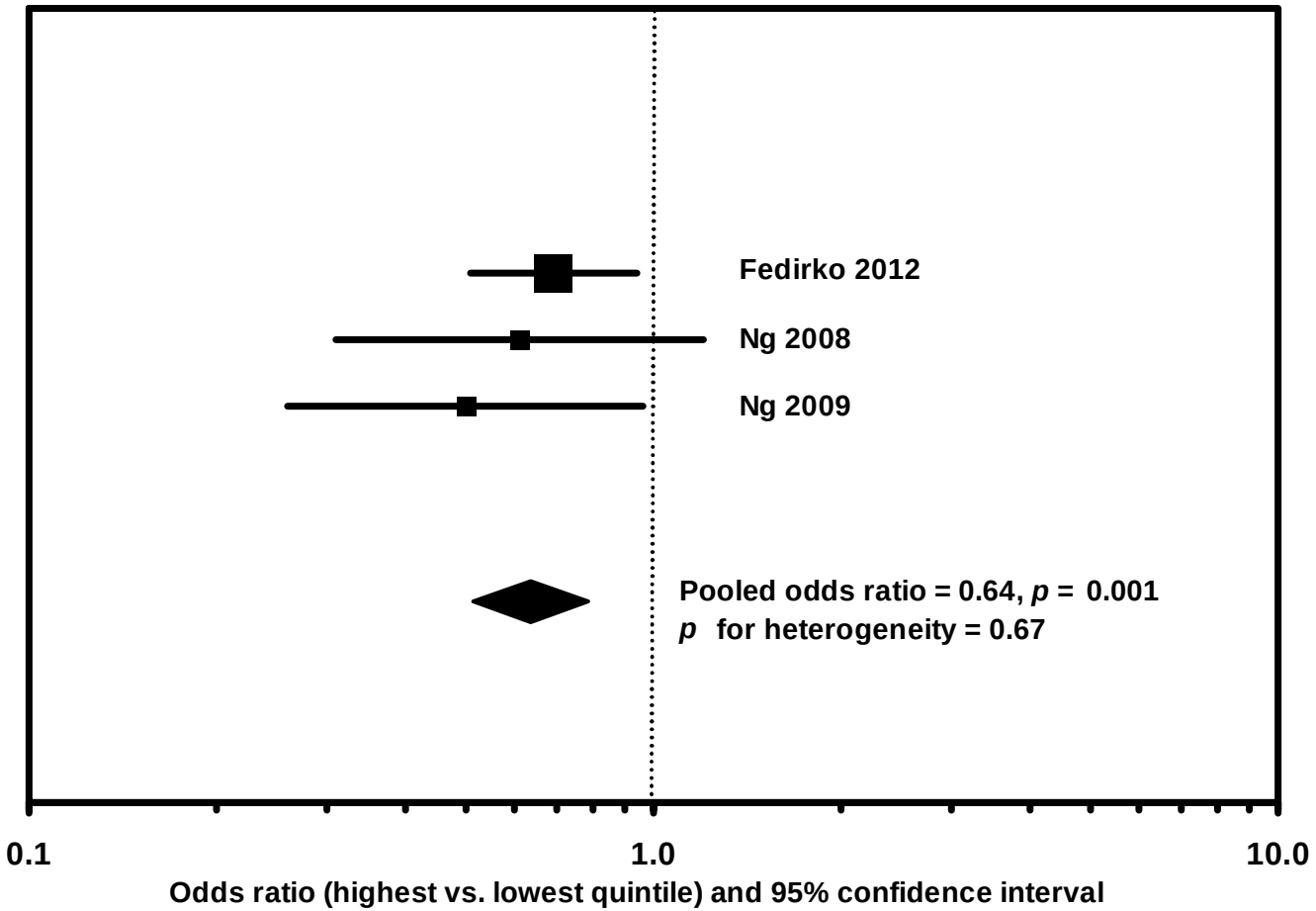
Age-adjusted hazard ratio for lowest (reference group) vs. highest quantile of serum 25(OH)D with 95% confidence interval

25(OH)D and risk of asthma

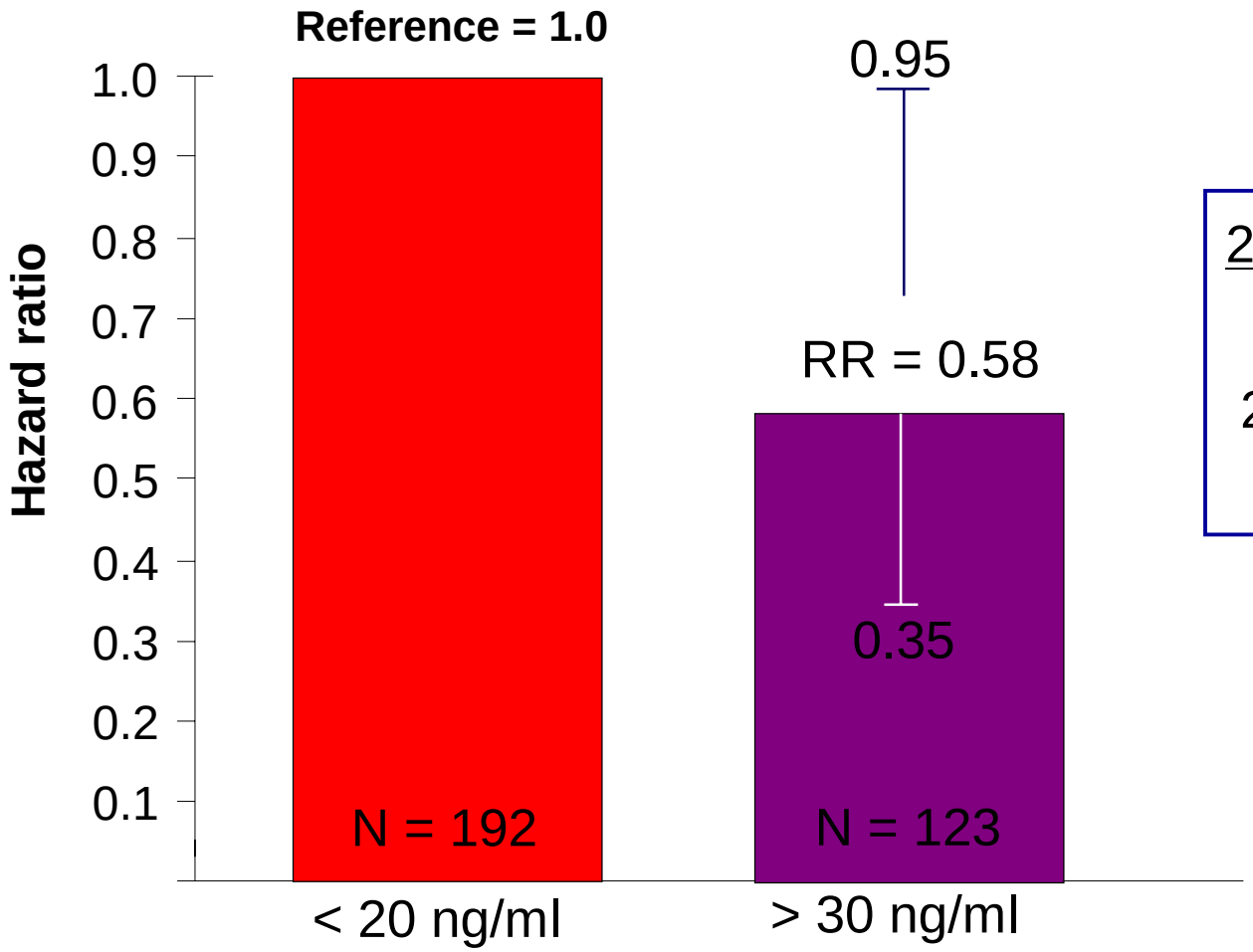


First Author, year	25(OH)D range ng/ml	Cases/controls or cases/total	Relative risk/Hazard ratio (95% confidence interval)	Type of study	Disease outcome
Ng	16.5	34/76	1.00 (referent)	Cohort	Colorectal cancer
2008	40	24/76	0.52 (0.29 - 0.94)		mortality
Ng	23.3	29/204	1.00 (referent)	Cohort	Colorectal cancer
2009	31	19/203	0.50 (0.26 - 0.95)		mortality
Fedirko	11.4	104/242	1.00 (referent)	Cohort	Colorectal cancer
2012	39.7	82/240	0.69 (0.52 - 0.92)		mortality
Ren	< 20	114	1.00 (referent)	Cohort	Gastric cancer
2012	$\geq$ 20	83	0.59 (0.37 - 0.91)		survival

Serum 25(OH)D and risk of death in colorectal cancer patients



Hazard of death, 512 women with breast cancer, by 25(OH)D level at diagnosis, median follow-up 11.6 years, Toronto, Canada

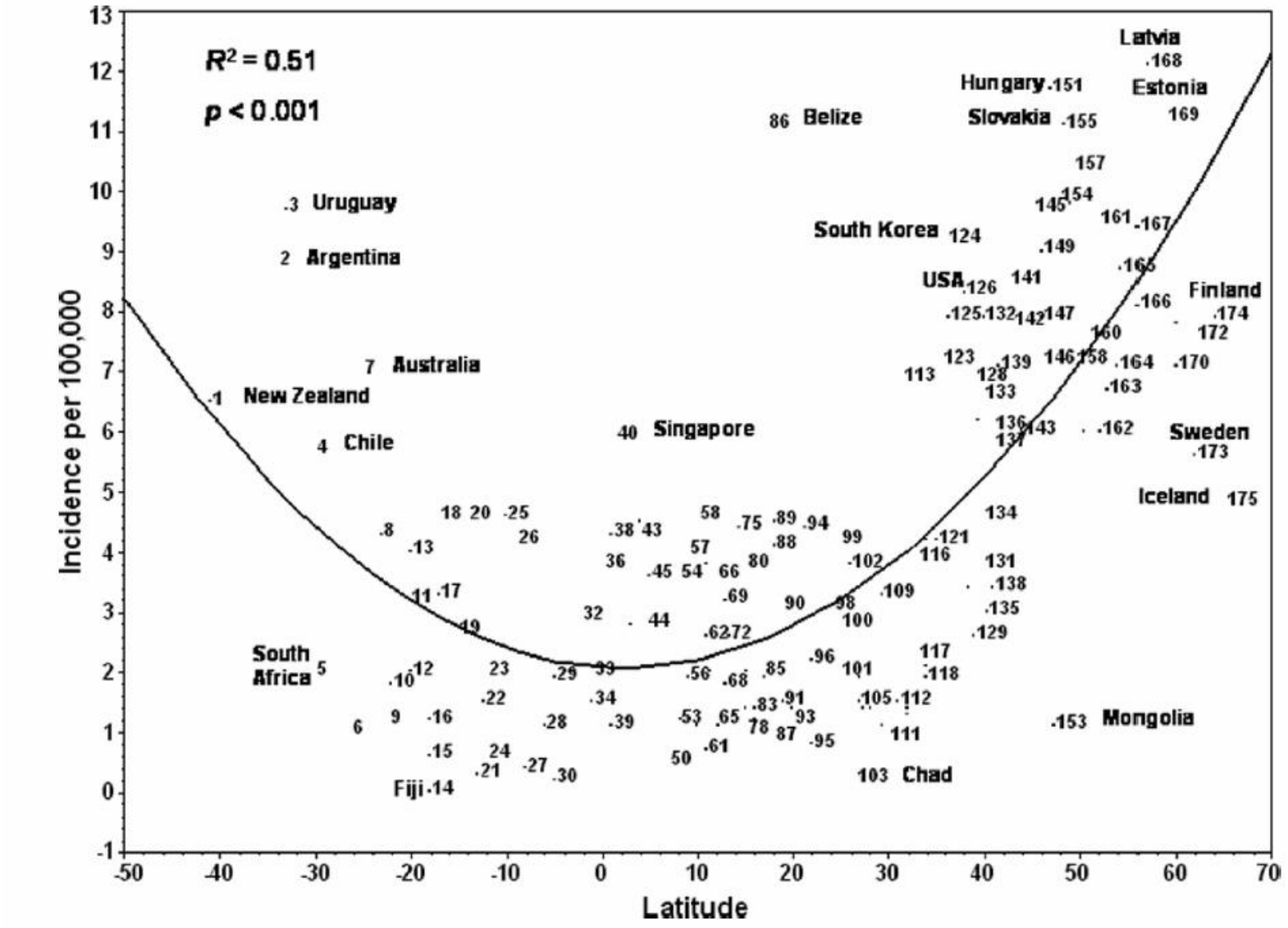


p = 0.02

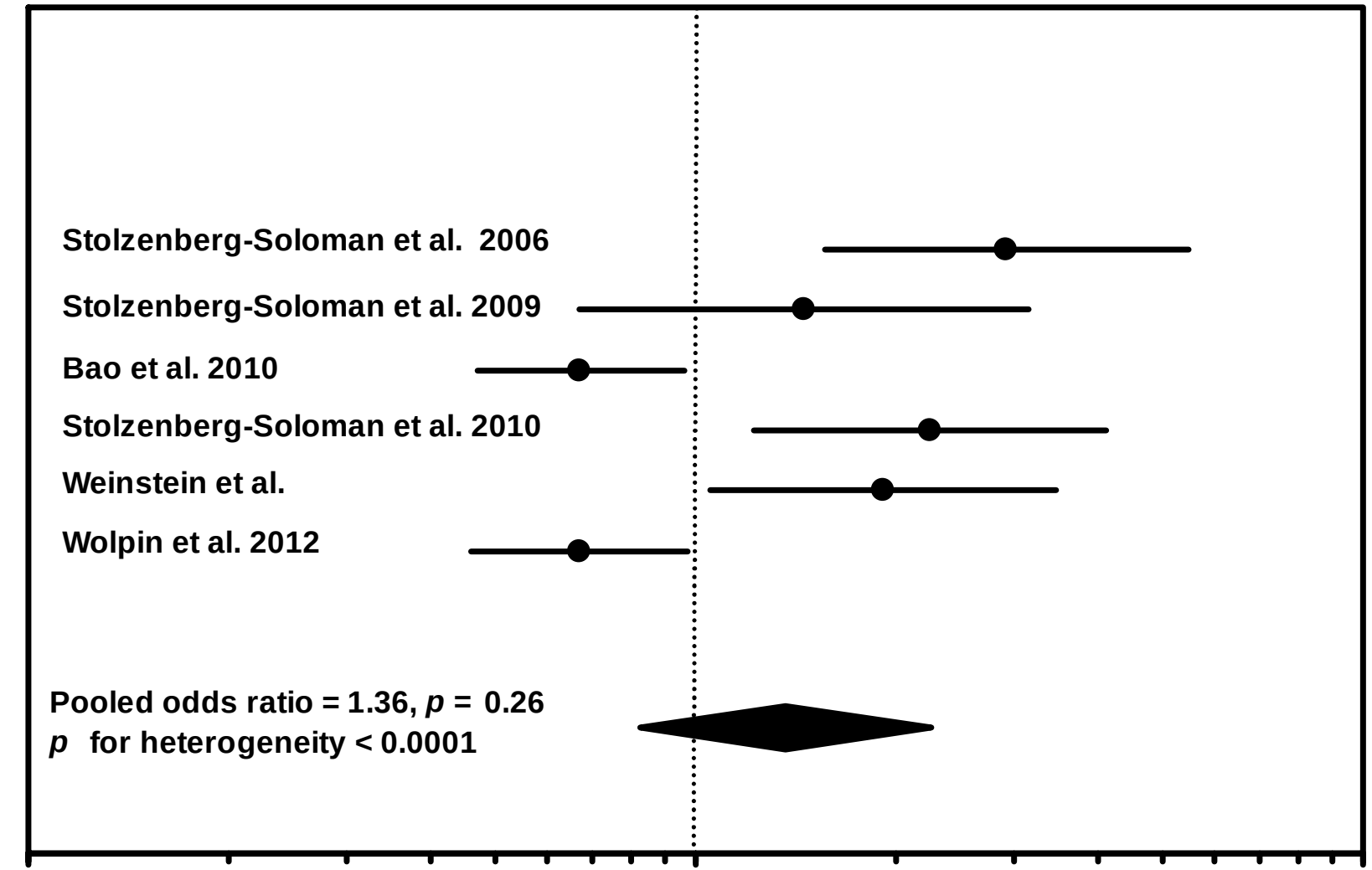
25 (OH)D at dx (ng/ml)	
< 20	N= 192
20 - 29.9	N= 197
> 30	N= 123

Hazard ratio and 95% confidence intervals for overall survival by 25(OH)D serum level at diagnosis, Toronto, Canada (latitude 43^0 40 N')

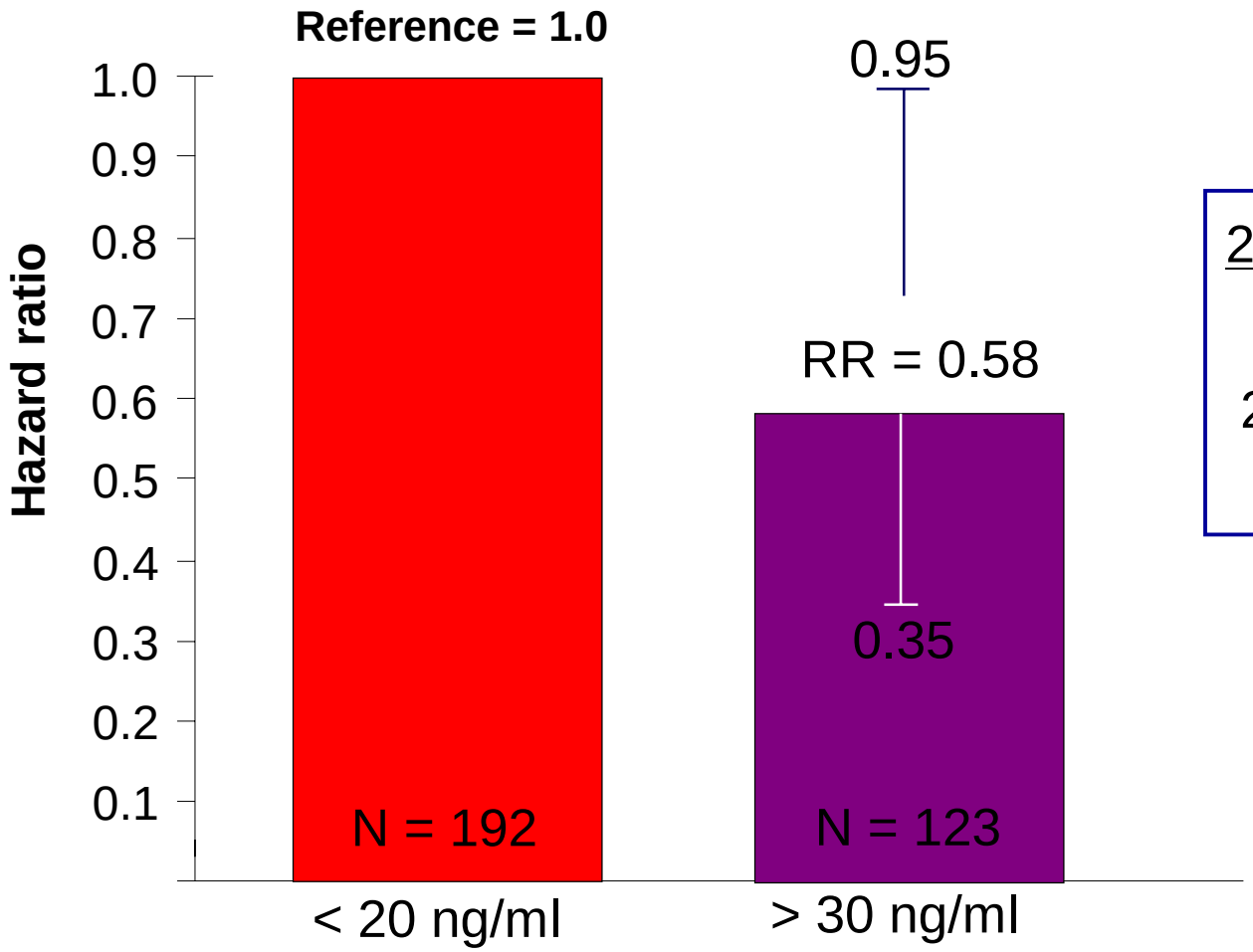
Latitude and pancreatic cancer



25(OH)D and risk of pancreatic cancer



Hazard of death, 512 women with breast cancer, by 25(OH)D level at diagnosis, median follow-up 11.6 years, Toronto, Canada

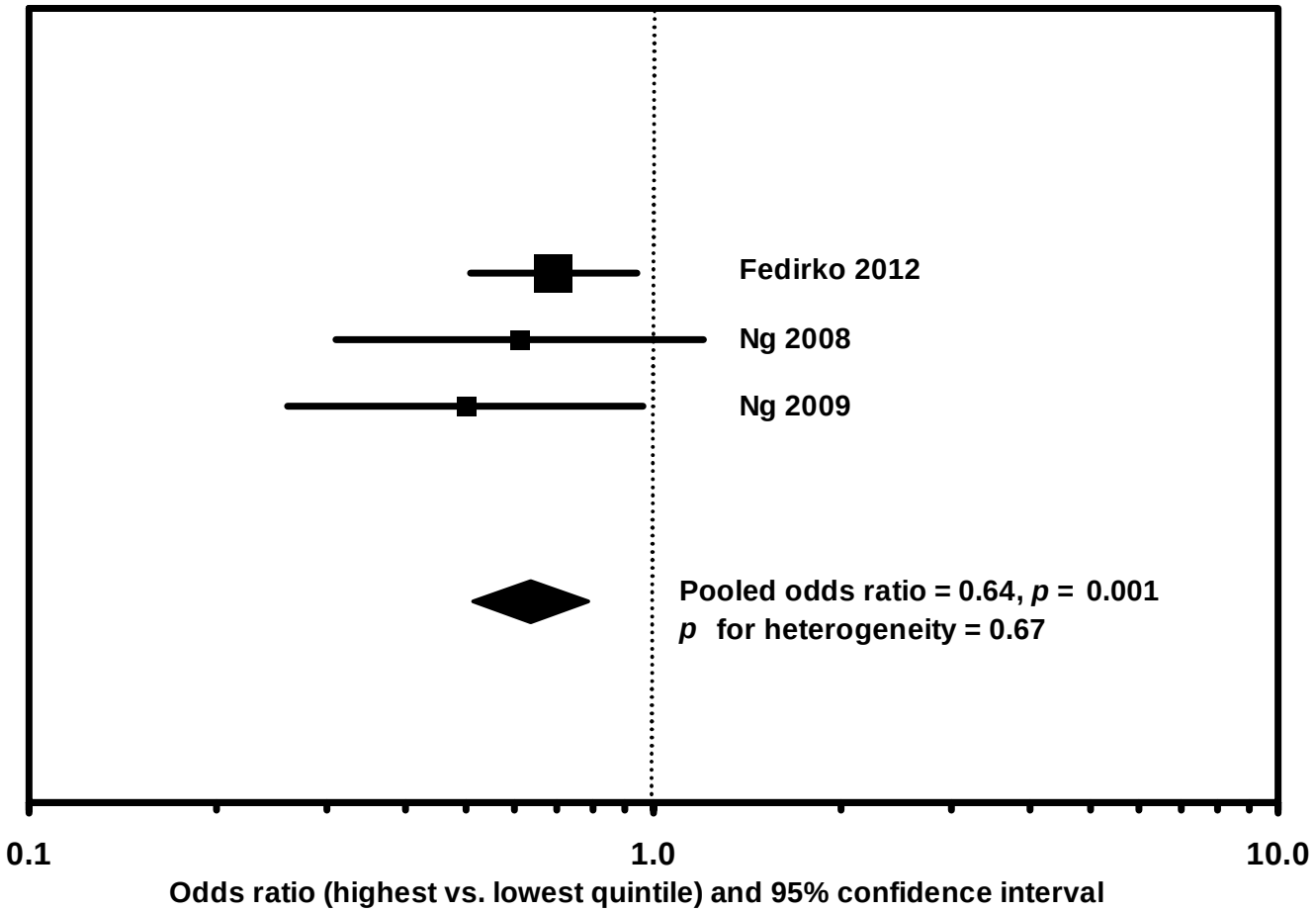


p = 0.02

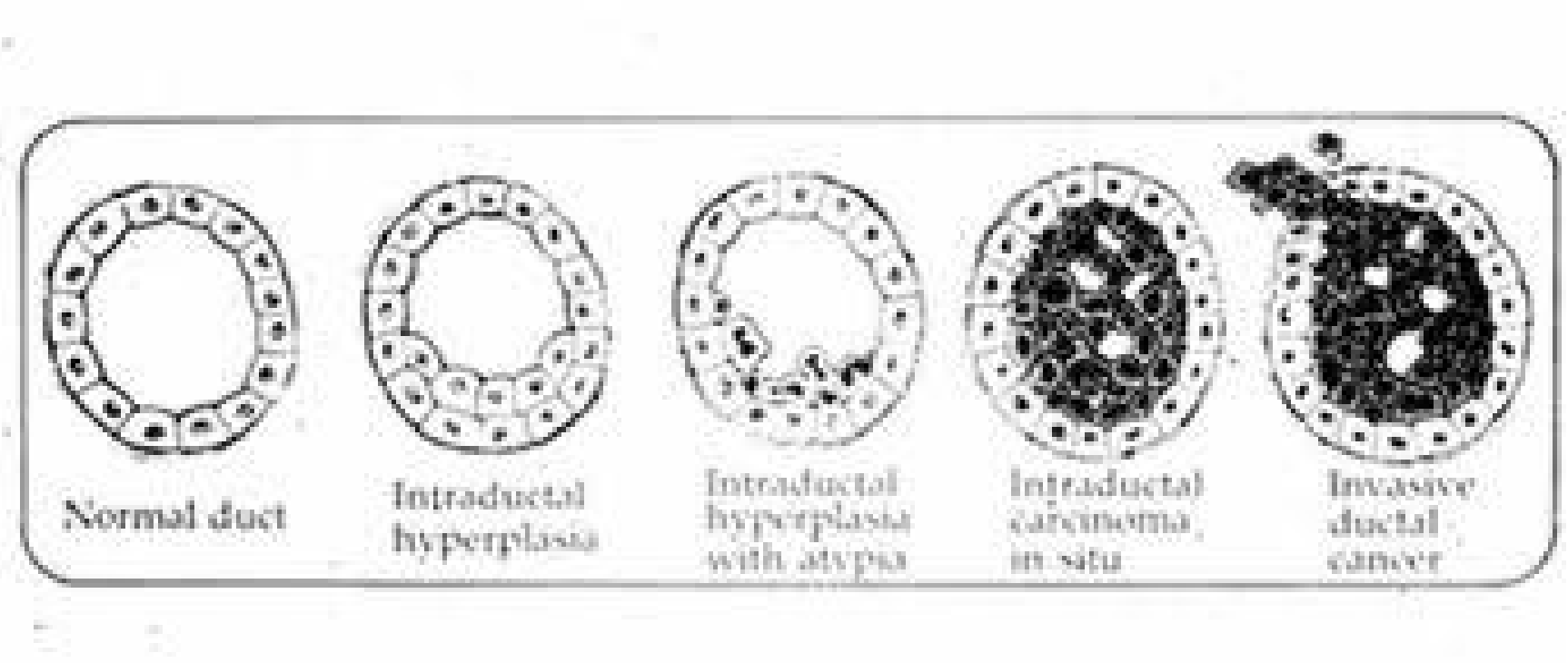
25 (OH)D at dx (ng/ml)	
< 20	N= 192
20 - 29.9	N= 197
> 30	N= 123

Hazard ratio and 95% confidence intervals for overall survival by 25(OH)D serum level at diagnosis, Toronto, Canada (latitude 43^0 40 N')

25(OH)D and risk of mortality from colorectal cancer



Breast cancer in TDU



Action

An End to Breast Cancer by 2020

- Breast Cancer Coalition has asked Pres. Bill Clinton to lead a program to defeat breast cancer by 2020
- An end by 2020 does not require a cure
- Actions we're taking against now and reasons they work badly, or not at all: Mammography, weak estrogen agonists, breast self-exam, physician breast exam, MRI, metformin
- New plans of action

Ineffective approaches

- Mammography – Useless below age 50 and probably above age 70; misses 85% of fatal cases; in some countries it does nothing; it does not prevent breast cancer in any setting
- Weak estrogen agonists – Produce early menopause and cause blood clots and pulmonary embolisms
- BSE, physician breast exam – Too little too late
- MRI, beter than mammo but not good enough
- Metformin, suspected of causing Alzheimer's

An End to Breast Cancer by 2020

- About 900 relevant studies have been done, and > 80% are positive
- A few null studies are expected but clinically are meaningless
- Once an association is found in a human population study, it is almost always real (Mount Everest effect)
- Further studies, while desirable, are not necessary

Plans of action

- Project Mary Lasker –Save Cancer Patient Lives -- Measure 25(OH)D in every breast cancer patient and start on vitamin D3. Most will need immediate repletion, with 50,000 IU/day, then 2000-8000 IU/day after repletion, with 25(OH)D monitoring and a check on serum calcium.

Plans of action

- Project Da Vinci –Primary Prevention -- Measure 25(OH)D in every female and restore to normal (40-80 ng/ml)

Plans of action

- Project Ramazzini - Develop a nationwide real time database for each breast cancer patient in the USA that includes serum 25(OH)D at diagnosis and active follow-up for survival and recurrences with 24/7 hour phone and live chat internet access