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Dietary Supplements and Cancer Risk

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Fred Hutchinson Cancer Research Center**

**American Institute for Cancer Research
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Why is this an important topic?

- Use of dietary supplements is a very common health behavior
 - ~ 52% of Americans report use of any supplement in NHANES (Cantor et al JAMA 2016)
 - ~ 10% use \geq 4 products (Cantor et al JAMA 2016)
- 30 billion dollar/year industry
- Important to understand whether there are risks or benefits in relation to cancer risk

How do we obtain the evidence?

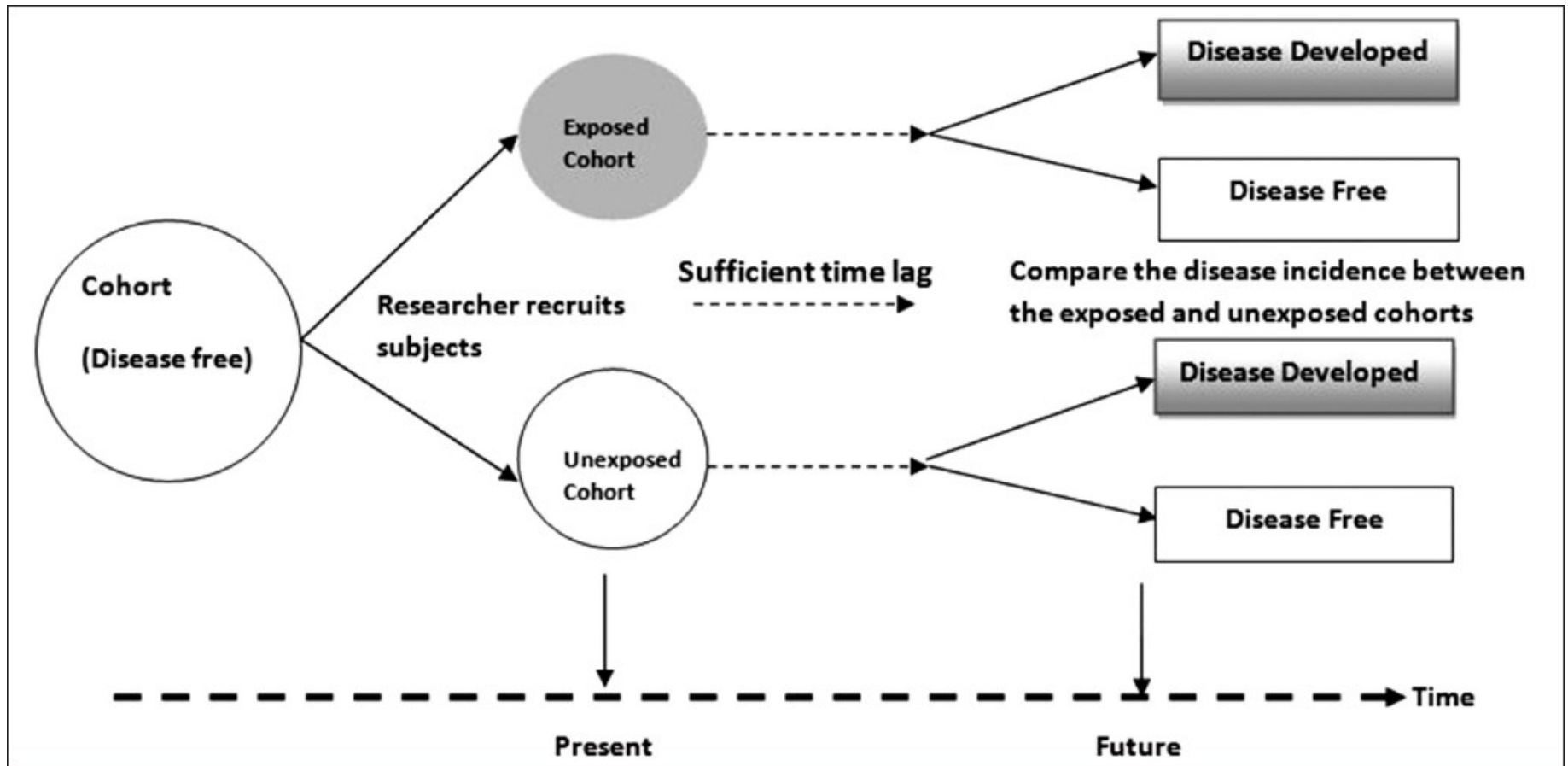
Randomized Controlled Trials

- The best type of evidence for drawing cause-effect inferences
- Expensive, short term
- Can test one or at most a few products
- High risk population or general population

Observational Studies

- Potential for being more generalizable
- Longer term; carcinogenesis process is lengthy
- Methodologic challenges

Cohort Study Methods



Assumptions about cohort designs and the “time lag”

- The baseline exposure is *typically* assumed to be “fixed” with little variability over time
- Thus, the exposure at baseline is the presumed exposure during the follow-up period in the cohort
- Some exposures are fixed with no assumptions about variation (i.e., birth of a child, vaccine, surgery)
- Time-varying exposures may change over the course of follow up

Smoking, weight, **dietary supplements**

Time-varying exposures

- If time dependency is ignored, then results can be biased
- Many methods exist to analyze time-varying exposures
- However, to do so requires good quality data on how the exposure may have changed
- Requires the ability to capture and measure the variability

Example: weight measured over time
medications (pharmacy records)

The challenge of time-varying exposures with dietary supplements

- Use is often sporadic
- People change brands and formulations differ by brand
- Product formulations change over time
 - Responds to emerging science
 - Responds to consumer demand
 - Examples: beta carotene, selenium, lycopene, vitamin D
- We do not have good ways to capture these time-varying changes in supplement exposure

Evidence to support or refute dietary supplements and cancer risk

- Randomized controlled trials
- Observational cohorts
- Consensus statements/recommendations
- Focus on multivitamins

PHS II - RCT

Multivitamins in the Prevention of Cancer in Men

The Physicians' Health Study II Randomized Controlled Trial

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William G. Christen, ScD

Vadim Bubes, PhD

Joanne P. Smith, BA

Jean MacFadyen, BA

Miriam Schwartz, MD

JoAnn E. Manson, MD, DrPH

Robert J. Glynn, ScD

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Context Multivitamin preparations are the most common dietary supplement, taken by at least one-third of all US adults. Observational studies have not provided evidence regarding associations of multivitamin use with total and site-specific cancer incidence or mortality.

Objective To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events among men.

Design, Setting, and Participants A large-scale, randomized, double-blind, placebo-controlled trial (Physicians' Health Study II) of 14 641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011.

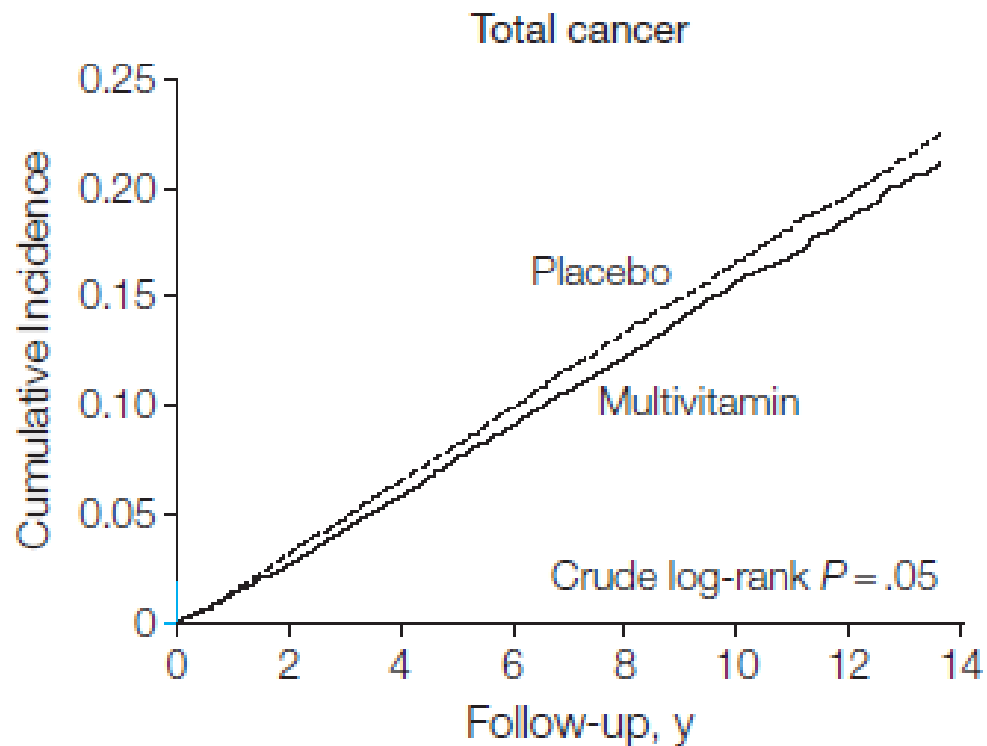
Intervention Daily multivitamin or placebo.

Main Outcome Measures Total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points.



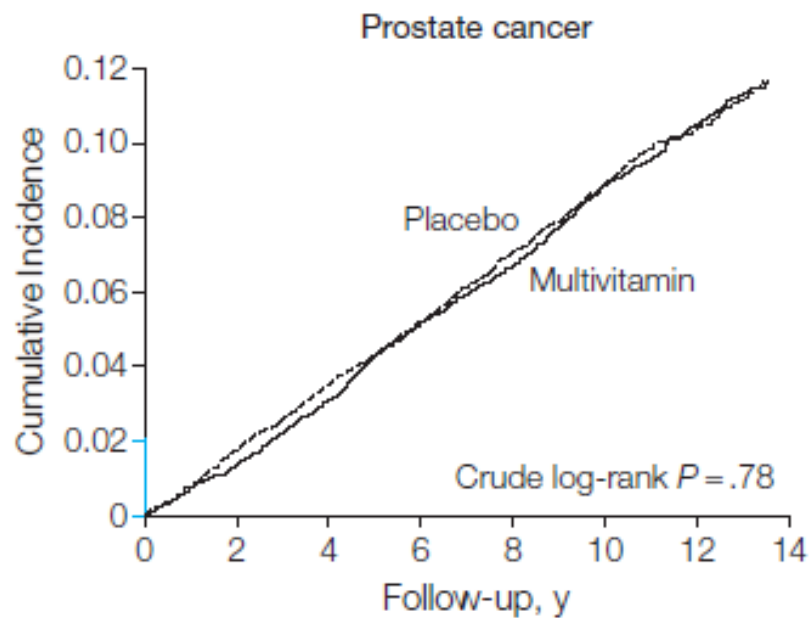
MULTIVITAMINS ARE THE most common dietary supplement regularly

JAMA 2012

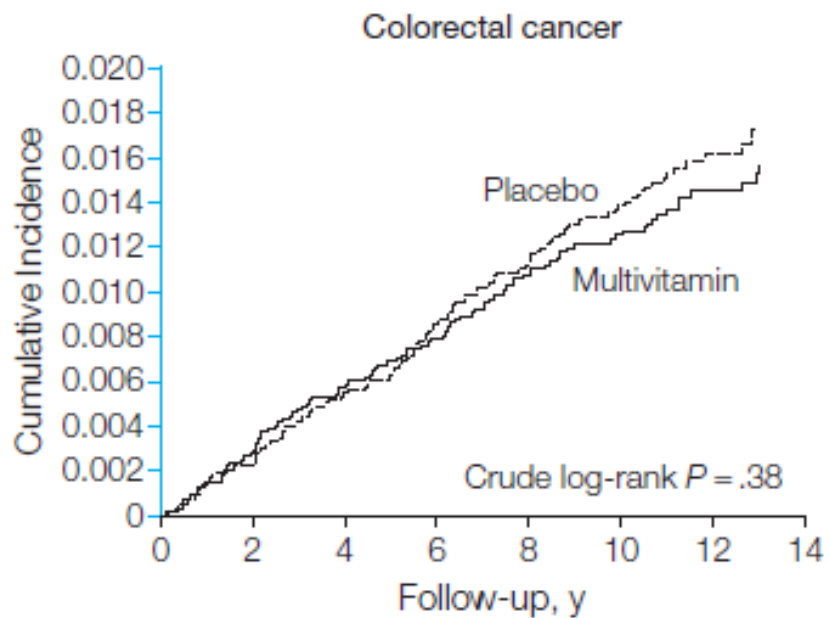


No. at risk

Placebo	7324	7006	6645	6260	5858	5441	2439
Multivitamin	7317	7023	6689	6321	5929	5514	2482



6992 6774 6505 6220 5886 5540 2537
 6988 6791 6546 6252 5951 5583 2529



7264 7137 6947 6726 6469 6178 2916
 7255 7128 6973 6777 6519 6252 2938

Other RCTs of multivitamins

- No other RCTs with available results on multivitamin and cancer risk in the U.S.
- Trials have been conducted in China (Linxian), France (SU.VI.MAX) and the UK (The Heart Protection Study).
- The COSMOS Study (PI, JoAnn Manson) is an RCT testing cocoa flavonols with or without a multivitamin vs. placebo on major cardiovascular events and total cancer in older men and women in the U.S. Currently in process; no results available

Women's Health Initiative (WHI)

3 Controlled Trials

27,347

Hormone Therapy Trials:
Coronary Heart Disease & Fractures.
Adverse effect for Breast Cancer?

36,282

Calcium/Vitamin D Trial:
Fractures & Colorectal Cancer

48,835

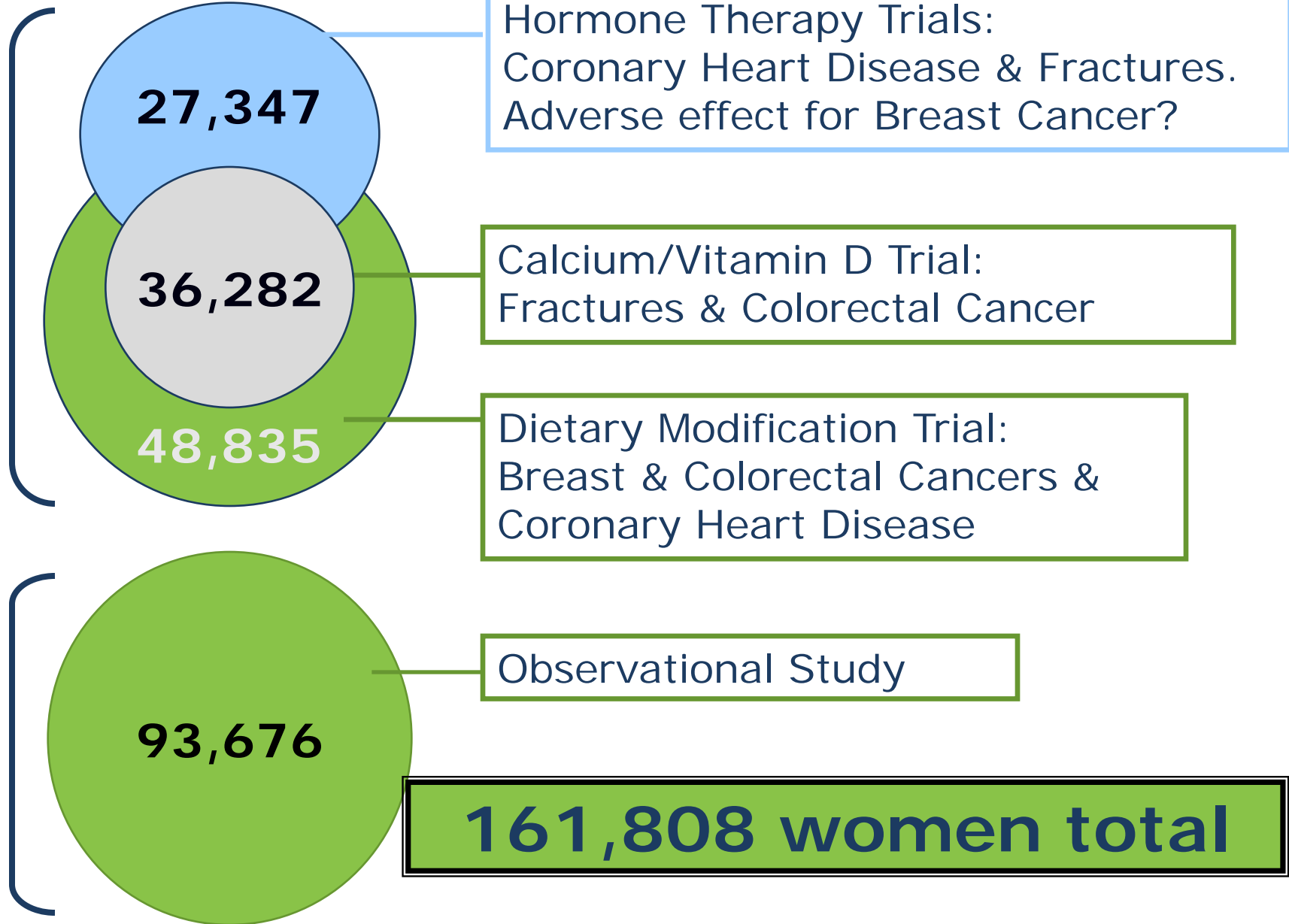
Dietary Modification Trial:
Breast & Colorectal Cancers &
Coronary Heart Disease

1 Observational Study

93,676

Observational Study

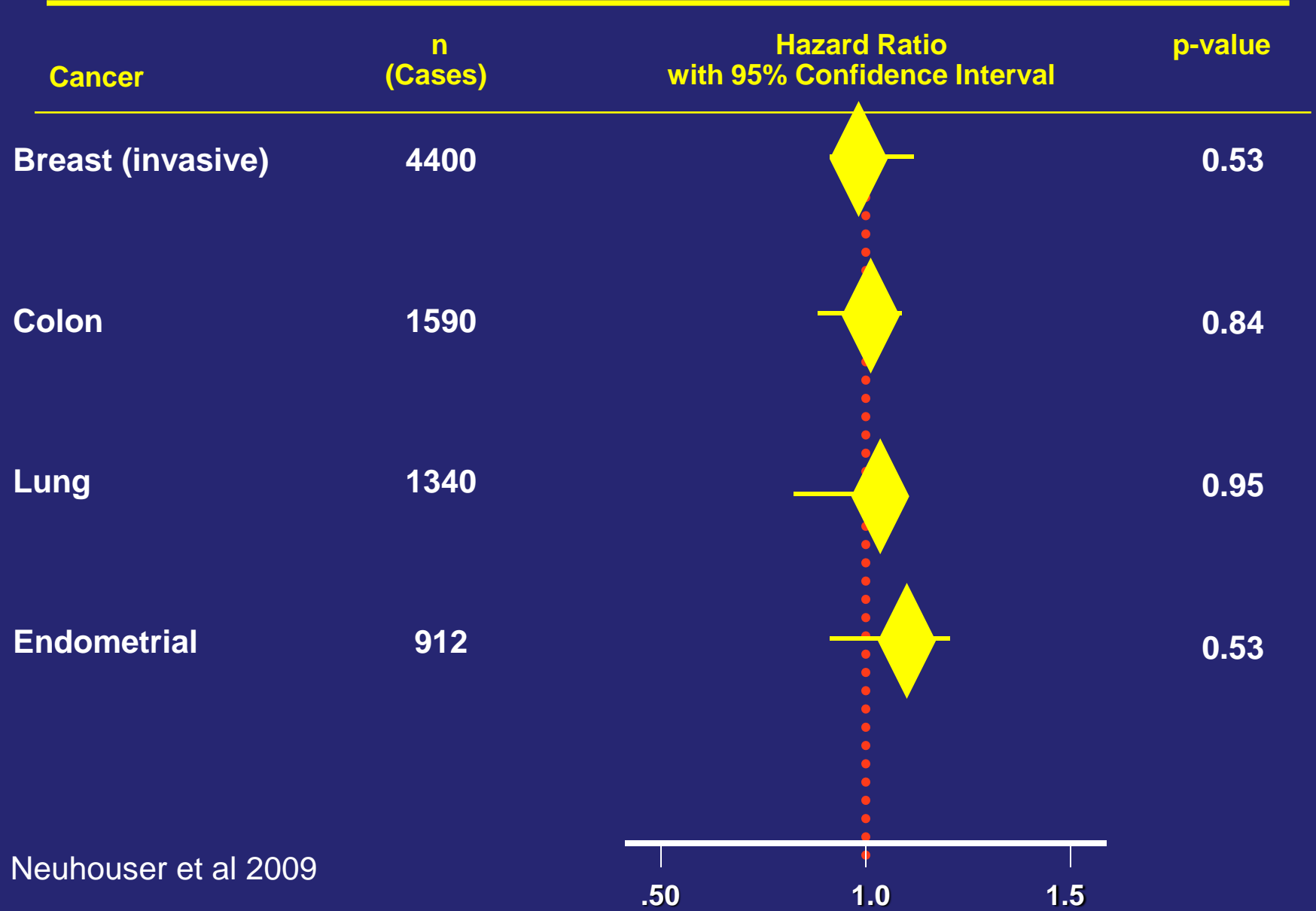
161,808 women total



Dietary Supplement Use in WHI

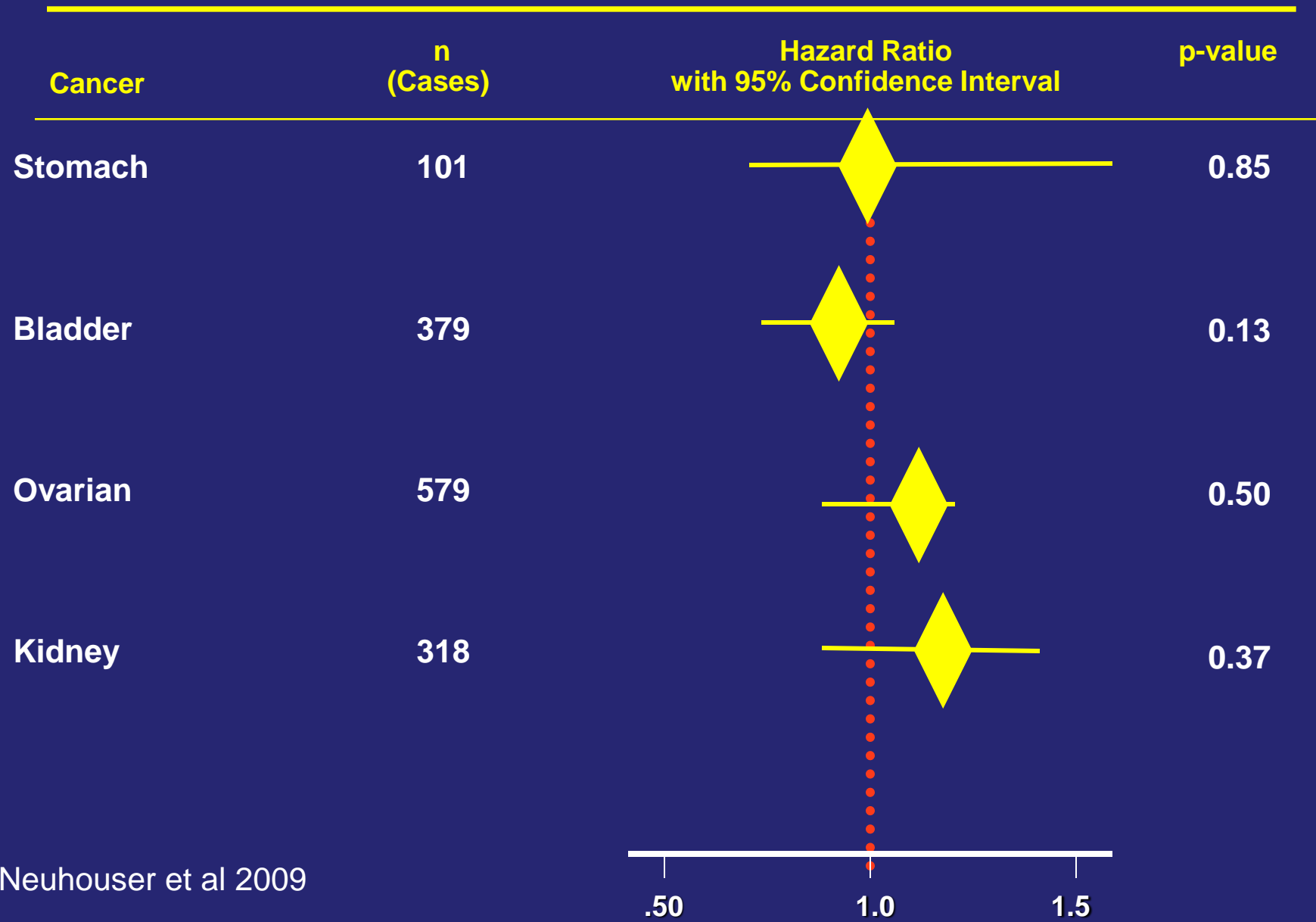
- Collected at baseline and each clinic visit
 - Baseline and Y3 in the Observational Study
 - Annually between 1993-8 and 2005 for the Clinical Trials
- Participants brought bottles to clinics and staff transcribed information on type and dose
- Considered state of the art data collection at the time
- New cancers were reported annually or bi-annually and confirmed by MD medical records review

Multivitamin Use and Risk of Cancer in WHI (n=161,808) (multivariate adjusted)



Neuhouser et al 2009

Multivitamin Use and Risk of Cancer in WHI (n=161,808) (multivariate adjusted)



Dietary supplement use & prostate cancer

- The Prostate Cancer Prevention Trial (PCPT)
- RCT testing finasteride (5- α reductase inhibitor) vs. placebo for prostate cancer risk reduction
- Diet and dietary supplements assessed at yr 1 by FFQ and a 2-page supplement questionnaire
- All men underwent protocol-specified prostate biopsy – central pathology review
- Data on supplement use and outcomes analyzed as a cohort
- No association of multivitamin use and prostate cancer risk (**HR=1.09, 95%CI 0.97-1.22**)

- Kristal et al *AJE* 2010

Consensus or Guidelines Statements

“There is little evidence that dietary supplements can reduce cancer risk. Some high-dose supplements can increase risk”

American Cancer Society, Kushi et al 2012

“Limited evidence support any benefit from vitamin and mineral supplements for cancer prevention.....two trials in men [PHSII and SU.VI.MAX] found modest lower cancer risk, but no evidence in women”

USPSTF Systematic Review, Fortman et al 2013


“Evidence is insufficient to determine the balance of benefits and harm of multivitamins for cancer prevention”

USPSTF Recommendation Statement 2014

Why is dietary supplement use common?

- Dietary supplements have always had a “magical” allure
- Cancer is often a devastating diagnosis and people want to “try anything” to prevent the disease
- Patients and the general public obtain health and nutrition information from informal channels
 - Social network groups
 - Blogs
 - Popular press

A Guaranteed CURE
FOR
RHEUMATISM
WHETHER
ACUTE, CHRONIC,
SCIATIC, NEURALGIC
OR
INFLAMMATORY
50c a Bottle.



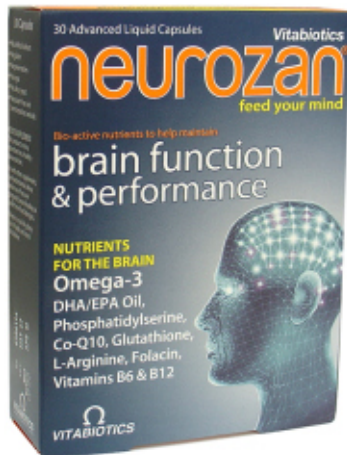
PREPARED FROM PURE
RATTLESNAKE OIL.

THE ONLY COMPANY IN
THE UNITED STATES
THAT MAKES THE
GENUINE
ARTICLE.
50c a Bottle.

SNAKE-OIL LINIMENT

Dietary supplements have been marketed as cures for > 100 years. Some promote a 'magical' effect or cure





The public can be swayed by TV doctors and TV personalities who promote supplements including those with false claims about their effects on health, which could include cancer prevention

Syrian Refugees: Flight Into the Unknown

MARCH 2015

NATIONAL GEOGRAPHIC

CLIMATE CHANGE DOES NOT EXIST

EVOLUTION NEVER HAPPENED

THE MOON LANDING WAS FAKE

VACCINATIONS CAN LEAD TO AUTISM

GENETICALLY MODIFIED FOOD IS EVIL

THE WAR ON SCIENCE



A WORKER ADJUSTS A DIORAMA OF A MOON LANDING AT THE KENNEDY SPACE CENTER.

We live in an age where a belief system may outweigh how consumers and patients process scientific data, including that related to multivitamins and cancer prevention

THANK YOU



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