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 > 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

Cohort (Disease free)

Exposed Cohort

Unexposed Cohort

Sufficient time lag

Disease Developed

Disease Free

Disease Developed

Disease Free

Compare the disease incidence between the exposed and unexposed cohorts

Present

Future

Time
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
Multivitamins in the Prevention of Cancer in Men
The Physicians’ Health Study II Randomized Controlled Trial

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Vadim Bubes, PhD
Joanne P. Smith, BA
Jean MacFadyen, BA
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Julie E. Buring, ScD

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

Calcium/Vitamin D Trial: Fractures & Colorectal Cancer

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

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)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>n (Cases)</th>
<th>Hazard Ratio with 95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (invasive)</td>
<td>4400</td>
<td>0.50</td>
<td>0.53</td>
</tr>
<tr>
<td>Colon</td>
<td>1590</td>
<td>0.84</td>
<td>0.84</td>
</tr>
<tr>
<td>Lung</td>
<td>1340</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>Endometrial</td>
<td>912</td>
<td>0.53</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Neuhauser et al 2009
# Multivitamin Use and Risk of Cancer in WHI (n=161,808) (multivariate adjusted)

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<th>Hazard Ratio with 95% Confidence Interval</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>101</td>
<td>0.50</td>
<td>0.85</td>
</tr>
<tr>
<td>Bladder</td>
<td>379</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Ovarian</td>
<td>579</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Kidney</td>
<td>318</td>
<td>0.37</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Neuhouser et al 2009

[Diagram showing hazard ratios and confidence intervals for different cancers with p-values]
The Prostate Cancer Prevention Trial (PCPT) tested finasteride (5-α reductase inhibitor) vs. placebo for prostate cancer risk reduction. Diet and dietary supplements were assessed at yr 1 by FFQ and a 2-page supplement questionnaire. All men underwent protocol-specific prostate biopsy – central pathology review. Data on supplement use and outcomes were 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
“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
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.
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