Publishing in High-Impact Medical Journals

Barry Kramer, M.D., M.P.H.
U.S. National Cancer Institute (consultant)

Disclosure/Disclaimer

- **No financial conflicts**
- **Opinions are mine, not official positions of the U.S. Federal Government**
- **My perspective:**
  - Editor-in-Chief, Journal of the National Cancer Institute: 1994-2012
  - No current affiliation with *JNCI*

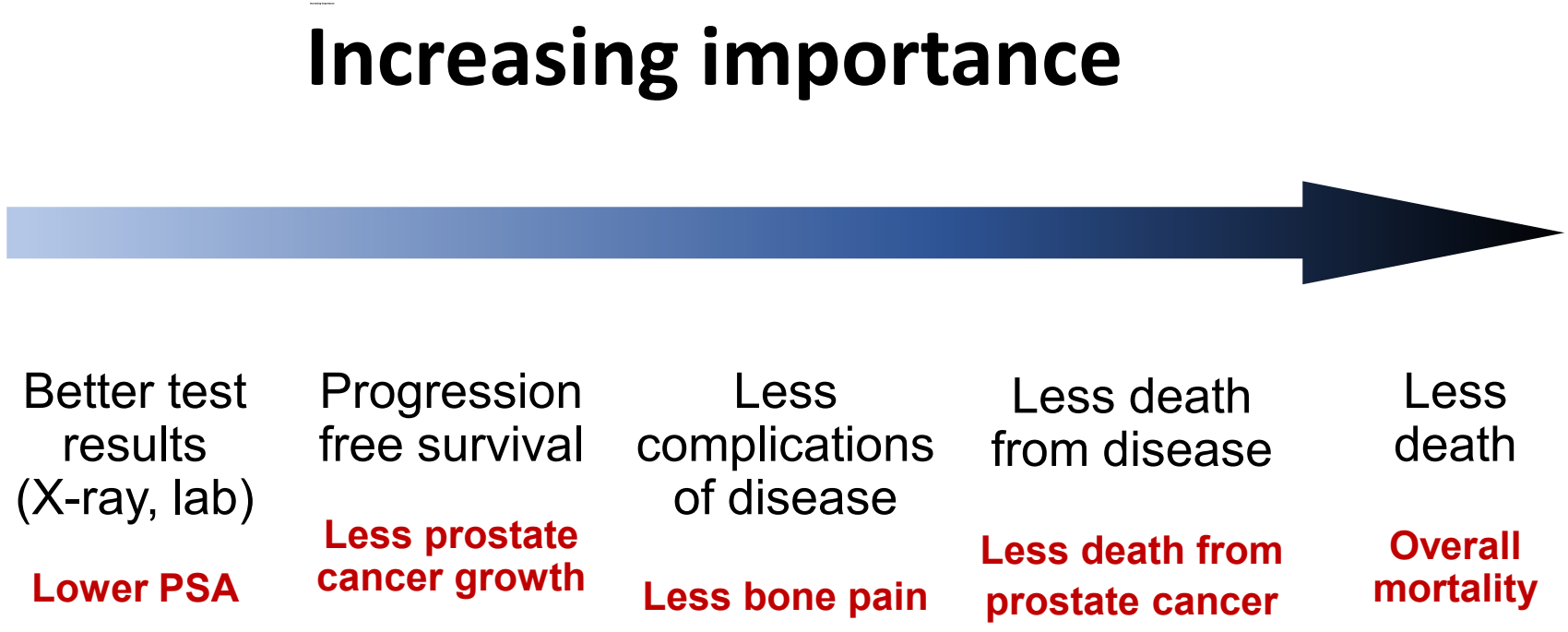
Advance Planning: Study Design Stage

- **Discuss the specific hypothesis**
  - The best studies are those in which a definitive negative result is as important as a definitive positive
- **Decide prospectively on study design**
- **Define endpoints/outcomes of interest**
  - Primary (drives sample size and power calculations)
  - Secondary: most important if the overall primary result is positive
  - Exploratory
- **Register in a recognized clinical trials database if a clinical trial (e.g., ClinicalTrials.gov)**
- **Work with a statistician from day 1**
  - Sample size, power calculation, most efficient statistical tests
  - Don’t rely on statistical packages

Questions to Address in Medical Research

- What is the exposure and what is the outcome?
- How certain is it that exposure causes outcome?
- How strong is the study design?
- How big is the effect?
- To whom does it apply?
- How important is the outcome?

Relative Importance of Outcomes



The Cover Letter

- Short and to the point
- Describe (and attach) all directly related manuscripts whether published or unpublished by any of the authors
- Planned future analyses of the same study/dataset

Writing Style

- Write for the full readership
- Avoid abbreviations if possible
  - List and define essential abbreviations
- Use an English editor if necessary

The Abstract

- Structured if an article
  - Background
  - Primary endpoint (secondary and exploratory endpoints if room)
  - Methods
  - Results
  - Conclusions: focus on the primary endpoint
- Results: quantitative
  - Absolute rates if possible
  - Emphasize 95% confidence intervals over P-values
- Conclusions should directly follow from the results

Use and Misuse of P-values

What is a P-value?: A way of gauging whether the observed result might reflect the play of chance:

- Formally, the probability (range 0 to 1) of seeing this result (or a more extreme result) if the intervention actually has no effect
- NOT the probability that the study hypothesis is true
- There is no magic P-value threshold (e.g., $P < 0.05$)

- Beware of "data dredging" (data torture, P-hacking): cherry-picking the data for a $P < 0.05$
- Provides NO information on effect size or clinical importance
- Provides NO information on study validity or possible confounding factors

Adapted from ASA Statement on Statistical Significance, 2016

Writing the Methods

- **Succinct, but sufficiently detailed to allow replication**
- **PICO formulation when possible**
  - Define the study and control populations
  - Define the intervention
  - Explicit comparisons being made
  - Outcomes: primary, secondary, exploratory
    - How endpoints were assessed
- **Informed consent process/animal welfare guidelines**
- **Randomization methods and blinding**

Writing the Methods (cont.)

- **Correction for multiple endpoints**
- **Methods used to authenticate cell lines**
- **Statistical section**
  - Power calculation
  - Statistical tests
  - Planned interim analyses
- **Funding source and role**

Writing the Methods: Biomarker Studies

- Define the study population and controls
  - Potential for spectrum bias!
- Clear description of specimen collection/handling in case patients, controls
- Cutpoint determination
  - Biologic rationale?
  - Standard cutpoint?
  - Sensitivity to endpoint choice?
  - Data driven (cutpoint optimization)?
- Measurement variability
- Potential for verification bias & how avoided

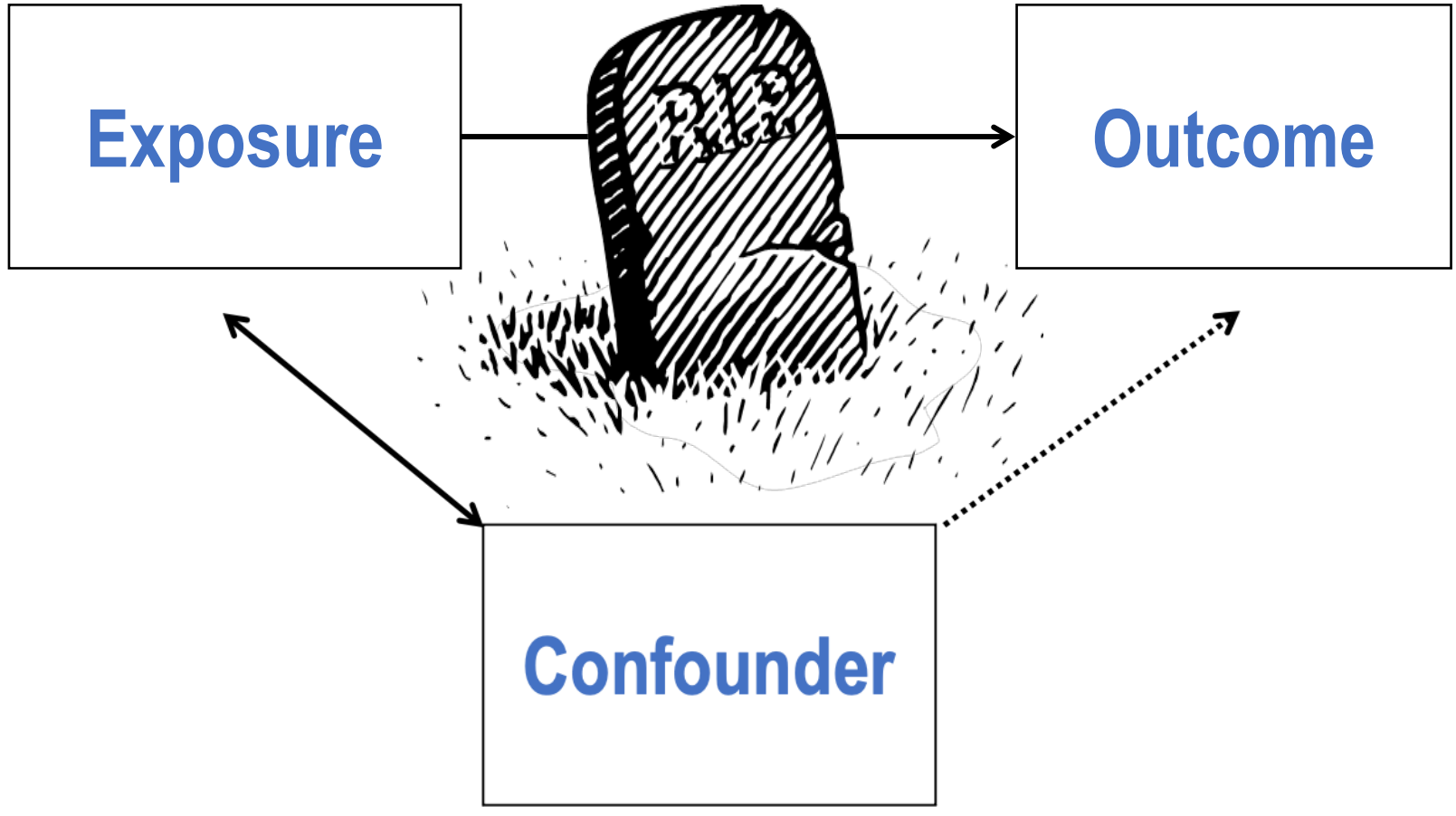
Writing the Results

- **Emphasis on health outcomes if a human study**
  - Overall mortality
  - Cause-specific mortality
  - Quality of life
- **Subgroup analyses: prospective vs. exploratory**
  - Sex
  - Ethnic group
  - Risk group
  - Other
- **Quantitative outcomes**
  - Emphasis on absolute vs. relative rates
  - Emphasis on estimation (with 95% confidence intervals) vs. hypothesis testing

Writing the Discussion

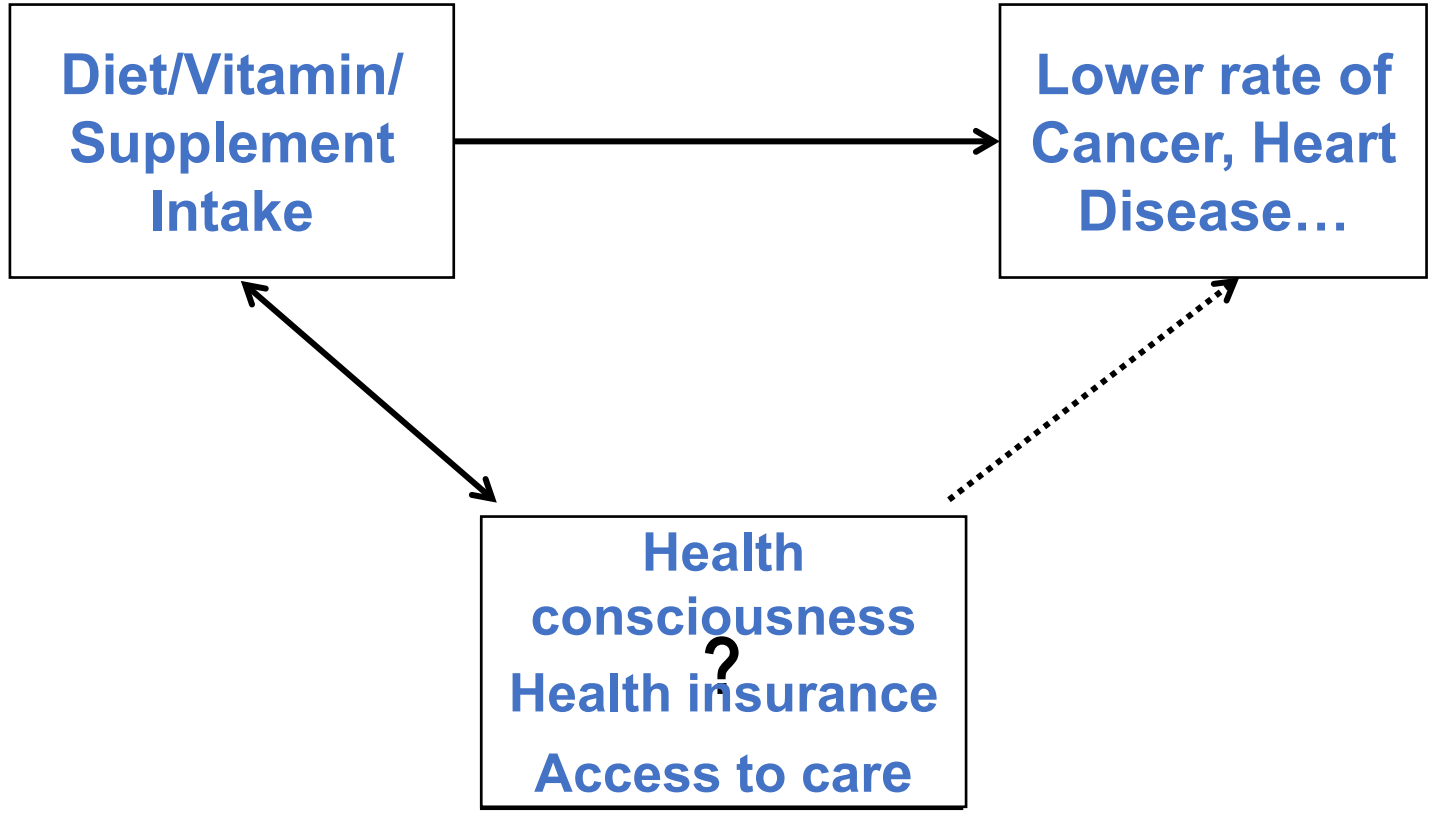
- DIRECT implications of the results
- Context within the field: What's REALLY new?
  - Other prior studies
- Future directions for research
- Study limitations: think hard
  - Threats to internal validity
  - Generalizability
  - Alternative explanations for the findings (think VERY hard)

Confounding Variables

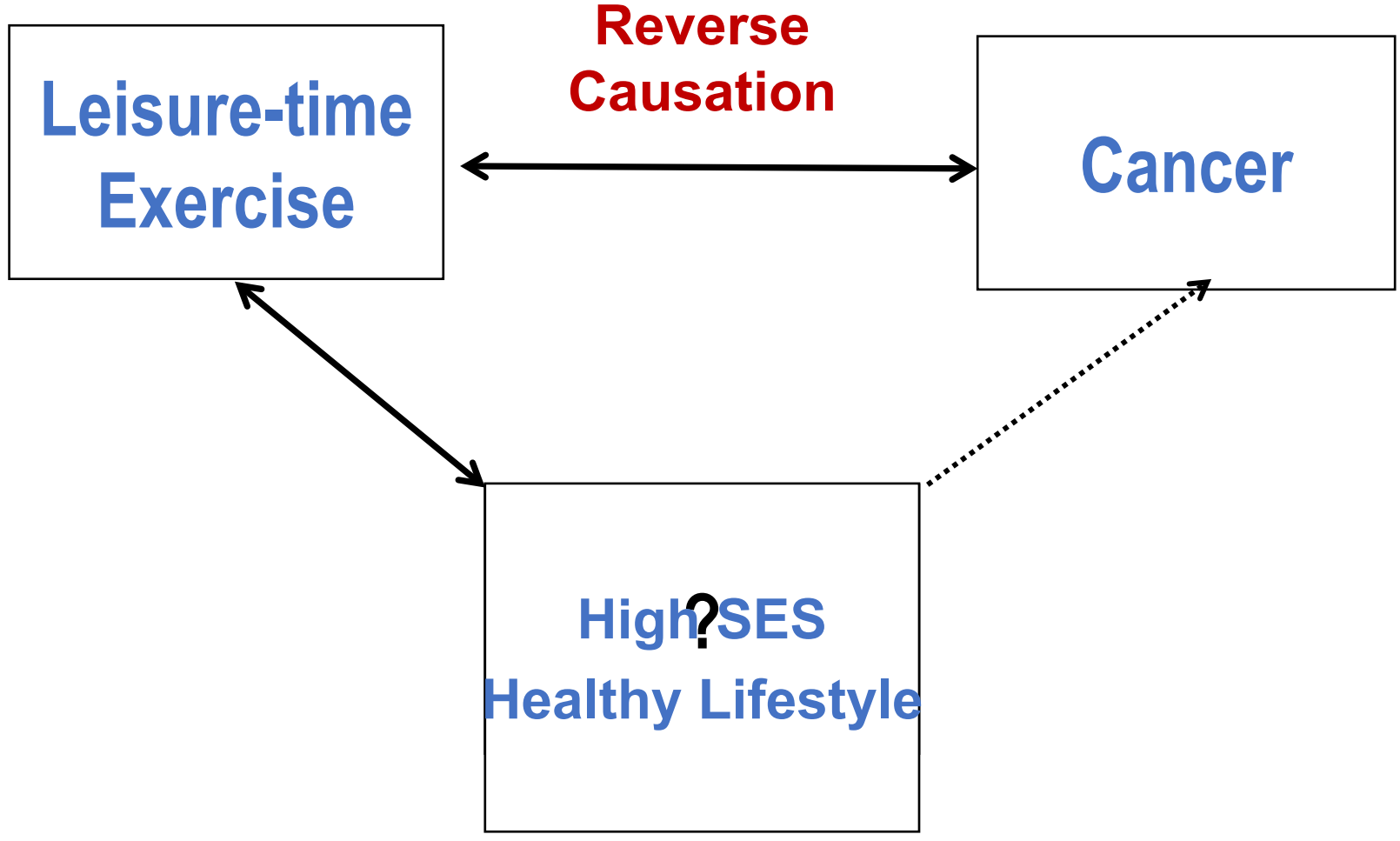


Confounding is the death of any study!

Confounding Variables



Confounding Variables



Confounding is a concern in any observational study!

Confounding is more likely when someone's choice (patient, doctor, etc.) determined who was in the exposed and unexposed group

(This even applies to animal studies!)

A Comparison of Observational Studies with Randomized Trials in Oncology

- MEDLINE search (2000-2016) → 350 observational studies, 121 matching randomized trials
- No significant correlation between HR estimates (correlation coefficient 0.083, 95% CI –0.068 to +0.230)
- No agreement beyond chance (Kappa statistic = 0.037)
- Only 38% of observational HRs fell within the 95% Cis of the matched RCT (more likely to show better survival than RCT)
- No improvement with adjustment for study quality, co-variates, propensity weighting, instrumental variables

Payal Soni et al.: J Clin Oncol 37(14): 1209-1216 [2019]

Practices to Avoid

- **Ghost writing**
- **Plagiarism**
  - **Verbatim duplication of *any* text from the literature without quotation & the reference is a form of plagiarism**
  - **Even from *your own* prior publications**
- **Grammatical, spelling errors**

Important Checklists

Clinical Trials: CONSORT

- Consolidated Standards of Reporting Trials: www.consort-statement.org/

Meta-analyses of Observational Studies in Epidemiology: MOOSE

- JAMA 283(15):2008-2012 (2008)

Meta-analyses of Randomized Trials: QUORUM

- Quality of Reporting of Meta-analyses: Lancet 354:18961900 (1999)
- https://journals.plos.org/plosntds/article/file?type=supplementary&id=info:doi/10.1371/journal.pntd.0000381.s002

Important Checklists (cont.)

Tumor Markers: REMARK

- Reporting Recommendations for Tumor Marker Prognostic Studies: JNCI 97(16):1180-1184 (2005)
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3362085/

Microarray and Proteomic Data

- MIAME: Minimum Information About a Microarray Experiment: Nat Genet. 29(4):365-371 (2001)
  - http://fged.org/projects/miame/

Diagnostic Tests: GRADE

- Grading Quality of Evidence and Strength of Recommendations for Diagnostics Tests and Strategies: BMJ 336:1106-1110 (2008)
- https://www.gradeworkinggroup.org/

Thank You