On the use of databases and registries to evaluate targeted therapies

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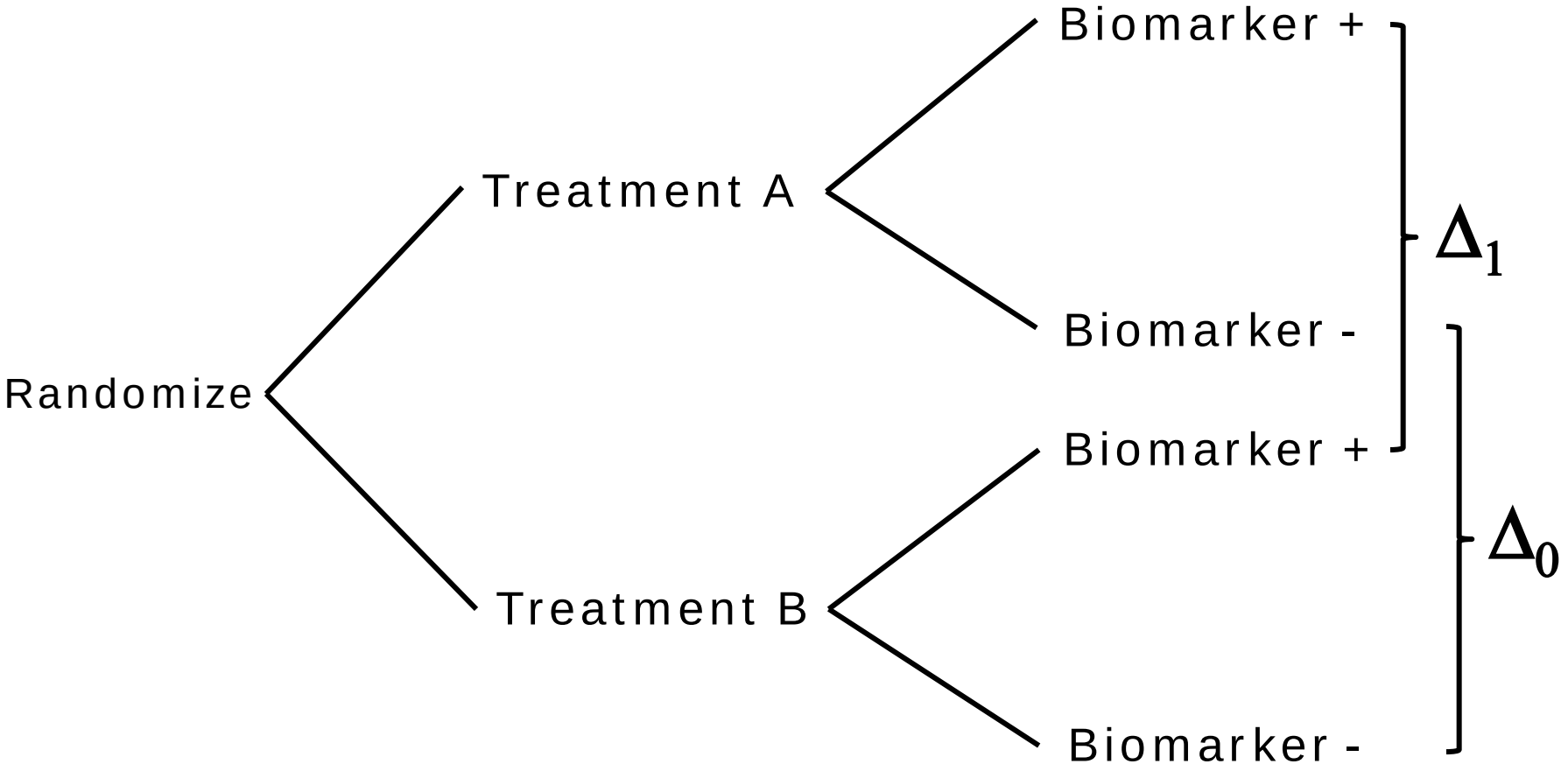
Evaluating patient selection in an existing RCT



Primary Analysis

- An interaction test: Does the treatment effect differ between the two biomarker groups?

  H: $\Delta_1 = \Delta_0$

  $\Delta_1 = \Delta_0$ implies no value of biomarker-guided treatment.

- Interaction is necessary but not sufficient for assessing marker performance
  - Janes et al., Annals of Internal Med 2011;154:253-259)

- If Δ_0 is not of interest, or we are willing to assume that $\Delta_0 = 0$, the study could be focused on Δ_1

Subgroup analysis an RCT by biomarker status

- Many strengths of the original design apply
- Cautions associated with subgroup analyses apply (Wang et al NEJM 2007;357:2189-2194)
  - Multiplicity of tests increases type I error
  - Usually underpowered for interaction test
- Logistical issues
  - Access to specimens
  - Quality of assay results

Can we use other (non-randomized) databases/registries to evaluate targeted therapies?

Underlying questions

- What is the reliability of inference from observational studies?
- What is needed in an observational study to assure reliable inference?

Menopausal hormone therapy

- Premarin approved by FDA in 1942 for relief of menopausal symptoms . . .

Prescribing of Noncontraceptive Estrogens and Progestins in the United States, 1974–86

Elina Hemminki, MD, Dianne L. Kennedy, RPh, MPH, Carlene Baum, PhD, and Sonja M. McKinlay, PhD

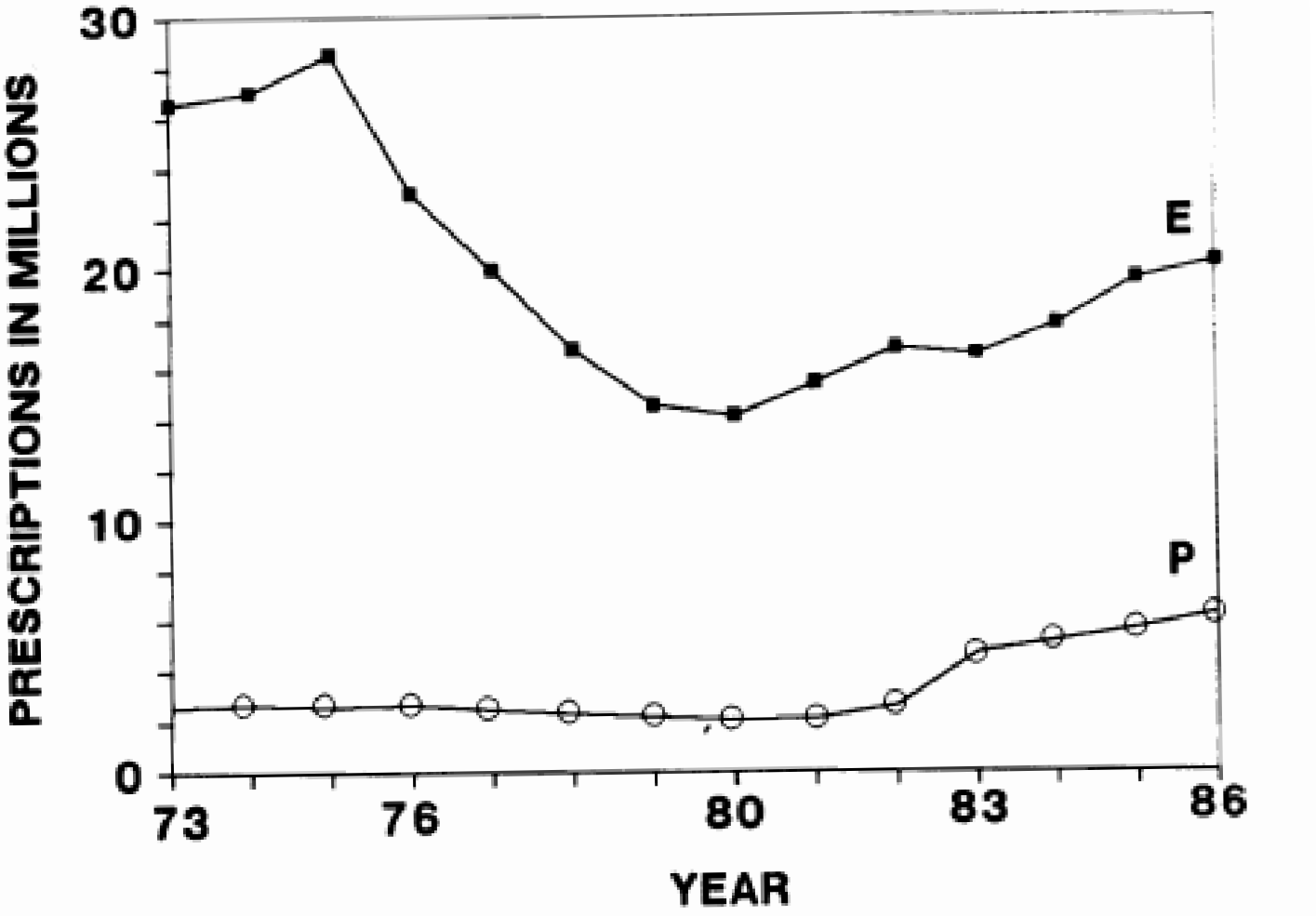


FIGURE 1—Numbers of Dispensed Prescriptions Containing Estrogens (E) and Progestogens (P) in 1973–86, in Millions (the NPA data).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Postmenopausal Estrogen Use, Cigarette Smoking, and Cardiovascular Morbidity in Women over 50 — The Framingham Study

Peter W.F. Wilson, Robert J. Garrison, and William P. Castelli

N Engl J Med 1985; 313:1038-1043

ORIGINAL ARTICLE

A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease

Meir J. Stampfer, M.D., Walter C. Willett, M.D., Graham A. Colditz, M.B.B.S., Bernard Rosner, Ph.D., Frank E. Speizer, M.D., and Charles H. Hennekens, M.D.

N Engl J Med 1985; 313:1044-1049

Framingham Study Abstract

We studied the effect of estrogen use on morbidity from cardiovascular disease in 1234 postmenopausal

. . . women reporting postmenopausal estrogen use at one or more examinations had over a 50 per cent elevated risk of cardiovascular morbidity (P<0.01) and more than a twofold risk for cerebrovascular disease (P<0.01)

Despite a favorable cardiovascular risk profile and control for the major known risk factors for heart disease, women reporting postmenopausal estrogen use at one or more examinations had over a 50 per cent elevated risk of cardiovascular morbidity (P<0.01) and more than a twofold risk for cerebrovascular disease (P<0.01) after the index examination. Increased rates for myocardial infarction (P<0.05) were

No benefits from estrogen use were observed in the study group; in particular, mortality from all causes and from cardiovascular disease did not differ for estrogen users and nonusers.

N Engl J Med 1985; 313:1038–43

NHS Abstract

To clarify the possible role of postmenopausal estrogen use in coronary heart disease, we surveyed 121,964 female nurses, aged 30 to 55 years, with mailed questionnaires, beginning in 1976. Information on hormone use and other

. . . the age-adjusted relative risk of coronary disease in those who had ever used them [postmenopausal hormones] was 0.5 (95 per cent confidence limits, 0.3 and 0.8; P = 0.007), and the risk in current users was 0.3 (95 per cent confidence limits, 0.2 and 0.6; P = 0.001).

the risk in current users was 0.3 (95 per cent confidence limits, 0.2 and 0.6; P = 0.001). The relative risks were similar for fatal and nonfatal disease and were unaltered after adjustment for cigarette smoking, hypertension, diabetes, high cholesterol levels, a parental history of myocardial infarction, past use of oral contraceptives, and obesity. These data

These data support the hypothesis that the postmenopausal use of estrogen reduces the risk of severe coronary heart disease.

HT use increased rapidly

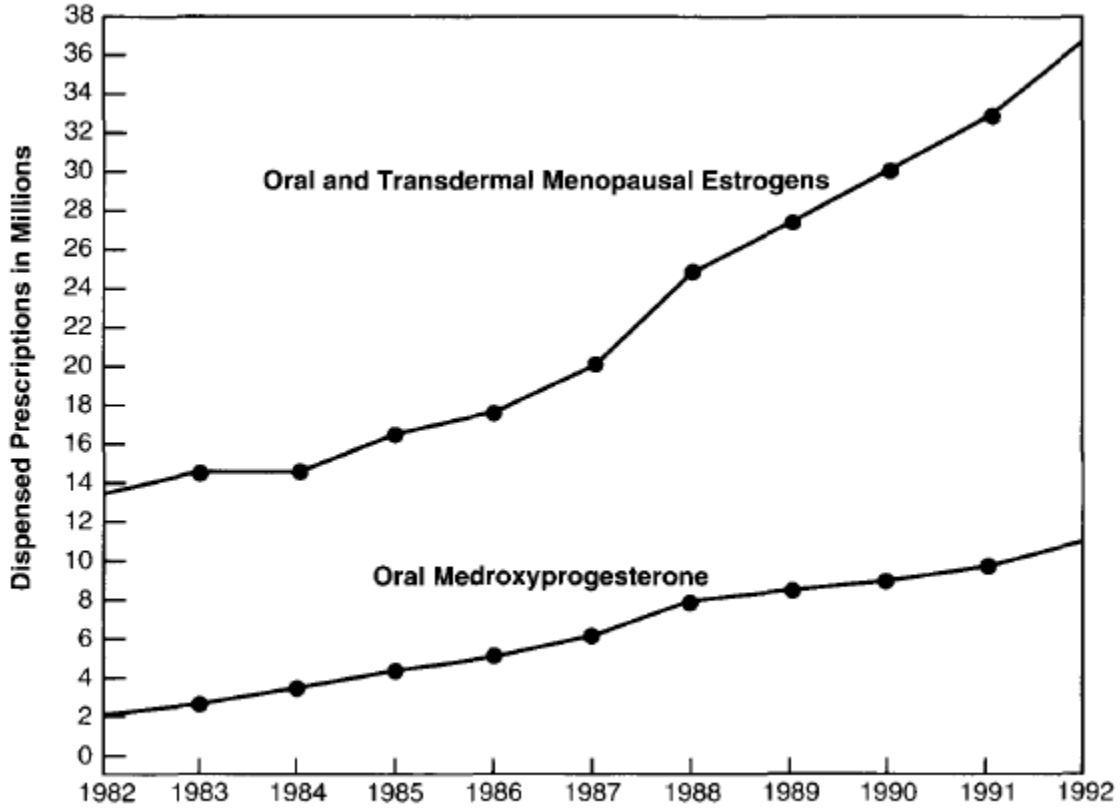
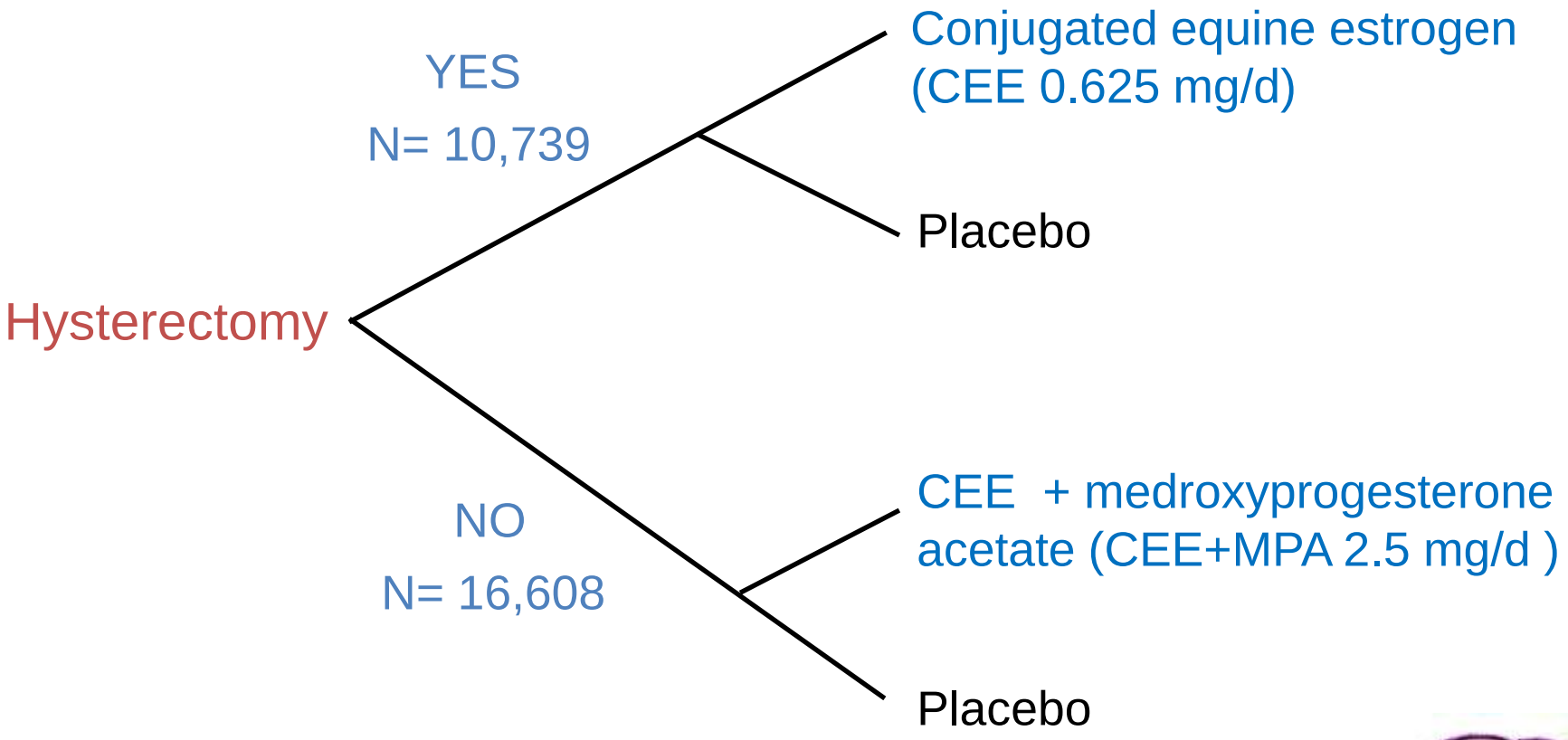


Figure 1. Estimated number of dispensed prescriptions (in millions) of oral and transdermal menopausal estrogens and medroxyprogesterone from 1982–1992 in the United States. These data are from the National Prescription Audit.

Wysowski,DK, Golden L, Burke L, Use of menopausal estrogens and medroxyprogesterone in the United States, 1982–1992, Obstetrics & Gynecology, 1995; 85(1): 6-10.

Design of the WHI randomized, double-blind, placebo-controlled HT trials



INSIDE HARKEN AND HALLIBURTON • THE OLDEST SKULL

Newsweek

July 22, 2002

newsweek.msnbc.com

A New Study Raises Fears About the Risks For Millions Of Women. Here's What You Should Do

Beyond Hormone Therapy

JULY 22, 2002

WALL STREET: LOSING SAVINGS—AND TRUST

TIME

IS THIS OUR FIRST ANCESTOR?

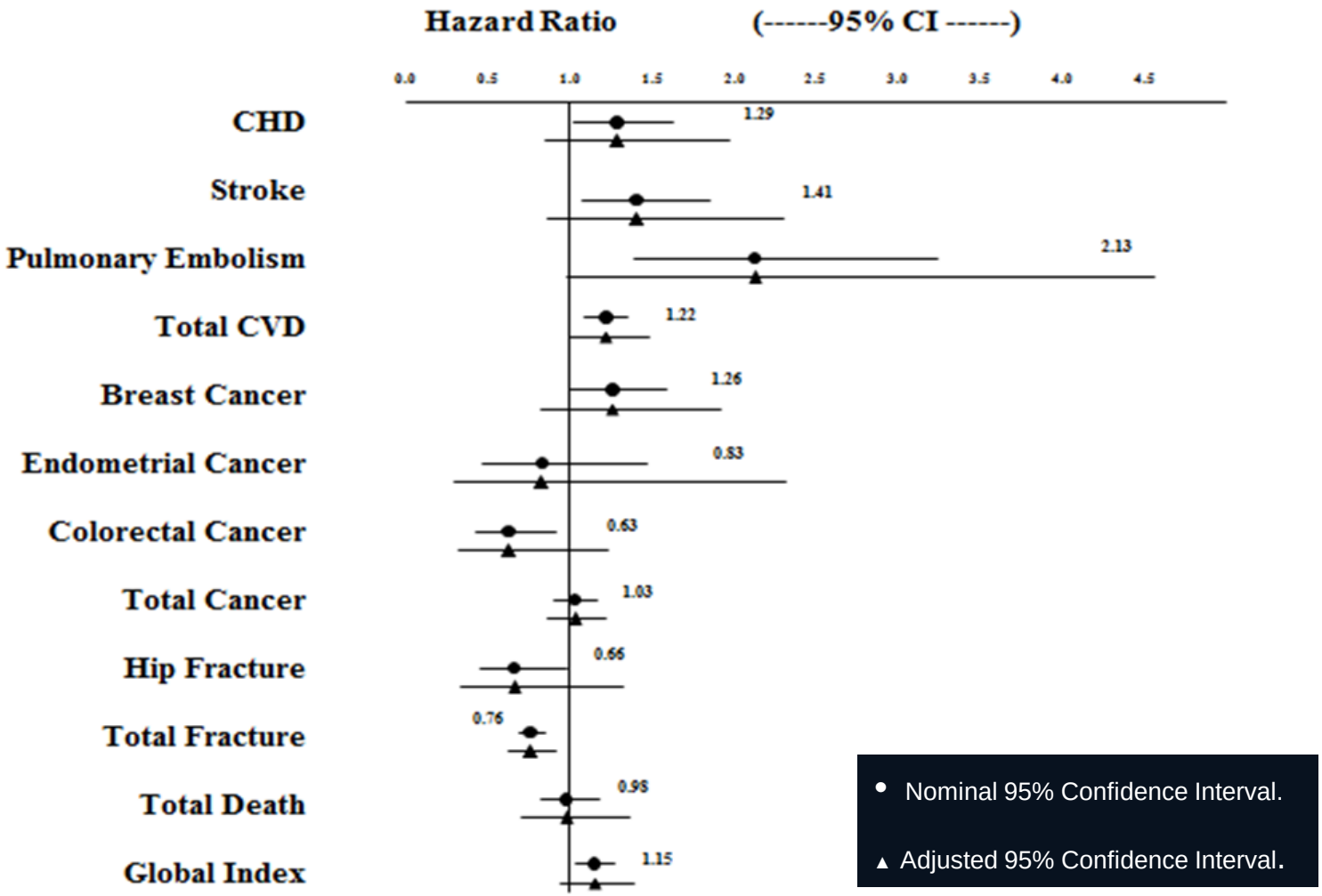
Susan Pierres, 60, of Miami, has been on hormones for 10 years. She is angry and confused but not yet ready to stop taking them

THE TRUTH ABOUT HORMONES

Hormone-replacement therapy is riskier than advertised. What's a woman to do?

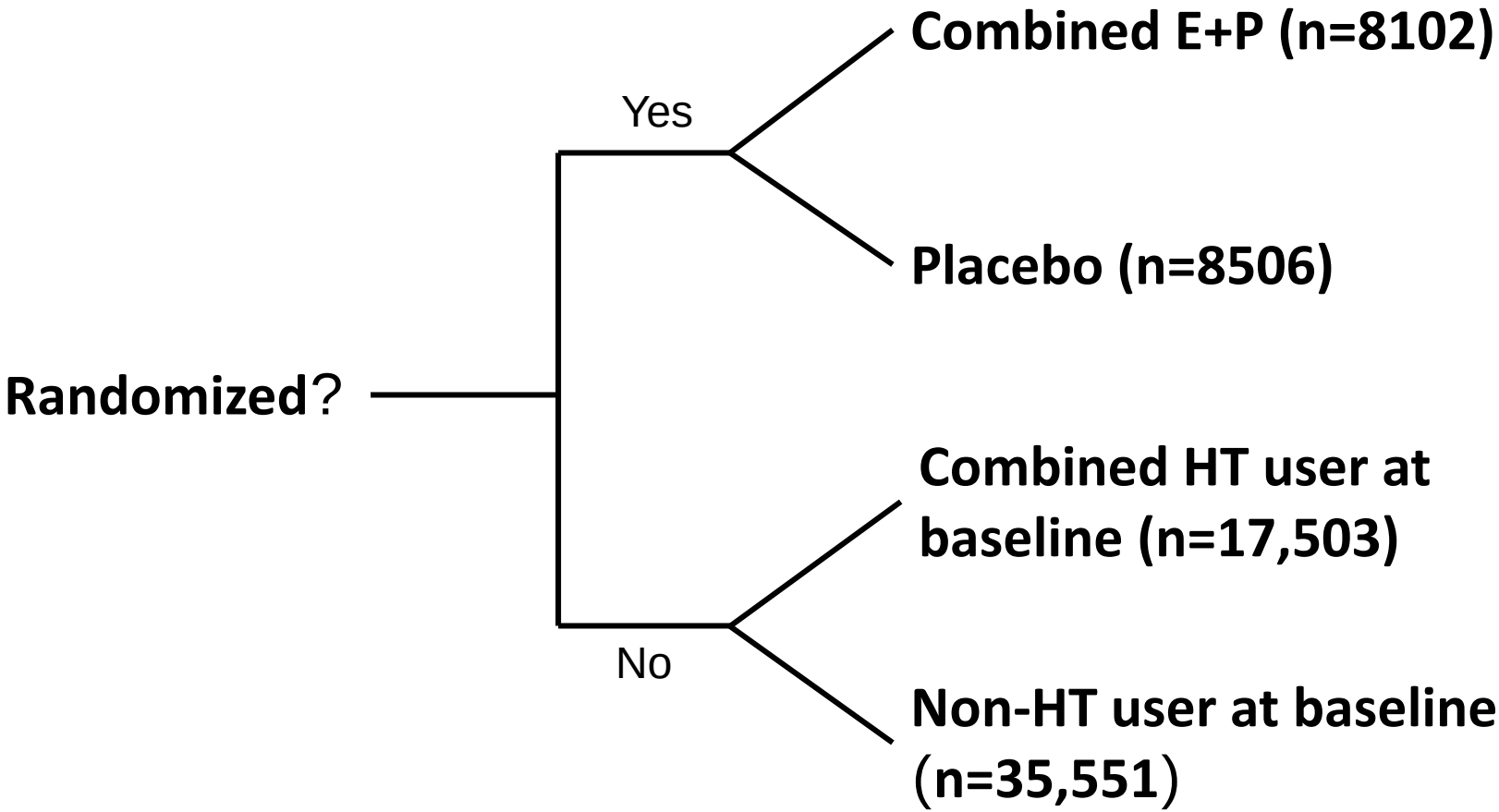
www.time.com AOL Keyword: TIME

Risks and benefits of E+P, 2002



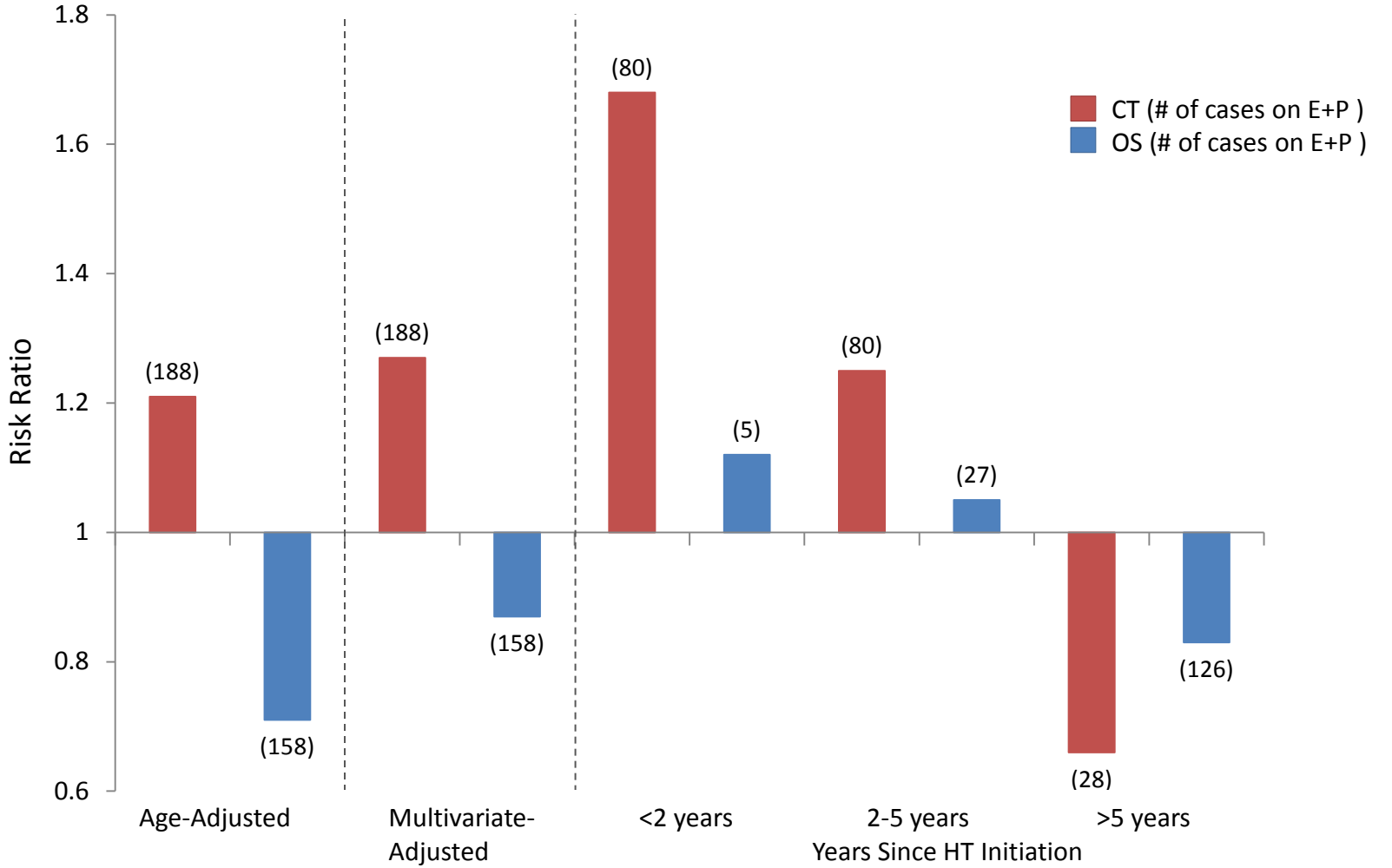
Rossouw et al. JAMA. 2002; 288(3):321-33.

A joint analysis of a randomized trial and an observational study



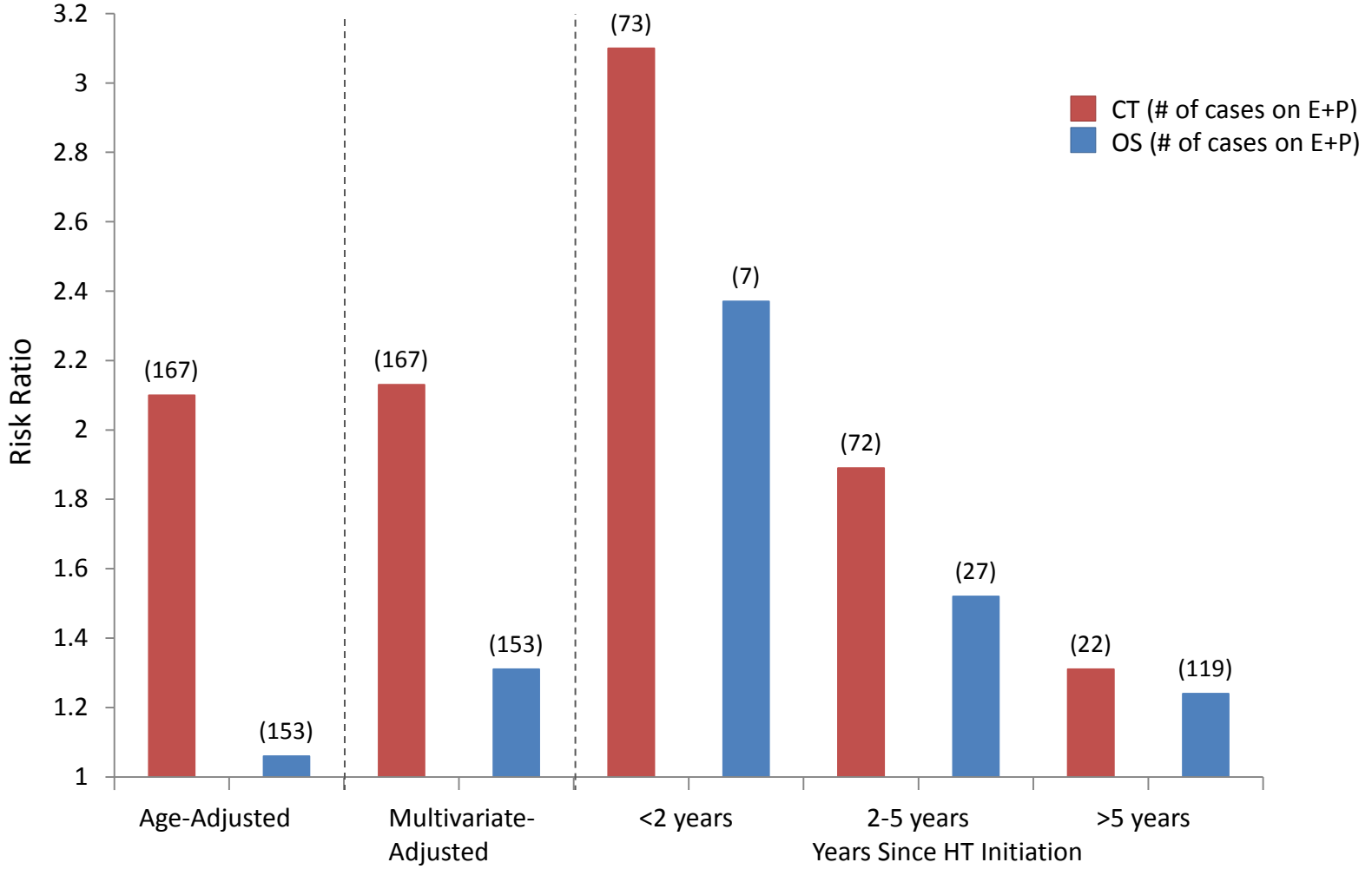
Adapted from Prentice et al., AJE 2005:162:404-414

Estimated Association between Estrogen + Progestin Therapy and CHD Risk in the WHI Clinical Trial and Observational Study



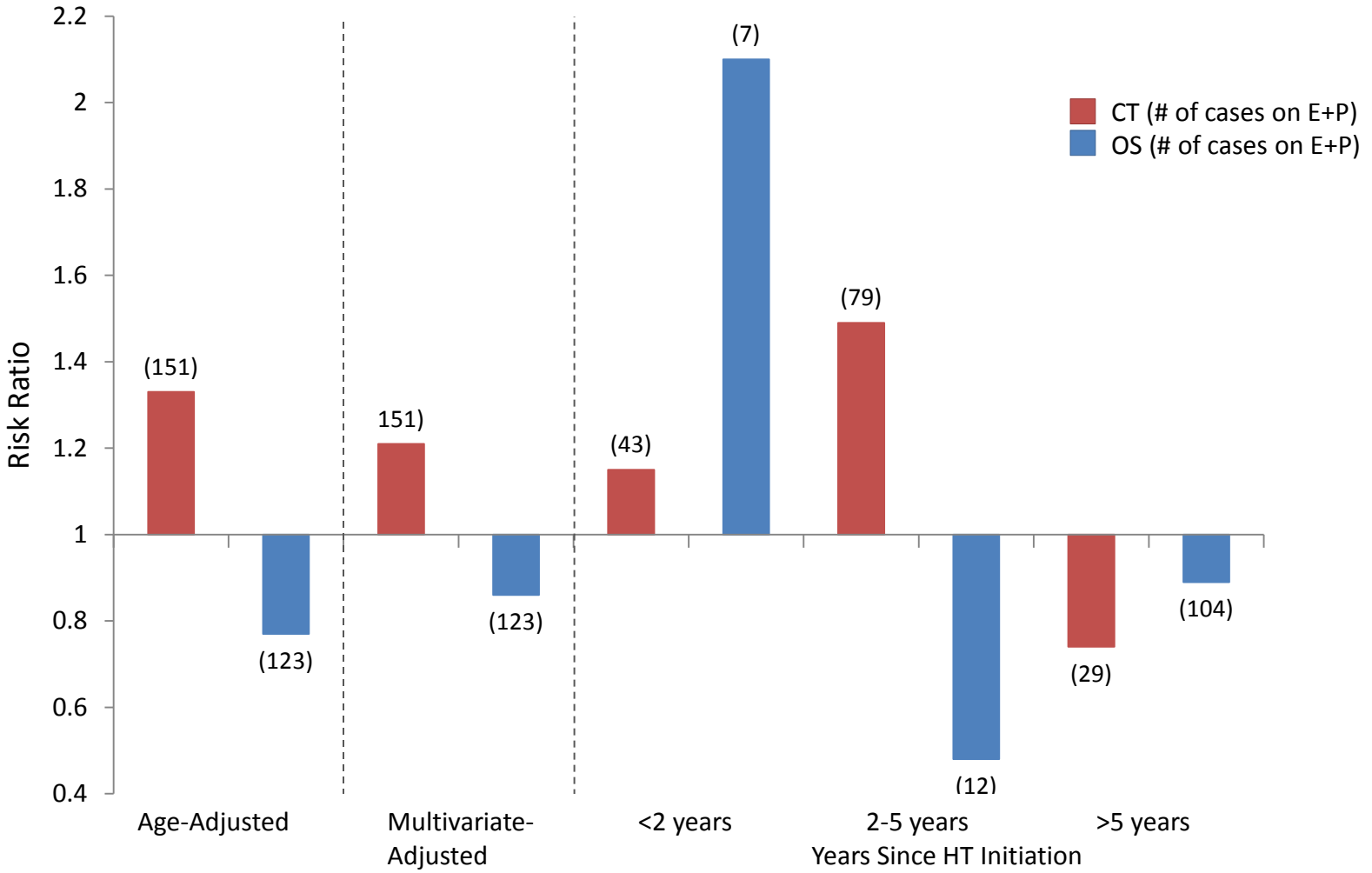
Adapted from Prentice et al., AJE 2005:162:404-414

Estimated Association between Estrogen + Progestin Therapy and Venous Thromboembolism Risk in the WHI Clinical Trial and Observational Study



Adapted from Prentice et al., AJE 2005:162:404-414

Estimated Association between Estrogen + Progestin Therapy and Stroke Risk in the WHI Clinical Trial and Observational Study



Adapted from Prentice et al., AJE 2005:162:404-414

Some reflections on this example

- Observational studies can have a profound impact on clinical practice and outcomes
- In most cases it was possible to align the randomized and non-randomized results.
- Alignment depended on
  - Creating a natural experiment within the observational study
    - Similar study population
    - Parallel, high quality follow-up
    - Use of a pseudo-intention to treat analysis paradigm
  - Capturing of all noteworthy potential confounders of treatment assignment
  - Insight gained from the analysis of the randomized trial itself

Considerations for using databases to evaluate therapies in other settings

- Emulate the randomized trial that you wish you could do
  - Hernán et al., Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. Nov 2008; 19(6): 766–779.
- Importance of specific elements may differ from this example
  - Potential confounders of treatment selection may depend more on the nature of the therapies
  - Time-dependent effects may not be the issue
  - Supportive care and surveillance mechanisms are likely important
  - May be outcome specific
- Most valuable when the database captures all relevant outcomes

Considerations for using databases to evaluate therapies in other settings

- The effort needed to control potential bias depends on the underlying effect size.
- Interactions tests
  - Require at least the same level of care in analysis as main effect
  - May have the same caveats as in clinical trials
- Need high quality biorepository with broad consent

Potential benefits of the observational setting

- May enhance inference by capturing
  - Larger and perhaps broader study population
  - Larger range of therapies
- Facilitates rapid evaluation of new biomarkers at lower cost per biomarker

- Note: All of these would be enhanced by a companion RCT

Who should build, maintain, have access to, and fund database/registry efforts?

Related thoughts

- Leverage existing high quality resources to the fullest
- Academic settings may be a better place to develop these resources when we are so early in the pipeline
  - Fewer conflicts of interest
  - Clearer oversight mechanisms
  - More open access
- Any resources developed de novo should have randomized trials at their core
  - Need novel trial designs

Thanks to:

Holly Janes, SCHARP statistician
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