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
  

• If \( \Delta_0 \) is not of interest, or we are willing to assume that \( \Delta_0 = 0 \),
  the study could be focused on \( \Delta_1 \)
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).
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

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.
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 observed particularly among the estrogen users who smoked cigarettes. Conversely, among nonsmokers estrogen use was associated only with an increased incidence of stroke \( P<0.05 \). 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.

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 potential risk factors was updated and the incidence of coronary heart disease was ascertained through additional questionnaires in 1978 and 1980, with a 92.7 per cent follow-up. End points were documented by medical records.

During 105,786 person-years of observation among 32,317 postmenopausal women who were initially free of coronary disease, 90 women had either nonfatal myocardial infarctions (65 cases) or fatal coronary heart disease (25 cases). As compared with the risk in women who had never used postmenopausal hormones, the age-adjusted relative risk of coronary disease in those who had ever used them 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 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 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.

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

Hysterectomy

YES
N= 10,739

- Conjugated equine estrogen (CEE 0.625 mg/d)

- Placebo

NO
N= 16,608

- CEE + medroxyprogesterone acetate (CEE+MPA 2.5 mg/d)

- Placebo
Risks and benefits of E+P, 2002

A joint analysis of a randomized trial and an observational study

- Randomized? (n=8102)
  - Yes
  - Placebo (n=8506)
- No
  - Combined HT user at baseline (n=17,503)
  - Non-HT user at baseline (n=35,551)

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

• 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
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