The Future

~ The WHI Legacy to Future Generations of Women ~
Opening, WHI Extension, BAA

- Opening Remarks (Putting It All Together)
  Moderator: Richard Hodes, MD, NIA

- WHI Extension Study
  Data and Specimen Resources
  Broad Agency Announcement (BAA)
  Jacques Rossouw, MD, NHLBI
Opening Remarks (Putting It All Together)

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WHI Extension Study
Data and Specimen Resources
Broad Agency Announcement (BAA)

Jacques Rossouw, MD
WHI Project Officer

National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
WHI Extension Study 2005-2010

- All participants in clinical trials and observational study invited
- Estimate that more than 116,000 will participate (80% of eligible)
- Participants asked to provide data on health outcomes, hormone use
- Rationale:
  - Study possible delayed effects of study treatments (e.g., breast and colorectal cancer in trial of low fat dietary pattern)
  - Collect greater numbers of outcomes for future studies
    - To study subgroups e.g., by race/ethnicity
    - To study less frequent outcomes e.g., ovarian cancer
Access to WHI Data for Publications

- Collaboration with WHI investigators
  - Writing group proposal
  - Review by study committees
  - www.whiscience.org

- Datasets available for research use
  - Observational study baseline data
  - E+P trial data (soon)
  - www.nhlbi.nih.gov/resources/deca/directry.htm
WHI Resource

- Bloods from
  - Baseline and Year 1 in Clinical Trials (N=68,135)
  - Baseline and Year 3 in Observational Study (N=93,676)
  - Serum, plasma, DNA, red blood cells
  - Urine in subsample (N=12,615)

- Data on wide range of clinical outcomes
- Data on wide range of demographic and exposure variables
Potential of the WHI Resource

- Large, well-documented data including women of diverse background
- Find predictors of health and disease in the blood samples (several studies already completed)
- Find genetic markers of disease (some studies completed)
- Interplay between genes and environment
- Better understanding of effects of specific treatments, e.g., effect of combination hormones on heart attack, stroke, and breast cancer (currently ongoing)
- Fits within broader NHLBI goal of encouraging studies of the entire gene in relation to disease (whole genome association studies)
Access to the WHI Resource

- Ancillary study in collaboration with WHI investigators (requires separate, non-WHI funding)

- Core study defined by WHI investigators (funded from WHI funds as subcontract with WHI Clinical Coordinating Center)

- Broad Agency Announcement (NHLBI contract funding for laboratory investigations)
BAAs are used for scientific study that advance the state of the art or increase knowledge or understanding rather than focusing on a specific outcome.

Translation: the investigators propose the studies to be done.

Contract mechanism.
Title: “Towards Maximizing the Scientific Value of the Biologic Specimens from the Women’s Health Initiative”

- Solicits the best ideas for research studies
- Open to WHI and non-WHI investigators
- WHI program intended to improve knowledge about some of the common diseases of older women
- Many studies have been completed, are still being done, or are being planning by WHI investigators and their colleagues
- The BAA makes available $17.5 million over 2 years for additional studies by experts from the entire scientific community
- A second BAA will be issued in late 2007
The current BAA will focus on laboratory studies of biologic markers for cardiovascular diseases, cancers of the breast, colon and rectum, and fractures. Studies involving other outcomes of interest will also be considered. Anticipate proposals will include application of genomics, proteomics, and other “high-dimensional” laboratory techniques to resource. Focused studies of candidate markers or genes will also be considered. Details of WHI resource can be found at www.whiscience.org.
National Guidelines, Recommendations & Potential Impact of WHI

- Heart and Brain (Stroke)  
  Marian Limacher, MD
- Brain (Cognitive Function)  
  Sally Shumaker, PhD
- Breast, Colon and Other Cancers  
  Dorothy Lane, MD, MPH
- Gynecological Health and Hormones  
  Susan Hendrix, DO
- Overall Recommendations for Older Women  
  Robert Wallace, MD
- Closing Remarks for Guidelines Session  
  Richard Hodes, MD
Heart and Brain (Stroke)

Marian Limacher, MD
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How WHI has modified Guidelines for CVD Prevention

- **Hormone Trials**
  - Substantial impact

- **Dietary Trials**
  - The discussions have begun....However,
    - Primary goal was cancer reduction
    - Intentionally targeted total fat reduction, not saturated fat or trans fat
    - this (lower fat, higher complex carb) is the most studied eating pattern of any we have--and it is safe and healthy.
    - There are evidence-based approaches to preventing morbidity and mortality from cancer and heart disease through screening and risk factor modifications that can and should be followed.
  - Stay tuned--longer f/u is underway and more studies are in the works.

(Evelyn Whitlock, email 2/9/06)
WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women’s Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.
…Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, **estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration** consistent with treatment goals and risks for the individual woman.
US Preventive Services Task Force Grading

- A : strongly recommends (good evidence)
- B : recommends (fair evidence)
- C : no recommendation (balance of evidence is too close)
- D : recommends against (at least fair evidence of ineffectiveness or harm outweighs benefits)
- I : insufficient evidence
USPSTF: Hormone Therapy

- Recommends against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women
  - Rating: D

- Recommends against the routine use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.
  - Rating: D

Class III interventions (Intervention is not useful/effective and may be harmful)

Hormone therapy: Combined estrogen plus progestin hormone therapy should not be initiated to prevent CVD in postmenopausal women. (Class III, Level A)

Combined estrogen plus progestin hormone therapy should not be continued to prevent CVD in postmenopausal women. (Class III, Level C)

Other forms of menopausal hormone therapy (eg, unopposed estrogen) should not be initiated or continued to prevent CVD in postmenopausal women pending the results of ongoing trials. (Class III, Level C)
Current Recommendations for CVD Prevention

Strategies we *should* be using!
2004 AHA Guidelines for CVD Prevention in Women

- **Lifestyle:**
  - Discourage cigarette smoking
  - Minimum 30 min. moderate physical activity on most, if not all, days of the week
  - BMI < 25 [between 18.5 and 24.9 kg/m²]
    - Waist circumference < 35 in
  - Heart Healthy Eating Pattern
    - Variety of fruits, vegetables, legumes, lean meats
    - < 10% cal sat fat
    - chol < 300 mg/day
    - Limited trans-fats

Individual Risk Factor Interventions

- **Blood Pressure**
  - Rx for BP >140/90
  - Goal BP <120/80

- **Treating Lipids**
  - LDL > 130 (Optimal < 100); *with CAD or DM, goal LDL < 100 or < 70 if high risk*
  - HDL > 45 (Optimal >50)
  - TG > 150 (Optimal < 150)
  - Statins = 1st line; niacin, fibrates for HDL, TG goals

- **Diabetes**
  - Goal: HgA1C < 7

Mosca et al, AHA Guidelines: *Circulation* 2004
Brain (Cognitive Function)

Sally Shumaker, PhD
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WHI Memory Study (WHIMS)

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Critical Issues Regarding Women and Aging:

- Brain-related disorders are on the rise
  - Women (and men) are living longer
  - Early detection of brain-related disorders is improving
- A major worry among older adults is dementia and cognitive decline
- There is an urgent desire for treatments or preventatives – giving rise to claims of efficacy for medications, herbal and nutraceutical agents that may not have been tested adequately
- WHIMS represents a well-designed response to this challenge
Trajectories of Cognitive Function over Life Span

Cognitive Function

Hi

Low

Years

NORMAL

SUB-CLINICAL
(Mild Cognitive Impairment)

CLINICAL
(Dementia)
Hormone therapy was presumed to prevent dementia before it was tested in a clinical trial.

WHI and WHIMS provided the first, long-term, randomized trial to investigate the effect of hormone therapy on thinking and memory.

7,500 women, 65 years and older, joined WHIMS.

We learned that hormone therapy does not protect against cognitive decline or dementia in post-menopausal women aged 65 and older – in fact, hormone therapy may accelerate cognitive decline.
WHIMS focused attention on related questions that need answers:

- If not beneficial, what effects do hormones have on the brain?
- Is there a “window of opportunity” in which younger women (less than 65) might benefit from hormones?
- Do the negative effects of hormones in women 65 and older persist once women stop taking the medication?

WHIMS demonstrated that important and complex questions about cognition & dementia can be addressed in large (multi-site) studies.

WHIMS underscores the need to carefully assess the effects of other agents on the brain to determine if there are unintended risks or benefits (for example, SERMS, Aromatase Inhibitors, Statins, etc.).

WHIMS keeps the spotlight on women’s cognitive health!
Breast, Colon and Other Cancers

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Changes in National Guidelines
U.S. Preventive Services Task Force

USPSTF evidence-based review of HT:

- Good evidence that use of E + P results in increased risk for breast cancer and fair evidence of a reduced risk of colorectal cancer

- Insufficient evidence to assess the effects of E + P on the incidence of ovarian cancer and mortality from breast cancer
Changes in National Guidelines
U.S. Preventive Services Task Force

For the prevention of chronic conditions in postmenopausal women, the USPSTF recommends:

- Against the routine use of E + P
- Against the routine use of E-alone in women who had a hysterectomy
WHI Messages for Cancer Prevention

- Reinforced adage “do no harm” when prescribing for healthy women without symptoms
- Highlighted importance of randomized, double-blinded, clinical trials to establish cancer risk/benefit ratios for preventive interventions
- CTs with cancer outcomes should be sufficiently large and long to yield definitive answers
WHI Lessons for Cancer Prevention

Preventive interventions can impact on cancer screening, e.g.:

- E + P increases abnormal mammograms
- E + P increases endometrial biopsies (to rule out cancer as a cause of bleeding)
- E-alone increases recommendations for a shortened interval between mammograms
WHI Lessons for Cancer Prevention

- Many U.S. women have adopted healthy lifestyles making it more challenging to measure intervention effects.
- Calcium/Vitamin D supplementation should not be recommended for prevention of CRC, at this time.
- Lifestyle dietary changes that reduce fat intake and increase fruits and vegetables can be accomplished and maintained over 8 years.
- Longer (extension) follow-up among low-fat diet group may reveal further reduction of breast and CRC risk.
- WHI-OS suggests increased physical activity is related to reduced breast cancer risk (requires CT testing).
Gynecological Health and Hormones

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Impact of WHI on Gynecological Issues

- Systemic estrogens still approved and prescribed for vaginal dryness

- No change in recommendations for use other than with respect to urinary incontinence
Postmenopausal Hormone Therapy (PHT) and Urinary Incontinence

PHT and Urinary Incontinence

Background

- PHT staple in the management of menopause, credited with many benefits well beyond the indications for symptomatic relief of hot flashes, night sweats, and vaginal dryness
- Purported benefits of PHT was to improve the symptoms of urinary incontinence (UI)

JAMA 2005;293:935-948
PHT and Urinary Incontinence
WHI Findings

- Significant increase in risk for new onset urinary incontinence among continent women

- Worsening of the characteristics of incontinence among incontinent women using CEE+MPA or CEE after one year

- Considerations regarding the use of hormone therapy by postmenopausal women for any duration should incorporate the current findings into the established risks and benefits of these agents.

JAMA 2005;293:935-948
PHT and Urinary Incontinence

- American College of Obstetricians and Gynecologists
  - Practice Bulletin on UI, June 2005
  - “Oral estrogen regimens cannot be recommended as treatment or prevention for any type of urinary incontinence”
  - No mention of evaluation or management of women who develop incontinence or have worsening on hormone therapy
American Urogynecologic Society

- Current patient information page on UI
- "Estrogen therapy-can help increase urine control by increasing blood flow to the genital tissues. Hormones work more quickly if they are applied directly to the vagina so vaginal estrogen creams or pills are often prescribed. Oral estrogen can also be successful."
- No mention of WHI findings
Gaps in Translation

- Informed consent does not include risk of new or increasing incontinence as a risk of therapy

- Lack of recommendations to temporarily discontinue hormones to see if incontinence improves, especially prior to surgery to correct incontinence
Gaps in Translation

- WHI has brought into question longstanding clinical practice
- It will take time to bring practice in line with the evidence
- The WHI investigators are committed to assisting in any way possible
Overall Recommendations for Older Women

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Closing Remarks for Guidelines Session

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Synthesizing, Celebrating, and Closing

☐ Women’s Health Questions of the Future?
  Vivian W. Pinn, MD

☐ Celebrating WHI Participants

☐ Audience Questions
  Richard Hodes, MD

☐ Closing Remarks for the Conference
  Elizabeth Nabel, MD
Women’s Health Questions of the Future?

Vivian W. Pinn, MD

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Celebrating WHI Participants

Final Words of Appreciation and Acknowledgement
Audience Questions

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Closing Remarks for the Conference

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Thank you!
To the 161,808 WHI participants

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WHI Web Sites

www.whi.org

http://orwh.od.nih.gov/WHICconference.htm

www.nhlbi.nih.gov/whi

www.whiscience.org