Hormone Replacement Therapy

What should we know?

Avrum Z. Bluming, MD, MACP
Clinical Professor of Medicine
University of Southern California

Bluming AZ, Tavris C. Hormone Replacement Therapy: Real Concerns and False Alarms.
Hormone Replacement Therapy: Benefits and Risks for the General Postmenopausal Female Population and for Women With a History of Previously Treated Breast Cancer
“The word ‘risk’ derives from the early Italian *risicare*, which means ‘to dare.’

In this sense, risk is a choice rather than a fate.
The actions we dare to take... are what the story of risk is all about.”

Before you can effectively communicate risk, you must first understand it!
“Journals have devolved into information laundering operations for the pharmaceutical industry.”

It would be naïve to conclude that bias is only a matter of a few isolated instances. It permeates the entire system.

Physicians can no longer rely on the medical literature for valid and reliable information.

The Los Angeles Times and Newsday have dismantled their once-sizedable staffs of expert science journalists.

In February, The Boston Globe closed its science and health sections.

Recently CNN disbanded its science unit, dismissing Miles O’Brien, one of America’s preeminent TV science journalists.

At a science journalism awards ceremony, at the AAAS meeting last month in Chicago, the winners in the newspaper category both noted they no longer had jobs.
Two kinds of science

Discovery and explanations

Interventions (observation or randomized studies)
  a. Hazardous
  b. Therapeutic
An accidental chromosomal abnormality

An abnormal fusion gene

Abnormal persistence of a cell survival protein

Damaged cells accumulate, avoiding programmed cell death.

Chronic Myelogenous Leukemia

Conclusions: As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomized controlled trials. Advocates of evidence-based medicine have criticized the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence-based medicine organized and participated in a double-blind, randomized, placebo-controlled trial of the parachute.

Interventions (randomized studies)

a. Hazardous

b. Therapeutic

Charlton BG. Second Thoughts: Attribution of causation in epidemiology: Chain or Mosaic? Journal of Clin Epidemiol 1996;49(1):105-7
A mosaic is a marvelous construction, which assembles something beautiful, and perhaps useful, from colorful fragments broken off artifacts that may have been intended for other purposes.

But for hauling the body of medical science up to greater heights of reliable knowledge, there is nothing to beat a purpose-built chain of necessary causes—with each link of evidence well tested, and cemented to its neighbors by bonds of strong inference.

Disproving even a single item of evidence can, in principle at least, overthrow a whole scientific hypothesis, because a causal chain is only as strong as its weakest link.

By contrast, epidemiological hypotheses are supported by a network of linked evidence from numerous disciplines, and cutting any single strand may weaken a net, but does not break it.

Contradictory findings cannot do more than alter the balance of probability of multifactorial epidemiological causation. This explains the long life, resilience, and apparent irrefutability of such epidemiological hypotheses in the face of powerful items of apparently contradictory evidence.

Koch’s Postulates

• The microorganism must be found in abundance in all organisms suffering from the disease.

• The microorganism must be isolated from a diseased organism and isolated in pure culture.

• The cultured microorganism should cause disease when introduced into a healthy organism.

• The microorganism must be re-isolated from the inoculated diseased experimental host and identified as being identical to the original specific causative agent.
The epidemiologic data are consistent and show a 10- to 30-fold (1000 to 3000%) increase in the risk of lung cancer in smokers compared to non-smokers.

80% of lung cancer patients are or were smokers.

Cigarette smoke has been shown to cause premalignant changes in the lungs of laboratory animals.

Similar changes have been seen in the lungs of smokers, including those who have developed lung cancer.

Increased dose and increased duration of cigarette smoking correlates with increased risk of lung cancer.

Taubes G. Epidemiology faces its limits. Science 1995;269:164-9
Hormone Replacement Therapy

The incidence of breast cancer is 100 times greater in women than in men.

In 2 of the 4 studies, a significant reduction in risk was found, but only when women who started their periods at 17 and older were compared to women whose periods began at 11 and younger. And both these groups represented a small percentage of the population.

None of the comparisons for any of the other ages resulted in differences that were significant in any of the 4 studies.


“The public wants certainty when choices almost always have to be made in the absence of certainty.”

Lord Leslie Turnberg - former President of the Royal College of Physicians - The 10/16/2000 Harveian Oration - Science, Society and the Perplexed Physician.

**Hormone Replacement Therapy**

**Benefits and Risks**

**Benefits**

- Quality of Life Improvement
- Decreased risk of osteoporotic hip fracture
- Decreased incidence of colon cancer

**Risks**

- Increased risk of uterine cancer when estrogen is used in the absence of progesterone
- Increased risk of DVT and pulmonary embolus
- Increased risk of stroke
Controversial Associations

Alzheimer’s Disease??

Atherosclerotic Cardiovascular Disease??

Breast Cancer??
Benefits

Quality of Life Improvement

Among women who reported moderate to severe vasomotor symptoms at baseline, there was significant relief of symptoms among those randomized to HRT compared to those randomized to placebo (p < 0.001).

Hormone Replacement Therapy
Benefits and Risks

Benefits

Quality of Life Improvement

Decreased risk of osteoporotic hip fracture

Estrogen has been reported to decrease the incidence of osteoporotic hip fractures by 25 to 50%.

Decreased incidence of colon cancer

HRT has been associated with a 34% decreased incidence of colon cancer.

Hormone Replacement Therapy

Benefits and Risks

Risks

Increased risk of uterine cancer when estrogen is used in the absence of progesterone

1975: The administration of estrogen to postmenopausal women is found to be associated with a four to eight fold increase in the risk of uterine cancer.


Mid 1980s: The addition of progesterone to estrogen use for postmenopausal hormone replacement therapy (HRT) is reported to eliminate the increased risk of uterine cancer associated with estrogen administration alone.

Hormone Replacement Therapy
Benefits and Risks

**Risks**

Increased risk of uterine cancer when estrogen is used in the absence of progesterone

Increased risk of DVT and pulmonary embolus

In a 2006 reanalysis of the published WHI data, an increased risk of DVT was seen only in women taking E+P, and the incidence of pulmonary embolism was not increased by either E or E+P Hormone Replacement Therapy.

Risks

Increased risk of stroke

For strokes, the incidence was not increased in year one or in year 6+, while in the intervening years the excess rates among estrogen plus progestin recipients ranged from 1.3 to 1.6 per thousand per year, respectively...The differences were small, there was no evidence of a monotonic gradient, the data collected after the warnings could have been biased and detection bias cannot be excluded as possible explanations for the observed excesses.

Shapiro S. Risks of estrogen plus progestin therapy: a sensitivity analysis of the findings in the Women’s Health and Initiative randomized controlled trial. CLIMACTERIC 2003;6:302-310. (Mailman School of Public Health, Columbia University)
The positive and negative predictive value of self-reported stroke were 41.5% and 71.6% respectively.

In stroke research, sensitive neuroimaging techniques rather than stroke self-report should be used to determine stroke history.

Hormone Replacement Therapy
Benefits and Risks

Controversial Associations

Alzheimer's Disease??

Women who used estrogen may have a nearly 50% lower risk of Alzheimer's as long as they begin using the hormone before age 65.

Estrogen plus progestin therapy increased the risk for probable dementia (RR=2.05) in women 65 and older...“with an increased incidence of dementia as early as 12 months after starting HRT but no increased incidence of mild cognitive impairment (1,267) the women in the estrogen/progestin arm of the WHIMS study had reported prior hormone use. A hazard ratio of 0.36 (0.16-0.85) for prior HRT users was 0.36 (0.16-0.85).

The authors found that the risk for all-cause dementia, which occurred in 60 women, was 0.54 (0.32-0.91) for prior users compared with other women.

They found that the hazard ratio for Alzheimer’s disease among prior HRT users was 0.36 (0.16-0.85)

Controversial Associations

Alzheimer’s Disease??

Atherosclerotic Cardiovascular Disease??

The number of women who die of this disease in this country each year is between 5 and 10 times the number who die of breast cancer.

An NEJM editorial in 1991 concluded that HRT decreased ASCVD mortality by as much as 50%.

Controversial Associations

Atherosclerotic Cardiovascular Disease??

A summary of published articles (1993) reported a 50% decreased risk of atherosclerotic heart disease and a 28% decreased risk of death from heart disease among women who took HRT.

Hormone Replacement Therapy
Benefits and Risks

Controversial Associations

Atherosclerotic Cardiovascular Disease??

The Harvard based Nurses Health Study reported, in 2000, that HRT may reduce the development of primary cardiovascular disease by 40%.

Hormone Replacement Therapy
Benefits and Risks

Controversial Associations

Atherosclerotic Cardiovascular Disease??

Randomized prospective studies have not confirmed the protective effect of HRT on atherosclerotic cardiovascular disease development or progression.

In the Heart and Estrogen/progestin Replacement Study (HERS) as in WHI, there was a statistically significant increase for coronary heart events in women receiving HRT during the first year of use. HERS also found a statistically significant reduction for events in women receiving HRT in the next 4 years.


Hormone Replacement Therapy
Benefits and Risks

Atherosclerotic Cardiovascular Disease?

HRT administration reduces oxidation of LDL and causes vasodilation in women without cardiovascular risk factors. Consequently, atherogenesis is prevented because of LDL reduction and improvement in endothelial function.


HRT administration can be potentially harmful on existing atheroma because it increases inflammation and expression of metalloproteinase (MMP), which causes disruption of the stable atheroma plaque.

HRT also promotes neovascularization of the plaque and potentially bleeding into the plaque. Therefore, studies that enrolled women of a younger age, like the Nurses’ Study, found that HRT had a protective effect on the appearance of heart events since it is less likely to find plaques in these women. In WHI, 70 percent of the women studied were 60-79 years old. In this age range it is expected that already formed plaques may exist, whereas only ten percent of them were 50-54 years old, ages at which HRT could have played a beneficial role. The fact that in WHI, despite the reduction in LDL, total cholesterol, and glucose, and an increase in HDL levels, no improvement of the incidence of cardiovascular diseases was noted could be attributed to the age of the women included in the trial. This contradiction perhaps emerges from the fact that the administration of HRT in WHI began in an advanced age when atheromatous disease may have already been established. Consequently, it could be proposed that the formation of the plaque is delayed in women who use HRT early in menopause (around 52 years). On the other hand, HRT has no protective effect on menopausal women who begin the use of HRT late (around 65 years).

Controversial Associations

Alzheimer’s Disease??

Atherosclerotic Cardiovascular Disease??

Breast Cancer??
A woman's chance of being diagnosed with breast cancer increases with age. For women ages 20 - 50, the average risk is just 2%, from 50 - 70 it is 6%, and from 70 to 80 it is 3%.

The 11 percent or one in nine figure is obtained by adding the risk in each age category, 2% + 6% + 3% = 11%.

When a woman who has the average risk reaches age 50 without a diagnosis of breast cancer, she has passed through 2% of her risk so her risk to age 80 is now 11% - 2%, which equals 9%.

When she reaches 70 without a diagnosis of breast cancer, her risk to age 80 is then 11% - 2% - 6% = 3%.

Incidence of breast cancer by age (2007):

Birth to 39  0.48 (1/210)
40 to 59   3.98 (1/25)
60 to 69   3.65 (1/27)
70 and older  6.84 (1/15)

$3.98 + 3.65 + 6.84 = 14.47 \div 3 = 4.82 \times 1.24 = 5.98$
Hormone Replacement Therapy

Women’s Health Initiative

Women’s Health Initiative - Postmenopausal Women 50-79 years old (Mean = 63 years)

5/100 6/100
The majority of women who develop breast cancer never took HRT.

The majority of women who develop breast cancer today, who had appropriate screening and receive appropriate treatment, will never have a recurrence and will die, eventually of some other cause.
“If something is true, really so, if you continue observations and improve the effectiveness of the observations, the effects stand out more obviously, not less obviously.”


“Truth is what stands the test of experience.”

Albert Einstein
1974 – 1989: Of the 26 most quoted reports during this period, studying the association between HRT (usually estrogen replacement therapy alone) and breast cancer,

5 report an increased risk,

7 report a decreased risk, and

14 report no significant association.
Hormone Replacement Therapy and Breast Cancer?


Fig 5. ERT and breast cancer risk. Case control studies (1974 to 1982).
Hormone Replacement Therapy and Breast Cancer?

1984: A study published in the Journal of the American Medical Association reports that conjugated estrogen administration (the most commonly prescribed HRT estrogen in the U.S.) does not increase the risk of breast cancer, even when taken for many years.

1989: A Swedish study, published in the New England Journal of Medicine, reports a 4.4 fold increased risk of breast cancer associated with administration of combined estrogen and progesterone for more than 6 years. However,

a) No increased risk of breast cancer is seen among women who used conjugated estrogen alone, the preparation most often used in this country.

b) This 440% increase in risk is based upon only 10 patients in the study who developed breast cancer while taking combination HRT.

c) The editorial accompanying the report in the same New England Journal issue, concludes: “For the average North American woman, who will be postmenopausal for one third of her life, the benefits of estrogen seem strongly established...In my opinion, the data are not conclusive enough to warrant any immediate change in the way we approach hormone replacement.”
The most striking “result” was in women who took estrogen combined with progestin for more than 6 years, and this was what made headlines. These women appeared to have 4.4 times the average risk of developing breast cancer. But there is a very important reason not to take this figure literally. There were only 10 women in this group, too few to provide a statistically stable result, the true value had a 95% chance of being 10% below the average, as high as 22.4 times average (an incredible figure), or somewhere in between.

Earlier research has given us no reason to expect a strong association between estrogen replacement and breast cancer.
Hormone Replacement Therapy and Breast Cancer?

**1992**: The first prospective, randomized, controlled study of combination HRT and breast cancer risk is published, reporting that the 22-year administration of estrogen-progestin HRT does not increase the incidence of breast cancer in a group of postmenopausal women.


**1995**: A study published in the Journal of the American Medical Association reports no increased risk of breast cancer in users of postmenopausal HRT even after more than 15 years of use.


- No increased risk of breast cancer when HRT ever users are compared to never users.
- No increased risk of breast cancer even when HRT users for over 10 years are compared to never users.
- Only when HRT users are divided into current users and those who had used HRT in the past and had stopped did the authors find an increased risk of breast cancer, and then only among those who were current users and had been using HRT for at least five years. They find a similar increased risk whether the current users are taking estrogen alone or combination estrogen-progestin.

For patients born under Gemini or Libra there was a slightly adverse effect of aspirin on mortality, while for patients born under all other astrological signs there was a strikingly beneficial effect.

Subgroup analyses should, perhaps, be taken less as evidence about who benefits than as evidence that such analyses are potentially misleading.

“Subset analysis is a common source of misleading conclusions. Whereas it is appropriate to examine subsets, findings should usually be viewed as hypotheses to be tested in independent data.”

“Most clinical investigators and statisticians view subset analysis as generating hypotheses to be tested in other similar studies.”

1996: An article published in Cancer Causes and Control reports that ever use of estrogen replacement therapy is associated with a 16% decreased risk of fatal breast cancer.

Hormone Replacement Therapy and Breast Cancer?

A study published in the Journal of the American Medical Association reports a 40% increased risk of breast cancer associated with HRT administration ...BUT

• No increased risk is seen among past users regardless of duration of use.

• The increased risk is seen only among those still taking the hormones within the previous four years.

• Only 4% of the studied population used combination estrogen and progestin. The remainder were taking estrogen alone.

• The increased risk is limited to those woman who weighed no more than 24.4kg/ m2 (approximately 90 lbs on average).


2000: A retrospective study finds an increased risk of breast cancer among estrogen only users, but only after 15 years of use. A barely significant increased risk of breast cancer among combination estrogen-progestin users is found after 5 years.


2001: A Harvard Medical School review of the literature on the administration of HRT to women with a previous history of treated breast cancer, concludes that thus far HRT has no significant effect on breast cancer recurrence.

July, 2002: The Women’s Health Initiative terminates the estrogen-progestin arm of the study prematurely, because of a reported increased incidence of adverse events, with special attention to an increased risk of breast cancer...BUT

• The increased risk of breast cancer is not statistically significant.
• There was no increased risk of noninvasive breast cancer.
• When the data were stratified according to years of follow-up, the incidence rates of invasive breast cancer were lower among estrogen plus progestin users during years one and two than among those not taking HRT.

“The 26% increase (38 vs 30 per 10,000 person-years) observed in the estrogen plus progestin group almost reached nominal statistical significance”

Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women. Principal Results From the Women’s Health Initiative Randomized Controlled Trial. JAMA 07/17/02;288:1-16.
The WHI investigators terminated the trial after an assessment of the overall risk-benefit ratio of this combined hormone therapy regimen failed to demonstrate a benefit. A statistically significant 26% increase in breast cancer incidence contributed to the overall negative effect of estrogen plus progestin.
and after 5.2 years of follow-up the WHI reported that CHRT was associated with a statistically nonsignificant 26% increase in breast cancer risk.
The latest update of the WHI, after adjustment for multiple factors recognized to influence the risk of breast cancer, found a Hazard Ratio of 1.2 (95% CI 0.94-1.53).

No significant increased risk of breast cancer was observed among study patients randomized to E + P who had no previous exposure to HRT.

Among women randomized to placebo, those who reported prior HRT use had a lower rate of breast cancer than never users.

<table>
<thead>
<tr>
<th>EATING SWEETS</th>
<th>CAVITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3%</td>
</tr>
<tr>
<td>No</td>
<td>2%</td>
</tr>
</tbody>
</table>

Absolute risk: \[3 - 2 = 1\%\]

Relative Risk: \[\frac{1}{2} = 50\%\]

When reporting clinical trials...stating relative risks alone is often deceptive; results should be provided in absolute numbers, not only as percentage changes.

Given their inherent potential for misinterpretation, relative risk measures should generally be avoided in discussions with patients.

The Confidence Interval is a measure of the magnitude of the effect being studied.

The Confidence Interval indicates the strength of evidence.

The Confidence Interval gives a range of uncertainty for estimates of risk.

Fish intake is positively associated with breast cancer incidence rate.
J Nutr 2003;133:3664 - 9
RR = 1.13 (1.03 - 1.23)

French fries - One additional serving per week during preschool years.
Int J Cancer 2006;118:749-54.
RR = 1.27 (1.12 - 1.44)

Antibiotic use in relation to the risk of breast cancer.
RR = 1.45 (1.24 - 1.69)

Icelandic flight attendant and risk of breast cancer.
RR = 4.1 (1.70 - 8.50)

Use of electric bedding devices and risk of breast cancer in African-
American women.
RR = 4.9 (1.5 - 15.6)
One-quarter or more of grapefruit intake per day was associated with a significantly increased risk of breast cancer.

RR = 1.3 (CI = 1.06-1.58)

## Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001, 2005</td>
</tr>
<tr>
<td>FA (Finnish)</td>
<td>1.87</td>
<td>1.15 - 2.23</td>
<td>1995</td>
</tr>
<tr>
<td>Placental Weight</td>
<td>2.05</td>
<td>1.15 - 3.64</td>
<td>2005</td>
</tr>
<tr>
<td>Antibiotic Use</td>
<td>2.07</td>
<td>1.48 - 2.89</td>
<td>2004</td>
</tr>
<tr>
<td>Left Handedness</td>
<td>2.41</td>
<td>1.35 - 4.30</td>
<td>2005</td>
</tr>
<tr>
<td>FA (Icelandic)</td>
<td>4.1</td>
<td>1.70 - 8.50</td>
<td>2001</td>
</tr>
<tr>
<td>Electric Bedding</td>
<td>4.9</td>
<td>1.50 - 15.6</td>
<td>2003</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

“One of the things our brain is designed to do is infer the causal structure of the world from limited information.”

Joshua B. Tenenbaum, an assistant professor in the department of brain and cognitive sciences at MIT, in Lisa Belkin: The Odds of That. NY Times Magazine. August 11, 2002 32-61

“In general, humans tend to have much greater confidence in their knowledge base than is warranted.”

“The lesson here is that if you’re capable of being glib and verbal, the odds are that you have no idea what you’re talking about but it sounds good, whereas if you know a great deal of what you’re saying the odds are you can’t get on a talk show because nobody can understand you.”

In the chapter on Newt Gingrich, Superstar, describing the books that influenced or changed or left an indelible impression on Newt Gingrich, including Two Cultures: Lectures of C. P. Snow In Political Fictions by Joan Didion, Alfred A. Knopf, NY, 2001 p.168
“The prize goes to the loud and the pithy. To be heard, you’re forced to be louder than you want to be, and you’re forced to be more simplistic than your true belief is.”

Helen Petruskas, Ford’s top safety executive, promoted air bags, in an interview with the Detroit News in 2001, at her retirement. Quoted in an LA Times obituary, 03/13/06
Hormone Replacement Therapy and Breast Cancer?

- The incidence of breast cancer is 100 times greater in women than in men.

- The earlier the menarche and the later the menopause, the greater the risk of breast cancer.
Estrogen is not a carcinogen - In a report from the NCI’s Division of Cancer Etiology, published in 1991, analysis of existing data concluded that estrogens are...not direct carcinogens for mammary cells.”


Some investigators have assumed that prolonged stimulation of breast tissue by estrogen is carcinogenic. But, the endometrium is more sensitive to the carcinogenic effects of estrogen than is the breast and if excess carcinogenic effects are the mechanism by which ages at menarche and menopause altered risk, then risk of endometrial cancer should also be related to these events, and it is not.

ER+ cells are not the ones proliferating - In the normal adult tissue, ER+ cells do not express markers of proliferation.


ER expressing cells of the mammary epithelium are distinct from the mammary stem cell population, and the effects of estrogen on mammary stem cells are likely to be mediated indirectly.


The p63 gene, involved in tumor differentiation, is overexpressed in estrogen-progestin users. This gene is expressed in normal tissue, partially expressed in ductal hyperplasia, and not expressed in invasive cancers.

“There is a worrying trend in academic medicine which equates statistics with science and sophistication in quantitative procedures with research excellence.”

“The corollary of this trend is a tendency to look for the answers to medical problems from people with expertise in mathematical manipulation and information technology rather than from people with an understanding of disease and its causes.”

“The seeking of algorithms for scientific decision-making is an offence best described as statistical malpractice.”

“Science is concerned with causes but statistics is concerned with correlations.”

“Statistical analysis is not causal but correlative.”

“The root of most instances of statistical malpractice is the breaking of mathematical neutrality and introduction of causal assumptions into analysis without justifying them on scientific grounds.”

“The difficulty is that statistical analysis is, apparently, applicable to any problem - just give it enough numbers and it will generate an answer. As a result, medicine has been deluged with more or less interpretable ‘answers’ generated by heavyweight statistics operating on big databases of dubious validity. Such numerical manipulations cannot, in principle, do the work of hypothesis testing. Yet this is precisely the use for which they are promoted.”

“Statistical analysis has expanded beyond its legitimate realm of activity. The seductive offer of precision without the need for understanding is a snare to the incautious because exactitude is so often mistaken for explanation.”
“The scientific method consists of the use of procedures designed to show not that our predictions and hypotheses are right, but that they might be wrong. Scientific reasoning is useful to anyone in any job because it makes us face the possibility, even the dire reality, that we were mistaken. It forces us to confront our self-justifications and put them on public display for other to puncture. At its core, therefore, science is a form of arrogance control.”

Tavris C, Aronson E. Mistakes were made (but not by me). Harcourt, Inc. Orlando, 2007 p108.
Bluming AZ. Hormone replacement therapy (HRT) in women with previously treated primary breast cancer. Update XIV. Proc ASCO June, 2008
Observational studies and randomized, controlled trials usually produce similar results.


A report comparing the 20-year validity of conclusions from published clinical studies reported a 20-year validity for:

- non-randomized studies 87%
- randomized trials 85%.

“The mathematically driven apparatus of modern risk management contains the seeds of a dehumanizing and self-destructive technology. Nobel laureate Kenneth Arrow has warned, ‘Our knowledge of the way things work, in society or in nature, comes trailing clouds of vagueness. Vast ills have followed a belief in certainty.’ In the process of breaking free from the past we may have become slaves of a new religion, a creed that is just as implacable, confining, and arbitrary as the old.”

Our lives teem with numbers, but we sometimes forget that numbers are only tools.”

FINIS
Hormone Replacement Therapy: Real Concerns and False Alarms

Avram Z. Bluming, MD and Carol Tavris, PhD

Abstract: From 2002 to 2008, reports from the Women’s Health Initiative (WHI) claimed that hormone replacement therapy (HRT) significantly increased the risks of breast cancer development, cardiovascular events, Alzheimer disease, and stroke. These claims alarmed the public and health professionals alike, causing an almost immediate and sharp decline in the numbers of women receiving HRT. However, the actual data in the published WHI articles reveal that the findings reported in press releases and interviews of the principal investigators were often distorted, oversimplified, or wrong. This review highlights the history of research on HRT, including a timeline of studies that have or have not found a link between HRT and breast cancer; discusses how to distinguish important, robust findings from those that are trivial; closely examines the WHI findings on HRT and breast cancer, most of which are weak or statistically insignificant; reviews the current thinking about possible links of HRT with cardiovascular disease and cognitive functioning; and reports research on the benefits of HRT, notably relief of menopausal symptoms, that affect a woman’s quality of life. On these complicated matters, physicians and the public must be cautious about accepting “findings by press release” in determining whether to prescribe or take HRT.

Key Words: hormone replacement therapy (HRT), estrogens, breast cancer, women’s health initiative (WHI), risk assessment

Received for publication January 5, 2009; accepted January 27, 2009.
Reprints: Avram Z. Bluming, MD, 16313 Ventura Boulevard, Suite 470, Encino, CA 91436. E-mail: avpl@haring.com

Copyright © 2009 by Lippincott Williams & Wilkins
ISSN: 1529-9117(2009)15(2);93-104

DATA DREDGING, RISK REPORTING, AND OTHER PROBLEMS IN RESEARCH

Should women who have menopausal symptoms deny themselves its benefits, whether is the short term or over many years, because they fear breast cancer, heart disease, or stroke? Are their concerns warranted by the data? When we took a close look at the findings in the published WHI articles, placing them in the context of the accumulating evidence, we concluded that the risks were so small as to be negligible.


Addendum

1. Decline of Breast Cancer Incidence.
Hormone Replacement Therapy and Breast Cancer?

A 7% relative decrease in breast cancer incidence was reported between 2002 and 2003 following publication in July 2002 of the Women’s Health Initiative.

A 12% relative decline was reported for women aged 50-69 with ER+ breast cancer during that same time period.

“…the most likely explanation was that some of the tumors were dependent on estrogen and when hormonal therapy was removed, they stopped growing.”

“We think it looks like it is hormones, and that the decrease was due to stopping hormone therapy”.

“We’re not claiming that we proved it - epidemiology can’t show two things are causally related, but there’s a very strong coincidence.”

Rosenthal ET. HRT & breast cancer epidemiological study: More definitive answers by year’s end, says Peter Ravdin. Oncology Times 02/10/07 p17.
“Though the study doesn’t prove a causal link between the drop in hormone usage and the slide in breast cancer rates, it is the only plausible explanation.”

Rowan Chlebowski.
Hormone Replacement Therapy and Breast Cancer?

But…the decline started before 2002

According to the NCI’s Surveillance, Epidemiology, and End Results (SEER) Program:

The incidence of breast cancer per 100,000 caucasian women 50 years and older was:

<table>
<thead>
<tr>
<th>Year</th>
<th>Invasive</th>
<th>Non - invasive (in situ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>412.2</td>
<td>1998 90</td>
</tr>
<tr>
<td>2000</td>
<td>400.6 (3% decline)</td>
<td>2000 89.8</td>
</tr>
<tr>
<td>2002</td>
<td>392.4 (2% decline)</td>
<td>2002 89.8</td>
</tr>
<tr>
<td>2003</td>
<td>352.4 (10% decline)</td>
<td>2003 86.5 (4% decline)</td>
</tr>
</tbody>
</table>
Hormone Replacement Therapy and Breast Cancer?

“If the decreased incidence of breast cancer were due to a decrease in stimulation of subclinical ER+ tumors…the decreased incidence should have been confined to small, early breast cancers. It was not.”

“…the incidence of breast cancer increases with age through menopause, and the majority of postmenopausal breast cancers are ER +.

If the authors’ postulate is correct, the incidence of breast cancer in this population of women, most of whom do not receive HRT, should decrease with age. It does not.”

Addendum

1. Decline of Breast Cancer Incidence.

2. Persistence of Risk 3 Years after Trial was Discontinued.
“Within 3 years of cessation of the trial intervention, both CVD risks and total and hip fracture benefits dissipated, and cancer risks increased. As a result, after a mean f-u of 2.4 years after the intervention, the overall assessment of health risks and benefits associated with CEE + MPA continued to be weighted toward risk, as suggested by an adverse trend in all-cause mortality and the global index.”

“Postintervention mortality from all causes was somewhat higher in women previously assigned to CEE + MPA than in those assigned to placebo (HR 1.15 CI 0.95-1.39), a difference that does not reach nominal statistical significance.”

“During the intervention phase all-cause mortality was almost identical in both arms of the trial. During the postintervention phase, mortality from all causes was higher by 15% in the group originally assigned to CEE + MPA than in those assigned to placebo, although the difference was not statistically significant.”

“The HR for overall risk of all malignancies increased from 1.03 (0.92-1.15) during the intervention phase to 1.24 (1.04-1.48) in the postintervention period.”

Hormone Replacement Therapy and Breast Cancer?

Although more breast cancers were diagnosed in the CEE + MPA group (HR 1.27 (0.91-1.78) after the intervention, (*this difference*) is not statistically significant."

“The apparent excess mortality (*not statistically significant*) in the CEE + MPA vs the placebo group observed during the postintervention phase was accounted for by deaths attributed to various cancers unrelated to the prespecified trial outcomes, most prominently lung cancers.”

Addendum

1. Decline of Breast Cancer Incidence.

2. Persistence of Risk 3 Years after Trial was Discontinued.

3. HABITS Study
39 of the 221 (17.6%) women in the HT arm and
17 of the 221 (7.7%) women in the control arm experienced a
new breast cancer event. (HR = 2.4 [1.3-4.2]).

The majority of first events in the HT arm were local recurrences
or contralateral breast cancers.
The absolute number of distant metastases as first event was
similar in the two arms.

Median follow-up was 4 years.

Did not control for size of primary tumor, # of involved nodes

Holmberg L, Iversen O-E, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J,
Increased risk of recurrence after hormone replacement therapy in breast cancer
Addendum

1. Decline of Breast Cancer Incidence.

2. Persistence of Risk 3 Years after Trial was Discontinued.

3. HABITS Study

4. WECARE Study
OC use after breast cancer diagnosis was not significantly associated with risk of contralateral cancer. (RR 1.56 CI = 0.71-3.45)

HRT use after breast cancer diagnosis was not significantly associated with risk of contralateral cancer. (RR 1.10 CI = 0.67-1.77)

Neither duration nor type of HRT were associated with increased risk.

### Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

---

The Women’s Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women’s Health Initiative Randomized Controlled Trial. JAMA 2004;291:1701-12
**Risk Factors Associated with the Development of Breast Cancer**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

## Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

### Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001,2005</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>


## Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001, 2005</td>
</tr>
<tr>
<td>FA (Finnish)</td>
<td>1.87</td>
<td>1.15 - 2.23</td>
<td>1995</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

# Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001,2005</td>
</tr>
<tr>
<td>FA (Finnish)</td>
<td>1.87</td>
<td>1.15 - 2.23</td>
<td>1995</td>
</tr>
<tr>
<td>Placental Weight</td>
<td>2.05</td>
<td>1.15 - 3.64</td>
<td>2005</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

## Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001, 2005</td>
</tr>
<tr>
<td>FA (Finnish)</td>
<td>1.87</td>
<td>1.15 - 2.23</td>
<td>1995</td>
</tr>
<tr>
<td>Placental Weight</td>
<td>2.05</td>
<td>1.15 - 3.64</td>
<td>2005</td>
</tr>
<tr>
<td>Antibiotic Use</td>
<td>2.07</td>
<td>1.48 - 2.89</td>
<td>2004</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

## Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001,2005</td>
</tr>
<tr>
<td>FA (Finnish)</td>
<td>1.87</td>
<td>1.15 - 2.23</td>
<td>1995</td>
</tr>
<tr>
<td>Placental Weight</td>
<td>2.05</td>
<td>1.15 - 3.64</td>
<td>2005</td>
</tr>
<tr>
<td>Antibiotic Use</td>
<td>2.07</td>
<td>1.48 - 2.89</td>
<td>2004</td>
</tr>
<tr>
<td>Left Handedness</td>
<td>2.41</td>
<td>1.35 - 4.30</td>
<td>2005</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

### Risk Factors Associated with the Development of Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001, 2005</td>
</tr>
<tr>
<td>FA (Finnish)</td>
<td>1.87</td>
<td>1.15 - 2.23</td>
<td>1995</td>
</tr>
<tr>
<td>Placental Weight</td>
<td>2.05</td>
<td>1.15 - 3.64</td>
<td>2005</td>
</tr>
<tr>
<td>Antibiotic Use</td>
<td>2.07</td>
<td>1.48 - 2.89</td>
<td>2004</td>
</tr>
<tr>
<td>Left Handedness</td>
<td>2.41</td>
<td>1.35 - 4.30</td>
<td>2005</td>
</tr>
<tr>
<td>FA (Icelandic)</td>
<td>4.1</td>
<td>1.70 - 8.50</td>
<td>2001</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.77</td>
<td>0.59 - 1.01</td>
<td>2004</td>
</tr>
<tr>
<td>Fish Intake</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>2003</td>
</tr>
<tr>
<td>PremPro</td>
<td>1.24</td>
<td>1.01 - 1.54</td>
<td>2003</td>
</tr>
<tr>
<td>French Fries</td>
<td>1.27</td>
<td>1.12 - 1.44</td>
<td>2006</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1.30</td>
<td>1.06 - 1.58</td>
<td>2007</td>
</tr>
<tr>
<td>Night Shift Work</td>
<td>1.51</td>
<td>1.36 - 1.68</td>
<td>2001, 2005</td>
</tr>
<tr>
<td>FA (Finnish)</td>
<td>1.87</td>
<td>1.15 - 2.23</td>
<td>1995</td>
</tr>
<tr>
<td>Placental Weight</td>
<td>2.05</td>
<td>1.15 - 3.64</td>
<td>2005</td>
</tr>
<tr>
<td>Antibiotic Use</td>
<td>2.07</td>
<td>1.48 - 2.89</td>
<td>2004</td>
</tr>
<tr>
<td>Left Handedness</td>
<td>2.41</td>
<td>1.35 - 4.30</td>
<td>2005</td>
</tr>
<tr>
<td>FA (Icelandic)</td>
<td>4.1</td>
<td>1.70 - 8.50</td>
<td>2001</td>
</tr>
<tr>
<td>Electric Bedding</td>
<td>4.9</td>
<td>1.50 - 15.6</td>
<td>2003</td>
</tr>
<tr>
<td>Tobacco &amp; Lung</td>
<td>26.07</td>
<td>6.58 - 103.3</td>
<td>2002</td>
</tr>
</tbody>
</table>