The Controversy over Hormone Replacement Therapy:
Evaluating Related Risk of Breast Cancer and Other Diseases

By William P. Kucewicz

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The Controversy over Hormone Replacement Therapy: Evaluating Related Risk of Breast Cancer and Other Diseases

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Introduction

Judgment calls are inescapable in the practice of medicine. Physicians and patients must choose among different courses of treatment based on imperfect knowledge and incomplete information. Medical practitioners do their best with what's available. That's the way it is and presumably always will be. What then are we to make of the misinterpretation or misrepresentation of research data that leads to erroneous conclusions and misinforms doctors and their patients as to the best course of treatment?

An example of just such a case is explored in a highly revealing article, “Hormone Replacement Therapy: Real Concerns and False Alarms” by Avrum Z. Bluming, M.D. and Carol Tavris, Ph.D., published in The Cancer Journal. In recent years, concerns have been raised about the possibility that hormone replacement therapy (HRT) significantly increases the risk of breast cancer, cardiac events, Alzheimer disease, and stroke. Apparently alarmed by the claims, the numbers of women receiving HRT declined by about half following the initial reports of a possible link beginning in 2002. (Hersh 2004) After reviewing the pertinent research data, however, Bluming and Tavris come to a startling and important conclusion – namely, that the reported findings that have been the source of so much concern were, in fact, “often distorted, oversimplified, or wrong.” And among those disseminating the alarmist information was the very institution conducting the HRT studies. (Bluming-Tavris 2009)

Dr. Bluming is a Master of the American College of Physicians, a Clinical Professor of Medicine at the University of Southern California, a former senior investigator for the National Cancer Institute and an oncologist in private practice. Dr. Tavris is a social psychologist, writer, and lecturer, fellow of the Association for Psychological Science, co-author of two leading psychology textbooks, and, most recently, of Mistakes Were Made (But Not by Me), with Elliot Aronson. The full text of their article, written at the suggestion of the American Council of Science and Health, whose panel of reviewers provided feedback to the authors, is available online for free from The Cancer Journal at:

and in PDF format at
What Is Hormone Replacement Therapy?

HRT specifically refers to the administration of estrogen, or estrogen plus progestin, to women who have reached menopause. Beginning in the 1950s, a growing belief among women and their physicians held that “replacing” the estrogen lost at menopause would prevent many of the manifestations of aging, including coronary heart disease, osteoporotic fractures, and declines in cognitive and sexual function. This “attractive and plausible view” led to widespread use of hormone therapy after menopause. (Hulley-Grady 2004)

Women who still have a uterus most commonly receive estrogen combined with progestin, because as far back as 1975 it was found that estrogen, taken alone, increases the risk of uterine cancer. This heightened risk is eliminated when progestin is added. Women who have had hysterectomies are therefore usually the only ones administered estrogen alone (a treatment known as Estrogen Replacement Therapy, or ERT). (USFDA 2004, Bluming-Tavris 2009)

HRT has been found to be highly effective in alleviating the most common symptoms associated with menopause, including so-called “hot flashes,” night sweats, palpitations, insomnia, frequent or uncomfortable urination, emotional upset, and painful sexual intercourse. (Greendale 1998) Most American women do not take any form of HRT during or after menopause. But of those who do, most take it for less than five years. (Cauley 1990, Brett-Madans 1997, Keating 1999) Symptoms typically associated with menopause are common in elderly women. In some women, hot flashes and other symptoms attributed to menopause persist for many years after the cessation of menses. HRT has been found to reduce many of these symptoms, too. (Barnabei 2002)

HRT is sometimes prescribed to women at high risk of developing osteoporosis -- a disease that makes bones prone to fracture -- because estrogen lowers the incidence of osteoporotic hip fracture by 25 percent to 50 percent. (Cauley 1995) Other medications also offer similar protective benefits, and those are often recommended by physicians over HRT. (Bluming-Tavris 2009) Hormone therapy is also administered in cases of sex reassignment.

The Risk of Breast Cancer

In industrialized countries, breast cancer is the second-leading cause of cancer-related deaths among women (following lung cancer), and it is estimated that 1 in every 8 women will develop the disease during their lifetimes. Among the factors associated with an increased risk of breast cancer are age, early age at menarche, late menopause, height, post-menopausal obesity, and family history of breast cancer. (Nkondjock 2005)

Most cases of breast cancer, the most common cancer among women, are probably related
to lifestyle or environmental factors, including diet and physical activity. Genetic susceptibility accounts for only an estimated 5 percent to 10 percent of breast cancer cases. Proper diet and regular physical activity may decrease the risk of death from this cancer. (Stasiołek 2002)

The International Agency for Research on Cancer estimates that 25 percent of breast cancer cases worldwide are related to obesity and a sedentary lifestyle. The preponderance of epidemiologic studies indicates that women who engage in 3 hours to 4 hours per week of moderate to vigorous levels of exercise have a 30 percent to 40 percent lower risk for breast cancer than do sedentary women. Women who are overweight or obese have a 50 percent to 250 percent greater risk for postmenopausal breast cancer. And alcohol use, even at moderate levels of two drinks per day, increases risk for both premenopausal and postmenopausal breast cancer. (McTiernan 2003)

These and other findings suggest a potential for prevention. The incidence of breast cancer between countries varies by more than sixfold, indicating that lifestyle or environmental factors likely play a role in the development of the disease. Immigrants moving from low-incidence areas to high-incidence ones show an increasing incidence of breast cancer. The rate increased almost fivefold in the course of a generation among Poles who migrated to California from low incidence areas. It doubled among Chinese and Japanese who moved to California. (Vatten 1991)

**HRT and the Women's Health Initiative**

The Women’s Health Initiative (WHI) launched in 1991, is described as a long-term national health study that has focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. Its clinical trials were designed to test the effects of postmenopausal hormone therapy, diet modification, and calcium and vitamin D supplements on heart disease, fractures, and breast and colorectal cancer. Its investigators are comprised of eminent physicians, statisticians, and epidemiologists from across the country. The original WHI study, sponsored by the National Institutes of Health, included 161,808 postmenopausal women between the ages of 50 and 79, enrolled between 1993 and 1998. The original cohort was followed until March 2005, after which participants were invited to enroll in the WHI Extension Study for follow-up through 2010. As of August 2007 there were 115,400 women enrolled in the Extension Study. (WHICCC 2009)

The tocsins began to sound in 2002 with the first publication of results from the WHI, claiming to have found a statistical connection between HRT and breast cancer, as well as between HRT and heart disease and stroke. On May 31, 2002, after a mean of 5.2 years of follow-up, the WHI’s data and safety monitoring board recommended stopping the trial of estrogen plus progestin because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding
benefits. (Rossouw 2002)

The estrogen plus progestin arm of the WHI randomized controlled trial had a planned duration of 8.5 years. It had recruited 16,608 postmenopausal women aged 50 to 79 years with an intact uterus at 40 U.S. clinical centers in 1993 to 1998. (Rossouw 2002) In commenting on the decision to stop the combined estrogen and progestin trial, Claude Lenfant, M.D., director of the National Heart, Lung, and Blood Institute of the National Institutes of Health, said, “The cardiovascular and cancer risks of estrogen plus progestin outweigh any benefits, and a 26 percent increase in breast cancer risk is too high a price to pay, even if there were a heart benefit.” (NIH 2002),

Quite remarkably, however, the WHI researchers admit in their published report that the increased risk of breast cancer said to be associated with the use of HRT in the trial was not statistically significant. The invasive breast cancer rates in the placebo group were consistent with design expectations. The 26 percent increase (38 vs 30 per 10000 person-years) observed in the estrogen plus progestin group almost reached nominal statistical significance and, as noted herein, the weighted test statistic used for monitoring was highly significant. No significant difference was observed for in situ breast cancers. Follow-up rates for mammography were comparable in the estrogen plus progestin and placebo groups. Colorectal cancer rates were reduced by 37% (10 vs 16 per 10000 person-years), also reaching nominal statistical significance. Endometrial cancer incidence was not affected, nor was lung cancer incidence (54 vs 50; HR, 1.04; 95% CI, 0.71-1.53) or total cancer incidence. (Rossouw 2002)

Then, in 2004, the WHI reports no increased risk of breast cancer associated with the use of estrogen alone. Matter of fact, preliminary results of the estrogen-alone study suggested a possible reduction in breast cancers. The trial was stopped early, however, because of an increased stroke incidence and no reduction in risk of coronary heart disease in postmenopausal women with prior hysterectomy over an average of 6.8 years. (WHISC 2004)

The WHI investigators later reported in 2006 that treatment with estrogen alone, even after more than 7 years, does not increase breast cancer incidence in postmenopausal women with prior hysterectomy. The report reaffirmed the WHI's 2004 finding of no increased risk of breast cancer from ERT use. (Stefanick 2006)

The U.S. Preventive Services Task Force of the U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality, however, has since recommended against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women and also against the routine use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. The group made the recommendations even though it conceded that results from two “good-quality” cohort studies (Colditz 1995, Sellers 1997) conflict on the effects of long-term hormone therapy on breast cancer mortality and that the U.K. Million Women Study
(Beral 2003), upon which it bases its recommendations, in part, is only a “fair-quality” study whose own “results are conflicting.” (USPSTF 2005)

One of the “good-quality” studies cited by the task force shows, in fact, that women diagnosed with breast cancer while taking HRT have been reported to have a better prognosis, regardless of what stage their cancer was in, than women diagnosed in the absence of HRT. (Sellers 1997) In comparison, the other cited “good-quality” study found that the risk of breast cancer increased significantly only among women currently using hormone therapy who had used such therapy for five or more years. However, it also found that women who had formerly used hormone therapy had no significant increase in risk as compared with women who had never used hormone therapy; this was true even for women who had taken hormones for five or more years in the past. (Colditz 1995)

**Problems in Risk Reporting**

Bluming and Tavris decided to take a close look at the WHI articles that had caused such a stir in the news media and that had concerned so many patients and physicians. They began by placing the WHI findings within the context of research carried out over decades on HRT, and what they discovered was disturbing: “[W]e were surprised by the enormous discrepancy we found between the belief that hormones are dangerous and the lack of supporting data.” (Bluming-Tavris 2009)

The authors home in on two particular errors concerning the WHI statistics. The first involves the basic question of how to present statistical data. Here, the problem concerns the difference between absolute and relative risk. While one representation of risk might arouse grave concern, the other may show the concern to be unfounded. Imagine a case were the numbers of women found to have developed breast cancer rose from 1 in 10,000 to 3 in 10,000. In relative terms, that's an increase of 200 percent, but in absolute terms, the increase is so small (i.e., only 2 cases in 10,000) that it is very likely nothing more than a random artifact (i.e., an artificial product of the study's methodology). If, however, the number of breast cancer cases rose from, say, 100 in 10,000 to 300 in 10,000 -- also a 200 percent increase -- such a large increase in absolute terms from the baseline number (i.e., 200 additional cases in 10,000) might reasonably be cause for concern. (Bluming-Tavris 2009)

Or consider another example of relative versus absolute risk provided by the authors: What if it is shown that 3 percent of chocolate eaters develop cavities, and 2 percent of non-chocolate eaters also develop cavities? In relative terms, that's a whopping 50 percent increase in cavities among chocolate eaters compared with non-chocolate eaters. In absolute terms, though, the increase is far less dramatic, for the results show a chocolate eater risk of developing cases rises to 3 in 100 from a baseline of 2 in 100. That surely wouldn't seem an inordinate risk for a chocolate lover to take. (Bluming-Tavris 2009)
“A reliance on relative risks can . . . create misleading, faulty comparisons,” Bluming and Tavris note, adding: “Many of the studies of HRT and risk of disease, especially breast cancer, have produced statistically modest or borderline results that have been made to look more impressive than they actually are by reporting them as relative risks.” (Bluming-Tavris 2009)

To illustrate their point, the authors compiled a list of a whole host of studies purporting to demonstrate a correlation between one or another supposed risk factor and the development of breast cancer. The selected risk factors include birth weight, fish intake, eating an additional serving of French fries per week as a preschooler, eating grapefruit, working the night shift, working as an airline flight attendant, suffering from severe caloric restriction during the 1944–1945 Dutch famine of World War II, taking antibiotics, and the use of electric blankets by African-American women. Not only are the relative risks very low in almost all these cases, but the use of HRT is seemingly less risky than, for instance, eating fish or grapefruit, using antibiotics, or being a flight attendant. (Bluming-Tavris 2009)

'Data Dredging' and Its Flaws

The other fault with the WHI reports cited by the authors is a questionable analytical technique often referred to as “data mining,” or “data dredging.” More formally known as “retrospective substratification” or “ex post facto subgroup analysis,” the practice involves a retrospective, or backwards, look at data that emerge from a prospective study. This usually is done in hopes of finding a “significant” risk factor that wasn't part of the study's original hypothesis. (Bluming-Tavris 2009)

Researchers, inappropriately, sometimes employ this technique after failing to find the statistically significant association that they had initially hypothesized when they first framed the study. Refusing to take “no” for answer, so to speak, these researchers sift through their data, hoping to spot a connection, however tenuous it may be, between one factor or another and the subject of the investigation. (Bluming-Tavris 2009)

Such data dredging has several serious flaws. A major one involves the element of chance. As Bluming and Tavris say, “[I]n a data set of many thousands of people, some relationship that is unearthed retrospectively will turn out to be statistically significant (i.e., P < 0.05) just by chance.” (Bluming-Tavris 2009)

Another flaw is poor methodology. In the hunt for interesting subgroups that may offer something “significant,” the principles of good experimental methodology are cast aside. This immediately calls into question the veracity of any “mined” findings. What is more, by accepting the “significant” results uncovered by data dredgers, other researchers may be
misled into expending scare resources on a wild goose chase, while other, more fruitful avenues of investigation are left unexplored. (Rao 2008)

A 'Jumble' of Conflicting Results

Finding that the relationship between HRT and breast cancer is still unclear, despite a vast amount of research over many decades, Bluming and Tavris painstakingly assembled a timeline of relevant events and key studies, dating from the first manufacture of estrogen tablets (with the trade name of Premarin) in 1942 to the recent HRT studies published in 2008. The authors describe their list as “a jumble of positive findings, negative findings, and meaningless findings.” Most important, they proceed to address the crucial question of why the results regarding HRT and breast cancer are so mixed and contradictory. (Bluming-Tavris 2009)

The reason for the seemingly contradictory findings appears to lie in the statistical interpretation of the clinical results and not in the results themselves. Again, it is the result of the inappropriate retrospective substratification, or mining, of the data. Bluming and Tavris bluntly state that “when you get results from retrospective analysis, rather than as a premeditated focus of investigation under controlled conditions, the findings are likely to be confusing, unreplicated in subsequent studies, and biologically improbable. . . . And that is the picture we get of the relationship between HRT and breast cancer.” (Bluming-Tavris 2009)

The authors offer a host of examples of seemingly manufactured findings, and one in particular stands out. It involves a 2000 study that used data mining and purports to have found a 40% increased risk of breast cancer associated with HRT. “It took some determination to get that result,” Bluming and Tavris impishly note, “because the increased risk applied only to women weighing not more than 90 pounds.” (Schairer 2000, Bluming-Tavris 2009)

The WHI Reports in Context

When the WHI's reports are placed within the context of decades of research on HRT, the findings of an alleged connection with breast cancer appear even more tenuous, if not dubious. Take as an example the very first prospective, randomized, double-blind study of women on HRT and breast cancer risk. The 22-year administration of estrogen-progestin did not increase the incidence of breast cancer in this small group of 84 pairs of continuously hospitalized postmenopausal women After the initial 10 years, the incidence of breast cancer in the placebo group was 4.8 percent, whereas no cancers were found in the HRT group. After an additional 12 years of follow-up, the overall incidence of breast cancer in the women who had never taken hormone replacement therapy was 11.5 percent, whereas no breast
cancers had developed in the women who had ever taken HRT. (Nachtigall 1992)

A study published in 1995 of slightly more than 1,000 middle-aged women (50 to 64 years) in western Washington State found on the whole that the use of estrogen with progestin HRT does not appear to be associated with an increased risk of breast cancer. Compared with nonusers of menopausal hormones, those who used estrogen-progestin HRT for 8 or more years had, if anything, a reduced risk of breast cancer. (Stanford 1995)

Similar results were found in another, much larger prospective cohort study of 41,837 female Iowan women 55 to 69 years of age designed to determine whether HRT is associated with increased risks for breast cancer and total mortality in women with a family history of breast cancer. The data suggest that HRT use in women with a family history of breast cancer is not associated with a significantly increased incidence of breast cancer but is associated with a significantly reduced total mortality rate. The age-adjusted annual mortality rate for women using HRT for at least 5 years was 46 deaths per 10,000 person-years, or roughly half the rate seen in women who had never used HRT. (Sellers 1997)

Or consider one of the very latest studies of HRT, published in 2008 in the prestigious Journal of the National Cancer Institute. An observational study of 472 postmenopausal women with a genetic predisposition to breast cancer (i.e., BRCA1 mutations), the research finds that hormone use, either as HRT or ERT, is not associated with an increased risk of breast cancer. On the contrary, the research finds hormone use is associated with a decreased risk of breast cancer. (Eisen 2008) The finding is important, as Bluming and Tavris note, for it supports an earlier large-scale study -- and its own follow-up -- that found the risk of breast cancer remained low in women with BRCA1 mutations following surgical removal of the ovaries and administration of estrogen (Rebbeck 1999, Rebbeck 2005, Bluming-Tavris 2009)

The use of oral contraceptives also sheds light on the question of estrogen and breast cancer. Birth control pills in fact used to contain more estrogen than HRT does (Bluming-Tavris 2009). Yet while the issue remains controversial, most studies have found oral contraception are not associated with an overall increased risk of cancer. (Marchbanks 2002, Davidson 2002, Silvera 2005, Hannaford 2007)

Most observational (or nonrandomized) studies, moreover, have similarly found no increased risk of breast cancer associated with HRT, even when the hormones are given to women with a family history of breast cancer. Furthermore, as Bluming and Tavris point out, both randomized and non randomized studies have their strengths and their weaknesses. The most important thing to consider is the overall pattern of evidence rather than any single study. And here, the evidence favors the view that HRT doesn't present an increased risk of breast cancer. (Bluming-Tavris 2009)

Observational studies are not, of course, the same as prospective, randomized, controlled studies, which are considered the “gold standard” of epidemiological trials. But the difference
in results between these two methods of investigation may not be all that great. A partially randomized trial conducted in 720 German breast cancer patients between 1984 and 1997 offered a unique opportunity to contrast results from the nonrandomized portion of the study with those for a randomized subcohort as a reference. An analysis, published last year in the *American Journal of Epidemiology*, finds essentially no difference between the two, which suggests not only that evidence from nonrandomized observational studies is relevant but also that these results may be more accurate and reliable than previously thought. (Schmoor 2008)

**A Drop in Breast Cancer Rates and HRT**

The propensity to condemn HRT in reference to breast cancer is nowhere more evident than in the claim by some investigators that a decline in breast cancer rates in 2003 could be attributed to the fall in HRT use in 2002 following publication of the first WHI report positing a link between hormone use and breast cancer. (Ravdin 2007, Stewart 2007, Jemal 2008) Surely, these researchers were aware of the length of time it takes for a malignant cell to develop into a clinically detectable breast cancer. Estimates range from 2 to 26 years, with an average of about 8 years. (Gershon-Cohen 1963, Speer 1984, von Fournier, 1985)

As Bluming and Tavris themselves say, “It is difficult to understand how a decrease in HRT use would be reflected in a decrease in breast cancer rates within a year.” (Bluming-Tavris 2009) Yet even the latest “Annual Report to the Nation on the Status of Cancer, 1975–2005,” compiled by the American Cancer Society, makes the claim that sharp declines in breast cancer incidence in 2002–2003 followed reduced HRT use. “The decline in breast cancer incidence attributed to HRT use is particularly notable,” the report states, “because of the short lag time between changes in exposure and resulting changes in incidence.” (Jemal 2008)

The explanation for the reported decline in breast cancer may indeed have nothing to do with HRT use. As the authors of the American Cancer Society’s annual report on cancer in the United States freely admit, “Changes in use of mammography may have also contributed to recent declines in breast cancer incidence trends that began in 1999. The prevalence of recent mammography began to stabilize or decline in the late 1990s after increasing for many years; this trend may have contributed to the decline in incidence, due to decreased detection or reduced number of undiagnosed prevalent cancers.” (Breen 2007, Li 2007, Jemal 2008)

It is significant that the declines in breast cancer incidence trends began in 1999, for that was years before the WHI published its initial reports on HRT and breast cancer. (Rossouw 2002) Because the breast cancer incidence rate began decreasing before 2002 (i.e., before the decrease in HRT use), other factors (e.g., differences in risk-factor prevalence, diet, and lifestyle) might be used to explain changes in breast cancer incidence rates, the Centers for
Disease Control and Prevention acknowledges, adding that mammography screening rates also might influence breast cancer incidence. (Stewart 2007)

**What of HRT and Heart Disease and Stroke?**

Bluming and Tavris furthermore look at two other medical conditions sometimes associated with HRT -- specifically, the risk cardiovascular disease and stroke. Cardiovascular concerns may be warranted, they find, although largely among women who are at an elevated risk of heart disease or who begin HRT in their mid-60s. The evidence connecting HRT and stroke is more elusive. (Bluming-Tavris 2009)

Following an exhaustive examination of the evidence, the authors reach three principal conclusions regarding HRT and heart disease:

- HRT may have beneficial effects on the heart for women who start taking hormones early in menopause (around age 50), because estrogen promotes healthy blood vessels and may help delay the formation of plaque.
- HRT probably has no protective effect on women who begin the use of HRT later, in their mid-60s.
- HRT is potentially risky for women who begin taking it in their 60s, at least for the first year, especially if they have pre-existing artery disease. (Bluming-Tavris 2009)

These conclusions are generally supported by an independent review of the recent literature, which finds that the differences in age at initiation and the duration of HRT are key points. The review finds that HRT appears to decrease coronary disease in younger women, near menopause; yet, in older women, HRT increases risk of a coronary event. (Palacios 2008)

Hormone therapy may indeed have different effects on blood vessels if it is started early in menopause as opposed to later, according to a recent American Heart Association-funded study. “Abnormal endothelial function is a marker of early heart disease. We have found that endothelial function is just as good, if not slightly better, among women who have risk factors for heart disease and have taken hormone therapy around menopause onset as it is among women who are about the same ages but have no risk factors for heart disease and are not taking hormone therapy,” said James Arrowood, M.D., lead author of the study and associate professor of internal medicine and cardiology at Virginia Commonwealth University Medical Center in Richmond, Va. (AHA 2008)

“Overall,” Bluming and Tavris state, “we share the conclusion of most cardiologists: there is no reason for women to take hormones primarily to help forestall or prevent cardiovascular disease, given that there are other effective ways of reducing heart-disease risk.” (Bluming-Tavris 2009)
As for the risk of stroke, the authors point to a revealing 2006 epidemiological investigation of the “pitfalls” of the WHI analysis. In 2004, the WHI announced it was stopping the estrogen-only arm of the study because the use of estrogen increased the risk of nonfatal stroke by 12 per 10,000 women per year. (Stefanick 2006) However, the WHI investigators had an extremely broad definition of “stroke,” including transient, “subtle neurologic deficits” that resolved in a day or two. (Bluming-Tavris 2009)

This small apparent increase was artificially introduced by a “detection bias” -- that is, women on HRT, having been made so sensitive to possible adverse effects of hormones, had become “hyperalert” to any symptoms. Indeed, a re-analysis of the WHI's findings that controlled for detection bias found no increased risk of stroke. These same outside investigators also found that the use of estrogens was not correlated to an increase of either breast cancer incidence or cardiovascular disease. Instead, a closer look at the results of the WHI trial reveals that the use of HRT for 5 years should not be considered deleterious for the appearance of breast cancer, cardiovascular diseases, strokes, and pulmonary embolisms. (Mastorakos 2006, Bluming-Tavris 2009)

Lessons of the HRT Controversy

Bluming and Tavris don’t mince words in criticizing WHI researchers for their apparent anti-HRT bias: “It is difficult to resist the conclusion that the WHI investigators have been doing everything they could to wring the bleakest possible interpretation from their recalcitrant data. They do not even acknowledge the single greatest benefit of HRT: its relief of menopausal symptoms.” Fact is, most symptomatic menopausal women begin to feel better in less than a week after starting HRT. (Bluming-Tavris 2009)

If, as the study by A. Eisen, et al. of the Hereditary Breast Cancer Clinical Study Group finds, HRT and ERT actually lessen the risk of breast cancer, even among women genetically predisposed to the disease, then any effort to skew the WHI data, either through misinterpretation or misrepresentation tending to reject the use of estrogen, or estrogen plus progestin, does an extreme disservice to the women not only of this country but the world. The WHI findings that the risks of treatment outweigh the benefits had a rapid and sustained impact on HRT utilization in a large population of Israeli women, for example (Silverman-Kokia 2009), and similar patterns are likely to be found elsewhere.

Studies should not mislead. Otherwise, they can adversely affect both clinical practice and future research. A review published in 2002 as a follow-up to a 1994 article found that poor methodology and reporting are widespread and that many published reports of randomized controlled trials are poor or even wrong. Peer review can and should weed out serious methodological errors. However, expert methodological input is in short supply. Only a third of
high-impact journals reported statistical review of all published manuscripts. The vast majority of research is published in low-impact journals, where peer review is less thorough. (Altman 2002)

In the general matter of statistical reporting, it is essential that researchers provide to the news media and to their professional peers both relative percentages and the baseline of absolute numbers upon which the percentages are calculated. Only in this way can physicians and patients assess actual versus inflated risk associated with alternative forms of therapy. Studies that have looked into the reporting of clinical trials indeed have found that portraying risk in relative terms alone can be deceptive and misleading. (Altman 2001, Moher 2001, Gigerenzer 2008)) Only with the reporting of the absolute numbers can the significance of any percentage change be properly interpreted and understood.

Members of the Lifestyle, Environment and Cancer Group of the International Agency for Research on Cancer in Lyon, France recently weighed in on the matter of “false-positive” results in cancer research and made a plea for “epistemological modesty” in the Journal of the National Cancer Institute:

False-positive results are inherent in the scientific process of testing hypotheses concerning the determinants of cancer and other human illnesses. Although much of what is known about the etiology of human cancers has arisen from well-conducted epidemiological studies, epidemiology has been increasingly criticized for producing findings that are often sensationalized in the media and fail to be upheld in subsequent studies. . . . Increased epistemological humility regarding findings in epidemiology would go a long way to diminishing the detrimental effects of false-positive results on the allocation of limited research resources, on the advancement of knowledge of the causes and prevention of cancer, and on the scientific reputation of epidemiology and would help to prevent oversimplified interpretations of results by the media and the public. (Boffetta 2008)

It is encouraging that the authors of the article do not lay all the blame for sensationalized reporting of medical or scientific results on the news media, but rather place most of the responsibility on the shoulders of the scientific and medical community, who after all are the ones devising the studies, conducting them, and then reporting on their results. If the results are distorted, misleading, or otherwise prone to misinterpretation, surely the fault lies not with the reporters covering the story but with those charged with compiling, interpreting, and disseminating the findings.

The HRT controversy also serves to underscore a very astute observation made by Richard P. Feynman, a Nobel Laureate in physics. He suggests an excellent test for truth in science, positing: “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.”
(Feynman 1998) His words are a reminder of one of the hallmarks of the scientific method – namely, verification through replication. Repeated observation and testing are required to ensure a finding's correctness. The aim of science, after all, isn't to come up with an answer; it's to come up with the correct answer. Unfortunately, in the chase for grant money, publication, and promotion, researchers can sometimes lose sight of this essential tenet of science.

Finally, as for whether or not menopausal women should avail themselves of HRT, Bluming and Tavris are clear in their conclusions: “Women in menopause who have symptoms that seriously affect the quality of their lives should feel secure in taking HRT at the start of menopause and for as many years after as they must to control those symptoms. Any woman worried about her health and longevity should quit smoking before she quits hormones, and have screening mammograms and colonoscopies while she is at it.” (Bluming-Tavris 2009)

References


The Women's Health Initiative Clinical Coordinating Center (WHICCC 2009), Fred Hutchinson Cancer Research Center, website, 2009.