The news that part of the Women's Health Initiative (WHI) was stopped early because women treated with combined estrogen-progestin therapy experienced higher rates of breast cancer, cardiovascular disease, and overall harm has rocked women and physicians across the country. But the most important part of this story has received little attention: why did the medical and research community ever believe that hormone replacement therapy (HRT) prevented or treated disease? Not a single controlled trial has ever shown that HRT prevented cardiovascular disease, stroke, Alzheimer's disease, or wrinkles, nor that it was an effective treatment for depression or incontinence. For decades, physicians have acted as an unwitting volunteer sales force for pharmaceutical companies that have promoted HRT for disease prevention in the complete absence of controlled trials supporting this claim.

Advertising and detailing have been only a small part of this campaign; far more effective is the hidden influence that pharmaceutical companies have on the information that physicians receive through continuing medical education activities, where the benefits of HRT had been espoused for decades.

**Cardiovascular Disease Prevention Claims**

Perhaps the most successful marketing campaign convinced physicians that HRT prevented cardiovascular disease before one single clinical trial with cardiovascular disease end points had ever been done. Even after the first randomized controlled trial of HRT with actual disease end points—the Heart and Estrogen/Progestin Replacement Study (HERS)—failed to show a benefit of HRT in women with heart disease, pharmaceutical companies persuaded physicians that HERS actually showed a benefit. More cardiovascular events occurred in the first and second years, but fewer in the third and fourth years; ergo, hormones just needed time to exert protective effects, and women should not stop taking them for cardioprotection. This astounding interpretation ignored the fact that cumulative cardiovascular events were similar between the treated and control groups; so women were protected from having cardiovascular events in the later years only by having those events earlier.

Pharmaceutical companies also argued that women with cardiovascular disease had dysfunctional cardiovascular systems that were too ravaged to respond appropriately to hormonal assistance, but that healthy women still would be expected to benefit.

Many presentations at medical meetings mentioned HERS only after a series of slides emphasized that observational studies showed that taking estrogen or estrogen plus progestin protected women against heart disease. It is true that several observational studies have shown that women receiving hormones had less cardiovascular disease than women not receiving hormones. However, observational studies can never prove benefit because the choices that distinguish the groups may be markers for other choices or circumstances that affect disease. This was certainly true for estrogen. Several studies indicated that women taking estrogen had fewer cardiovascular risk factors to begin with, and they were more likely to make lifestyle changes...
that reduce cardiovascular disease risk than were nonusers.

Nonusers may have had more heart disease than hormone users because in the good old days, physicians avoided giving high-risk women estrogen because of its known thrombogenic effects. Hormone replacement therapy was a marker, not a cause, of reduced cardiovascular risk, and that information has been available in the medical literature for a decade. Another problem with retrospective observational studies is that they miss deaths that have already occurred, resulting in a falsely optimistic view of the health of hormone survivors.

A common tactic used by hormone promoters was to emphasize selected surrogate measures from human studies so that the hypocholesterolemic effects and arterial dilation caused by estrogen were emphasized to clinicians. Hormone promoters remained silent about HRT’s known thrombogenic and triglyceride-increasing effects.

Compelling evidence from randomized controlled trials now exists that shows that HRT does not benefit women with cardiovascular disease and may harm healthy women. The WHI, a very large National Institutes of Health–funded series of studies, includes randomized controlled trials of several interventions on many disease end points. Interventions tested were administration of estrogen (in hysterectomized women) and estrogen-progestin (in non–hysterectomized women), ingestion of a low-fat diet, and calcium and vitamin D supplementation. The abandoned estrogen-progestin arm consisted of 16,608 healthy women aged 50–79 years at enrollment. The intervention was administration of conjugated estrogens 0.625 mg/day and medroxyprogesterone acetate 2.5 mg/day. The WHI demonstrated that HRT increased the risk of coronary heart disease, stroke, pulmonary embolism, and breast cancer. There is no risk-free duration of HRT use. The risk of pulmonary embolism began to rise shortly after the trial began; stroke risk increased after the first year. Invasive breast cancer rates did not rise until the fourth year. Risks of colorectal cancer and hip fracture were reduced, but a global index found that the risks outweighed the benefits.

Three double-blind, placebo-controlled, randomized, controlled trials in women with heart disease found no benefit of HRT (all received the same interventions as those in the WHI). The HERS trial, conducted in 2763 women with coronary disease, showed no benefit of HRT in preventing cardiovascular events at 5 or 6.8 years; the Estrogen Replacement and Atherosclerosis (ERA) study, conducted in 309 women with angiographically confirmed coronary disease, showed no benefit of either HRT or estrogen alone in preventing progression of atherosclerosis; and a randomized controlled trial of 293 women with unstable angina found no benefit of intravenous estrogen followed by 3 weeks of HRT or conjugated estrogens alone on ischemic events in women with unstable angina.

Memory, Mental Health, and Incontinence

It is not just the heart that hormones have not helped. Many clinicians believe that HRT prevents Alzheimer’s disease and improves mood, incontinence, and general well-being. Randomized controlled trials have proved each of these marketing claims to be false.

Three randomized controlled trials showed no benefit of HRT on mood in menopausal women. One study found that HRT (but not estrogen alone) significantly increased daily depression compared with pretreatment levels. Two studies in depressed perimenopausal women found a benefit of short-term (3 or 12 wks) estradiol, given without progestin.

Hormone replacement therapy does improve mood in women with hot flashes (probably because women are getting more sleep!). The HERS trial found that women with hot flashes who received HRT had improved mental health and fewer depressive symptoms, but that women without hot flashes had greater declines in physical function and energy than those given placebo.

Four randomized controlled trials have shown no benefit of HRT for incontinence; the HERS (the largest study) found that HRT worsened incontinence.

Future Marketing

As you read this, pharmaceutical companies are planning marketing campaigns to create the next best-selling drug. Candidates include lower-dose or different-formulation estrogen-progestin.
therapies, and a resurgence of estrogen-only therapy. Estrogen-only therapy increases endometrial cancer rates, but there will be serious discussions about monitoring women with endometrial biopsies or ultrasound, or perhaps combining estrogen with hysterectomy. There is no reason to assume that estrogen alone is superior to estrogen-progestin combinations. The ERA study showed no benefit of estrogen alone, and a randomized controlled trial that tested 17βestradiol 1 mg/day in 664 postmenopausal women after a recent stroke or transient ischemic attack found that those treated with estrogen had a higher rate of fatal stroke (relative risk 2.9, 95% confidence interval 0.9–9.0) compared with those receiving placebo.

Estrogen does help hot flashes and vaginal dryness, but these are conditions, not diseases, and more alternatives to HRT should be explored. Therapies given to a healthy population must be held to a higher standard of safety than therapies used to treat disease.

The WHI found that HRT reduces the risk of osteoporotic fractures and colorectal cancer. We can expect pharmaceutical companies to continue to emphasize the horrors of hot flashes, sound the alarm on the hidden epidemic of colorectal cancer, and ratchet up the campaign to convince women that their bones will dissolve without pharmaceutical propping up. The risks of HRT will be minimized, with absolute rather than relative risks emphasized. Hormone promoters already have trivialized HRT-caused breast cancers as “better behaved” breast cancers.

Persuading the medical community that healthy asymptomatic women should take hormones as a health-promoting tonic was a brilliant and profitable move on the part of pharmaceutical companies. The medical community that was convinced to suspend the usual requirement for data from randomized controlled trials can understandably feel betrayed.

More constructively, health care providers can avoid being a voluntary sales force for pharmaceutical companies in the future. Health care providers and researchers owe it to women to reject any claims for efficacy that are not based on randomized controlled trials with appropriate end points. It is time to separate science from advertising, and it is time to get pharmaceutical company influence out of medical education.

References

20. Fantl JA, Bump RC, Robinson D, McElish DK, Wyman JF. Efficacy of estrogen supplementation in the treatment of...


An adolescent male Kodiak bear (which can grow to be over 11 feet tall) brings his fresh salmon lunch to high ground. The structure in the lower right corner is a “salmon ladder,” erected by the fish and game department at otherwise impassable points in the river, to aid salmon in their annual sojourn upstream. The bears quickly learn that large concentrations of salmon congregate nearby each ladder. Kodiak Island, Alaska, 2002. Photo by Richard T. Scheife.