Invited Commentary

Invited Commentary: Postmenopausal Unopposed Estrogen and Breast Cancer Risk in the Women’s Health Initiative—Before and Beyond

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Three large clinical trials provoked major debate when hormone replacement therapy (HRT) did not reduce coronary heart disease in postmenopausal women as expected from observational epidemiologic studies. Less discussion has ensued about breast cancer or other adverse events. In this issue of the Journal, investigators from the Women’s Health Initiative (WHI) compare breast cancer findings from the randomized trial of unopposed estrogen with those from the large WHI observational study. This commentary briefly summarizes historical highlights of menopausal hormone use; risk-versus-benefit evaluations; scientific, clinical, and policy influences immediately before and during the WHI trial; breast cancer incidence trends; and the posttrial response in US clinical practice. Factors complicating interpretation of the results include differences in breast cancer risk profiles between women in the trial and those in the observational study cohort as well as heterogeneity in the definitions of menopause and prior use of HRT as applied by the WHI investigators to the two populations. Because millions of women use HRT, it is important to consider how the WHI and other research investigations might contribute to reducing gaps in understanding the relation between HRT and breast cancer risk.

breast neoplasms; clinical trial; epidemiologic studies; estrogens; hormone replacement therapy; menopause; risk-benefit assessment

Abbreviations: HRT, hormone replacement therapy; WHI, Women’s Health Initiative.

To explore further the breast cancer risks associated with hormone replacement therapy (HRT) in the Women’s Health Initiative (WHI) randomized trial of combined estrogen plus progestin therapy, Prentice et al. (1) carried out a detailed comparison with findings from the WHI observational study. Three major (2–5) and several smaller (6–11) clinical trials demonstrated that HRT did not reduce primary (2, 3) or secondary (4–11) coronary heart disease as anticipated from extensive observational epidemiologic studies (12, 13). In voluminous debate, epidemiologists have invoked differences among populations, duration of use or timing of HRT initiation in relation to menopause, problematic trial design, or inadequate adjustment for confounding to reconcile clinical trial with observational study findings (14–17). Post hoc arguments have swirled about reasons why the reduced risks of coronary heart disease linked with HRT in seminal meta-analyses of observational studies (12, 13) were not confirmed in the major randomized trials (2, 3, 18). Less discussion has ensued about breast cancer or other adverse events in these trials. In a similar vein, important US medical societies recommended in 1992–1993 that HRT be offered to all postmenopausal women to prevent coronary heart disease after concluding that potential HRT-related increases in breast and endometrial cancers did not outweigh the hypothesized substantial reduction in coronary heart disease (19, 20). As the risk-versus-benefit equation has shifted, Prentice et al. have undertaken a timely assessment of the breast cancer findings from the WHI.
randomized trial and observational study in this issue of the Journal (1).

US MENOPAUSAL HORMONE USE, 1941–2001

The US Food and Drug Administration approved marketing of diethylstilbestrol in 1941 and conjugated equine estrogen in 1942, decades after physicians began prescribing hormonal treatments for menopausal symptoms (21, 22). Books and media touting numerous beneficial effects of HRT stimulated increases in prescriptions to 30 million women annually (23, 24), despite reports linking thrombosis and severe hypertension with high-potency oral contraceptives (25) and myocardial infarction with unopposed estrogen among men in the Coronary Drug Project secondary prevention trial (26).

Animal studies have long associated breast and other cancers with exogenous estrogens and more recently with progestins (27–29), but early clinical studies reported reduced risks (30–32). After investigators linked HRT use with endometrial (33–35) and breast (36–38) cancer in the mid-1970s, prescriptions for HRT declined precipitously to 15 million annually (24).

Evidence that progestins could counteract the estrogen-induced endometrial hyperplasia (39) led to a resurgence in the early 1980s of HRT, particularly combined estrogen-progestin preparations (24). A 1984 National Institutes of Health consensus conference (40) and 1986 Food and Drug Administration announcement, which concluded that short-acting estrogens prevented osteoporosis (41), along with the widely disseminated 1991 meta-analysis that supported a protective effect of HRT on coronary heart disease risk (13), sparked an increase in HRT prescriptions to 36 million in 1992, 58 million in 1995, and 91 million (representing 15 million women, including 42 percent of those aged 50–74 years) in 2001 (42, 43).

SCIENTIFIC AND CLINICAL PRE–WHI TRIAL INFLUENCES

During planning of the WHI randomized trials, key meta-analyses concluded that use of unopposed estrogen was associated with no excess or very small increases (25–30 percent) of breast cancer first manifest 5 or more years after initiation of HRT (12, 44), while sparse and problematic literature precluded estimation of breast cancer risks associated with combined estrogen-progestin therapy (12, 45).

In a risk-versus-benefit assessment commissioned by the American College of Physicians, the investigators estimated that use of HRT reduced risks of coronary heart disease and hip fracture by 35 percent and 25 percent, respectively, and demonstrated no clear effect on risk of stroke. The investigators noted that endometrial cancer incidence could be increased up to eightfold but that the occurrence was relatively rare (12). The authors concluded that “hormone therapy should probably be recommended for women who have had a hysterectomy and for those with coronary heart disease or at high risk for coronary heart disease. For other women, the best course of action is unclear” (12, p. 1016). This analysis (12) was the basis of the American College of Physicians’ Guidelines for Counseling Postmenopausal Women about Preventive Hormone Therapy (19) and similar recommendations by the American College of Obstetrics and Gynecology (46) and the American Heart Association (20). The guidelines, published shortly before initiation of recruitment for the WHI clinical trials, may have led to variability in enrollment by geography (e.g., women in some regions were more likely to already be using HRT and thus be unwilling to enroll in the clinical trial component of the WHI study) and sociodemographic characteristics (47).

During recruitment for the WHI, a 1997 landmark assessment of HRT, menopause, and breast cancer from 51 epidemiologic studies (48) found that breast cancer risks for postmenopausal current users of HRT rose by a factor of 1.023 for each year of use, were 35 percent increased after 5 or more years, declined after women stopped using HRT, and disappeared 5 years after cessation of use. A 1998 meta-analysis of observational epidemiologic studies through mid-1997 found that use of unopposed estrogen was linked with a 30 percent reduction in risk of coronary heart disease, based on 25 studies, and that use of combined estrogen-progestin was associated with a 34 percent reduction, based on seven studies (49).

FEATURES OF THE WHI STUDIES

The WHI randomized clinical trials consisted of double-blind, placebo-controlled investigations of unopposed estrogen (e.g., 0.625 mg of conjugated equine estrogen) alone for women with a prior hysterectomy (3) and of combined estrogen-progestin (e.g., the progestin component consisted of 2.5 mg of medroxyprogesterone acetate) for women with a uterus (2, 47). Other intervention components of the WHI trial were a dietary modification aimed at cancer and cardiovascular disease prevention and a calcium and vitamin D component focused on reduction of hip fractures (47). Subjects were recruited for the randomized trials during 1993–1998. The investigators recognized the potential for increased breast cancer and implemented safeguards in the exclusion criteria, study methods, and requirements for continuing participation (47). The WHI observational study cohort included women who were screened for the clinical trial components but were ineligible or unwilling to be randomized to the HRT or dietary modification components (50).

In 2000 and 2001, the investigators notified trial participants of increases in myocardial infarction, stroke, and pulmonary embolus/deep vein thrombosis but indicated that the trials would continue because of uncertainty in the balance of risks versus benefits. The combined estrogen-progestin trial was halted in May 2002 because of excess breast cancer and a global index demonstrating overall harm (2). The National Institutes of Health ended the unopposed estrogen trial early (February 2004) because of excess stroke (3). Both trials had higher than expected discontinuation in the active treatment arm (42 percent for the estrogen-progestin trial, 54 percent for the unopposed estrogen trial) and crossover to active treatment in the placebo arm (10.7 percent and 9.1 percent, respectively).
POST–WHI TRIAL EFFECTS

The peak of 90 million HRT prescriptions dispensed annually to 15 million women during 1999–2002 declined by 66 percent for combined estrogen-progestin and 33 percent for unopposed estrogen between January–June 2002 and January–June 2003 after publication of the combined estrogen-progestin results (42).

The National Cancer Institute’s Surveillance, Epidemiology, and End Results population-based cancer registries showed a steady decline in age-standardized, delay-adjusted (accounts for expected reporting delays and data correction), invasive breast cancer incidence beginning in 1999 following a 6.6 percent increase per year during 1981–1998 (51). The decrease in breast cancer for women aged 45 years or older with smaller and localized tumors—but not for women with larger tumors, advanced-stage disease, or in situ breast cancer—was consistent with a plateau in screening mammography (51). In contrast, a sharp decline in breast cancer incidence from 2002 to 2003, mostly restricted to women aged 50–69 years with estrogen receptor positive/progesterone receptor positive tumors, was ascribed to the notable drop in prescriptions for HRT (51). Breast cancer incidence leveled off in 2004 (52).

GAPS AND FUTURE RESEARCH NEEDS

In ferreting out reasons for the unexpected 20 percent lower incidence (95 percent confidence interval: 0.62, 1.04) of invasive breast cancer in women randomized to unopposed estrogen compared with those on placebo, Prentice et al. noted that most of the lower risk was found for women who had not previously used HRT, and many randomized to unopposed estrogen were placed on hormone therapy several years after menopause (1). The investigators estimated a 43 percent higher risk of breast cancer in the observational study compared with the unopposed estrogen trial after adjusting for prior use of HRT and confounding factors in the observational study. By controlling additionally for time from menopause to first use of hormone therapy, Prentice et al. found that breast cancer risks were very similar in the trial and the observational study. Interpretation of the findings is not straightforward because of heterogeneity in the definitions of menopause and differing definitions of prior use of HRT between the trial and observational study populations. Preliminary results published earlier by WHI investigators (47) also suggest fewer known risk factors for breast cancer among women in the unopposed estrogen trial than among those in the observational study.

Earlier preliminary results demonstrated a younger age at menopause among those in the WHI unopposed estrogen trial than among those in the observational study (e.g., 23.3 percent vs. 9.3 percent were less than age 40 years, 30.0 percent vs. 39.0 percent were aged 40–49 years, and 46.7 percent vs. 51.7 percent were aged 50 years or older, respectively) (47). Frequency distributions of baseline information also showed that women in the unopposed estrogen trial were twice as likely to have had bilateral oophorectomy and to be younger at first pregnancy, less likely to have never been pregnant, more likely to have had two or more pregnancies, less likely to have had a mammogram in the preceding 2 years, less likely to have ever used HRT or to have used HRT for 5 or more years, and substantially less likely to be “current” users of combined estrogen-progestin than women in the observational study cohort. Thus, the two populations appear to differ in breast cancer risk profiles.

Age at menopause, an important risk factor for breast cancer (53), was not ascertained explicitly from the women in the unopposed estrogen trial but was defined as the age at which a woman last experienced menstrual bleeding, underwent a bilateral oophorectomy, or began using HRT. Investigators have found errors in recall of age at last menstrual period that increase with time since menopause (54), variability in age and menopausal status at first use of HRT (48), and biased estimates of breast cancer risk associated with most approaches for assigning age at menopause to women who have undergone simple hysterectomy (55). Data from the Healthy Women Study, Allegheny County, Pennsylvania (56, 57), and the multiethnic cohort Study of Women’s Health Across the Nation are increasing our previously limited understanding of the characteristics and determinants of age at menopause, although small numbers using various HRT regimens and restriction of the Study of Women’s Health Across the Nation to women with a uterus, at least one ovary, and not taking HRT (58, 59) limit inferences. Cohort studies are needed that include sizable numbers of women who undergo natural menopause, surgical menopause, use no HRT, or are treated with a wide range of HRT regimens to improve understanding of the determinants of age at menopause.

The decision to include previous or current HRT users in the eligibility criteria for the WHI randomized trials was important for generalizability, given documented differences in cardiovascular risk profiles between women who choose to use HRT and those who do not (60–63). Unusual and differing definitions of prior use of HRT for women enrolled in the unopposed estrogen trial (e.g., prior use is defined as yes or no HRT before randomization) versus those in the observational study (e.g., prior use is defined as “no” unless women used HRT for two or more distinct periods separated by an interval of a year or more) complicate efforts to interpret the findings reported by Prentice et al. (1).

Many gaps remain in our understanding of the relation between HRT and breast cancer risk. Are women treated with HRT who develop breast cancer genetically predisposed? Are there specific pretreatment clinical or laboratory characteristics that predict which women treated with HRT might be at increased risk of developing breast cancer? With newer developments in imaging, is it possible to identify early HRT-related mammographic changes predictive of higher risk of onset of breast cancer? Further clarification is needed of breast cancer risks associated with different doses, types, and modes of administration of HRT as well as risks for long-term users in their seventies and older. Follow-up of women who were enrolled in active hormonal treatment arms of the WHI and other clinical trials but had not previously used HRT is under way. Recently, higher risks of invasive breast cancer were reported during the...
postintervention follow-up for women in the treatment arm than in the placebo group of the WHI trial of combined estrogen and progestin (64). It would also be useful to ascertain whether first use of HRT several to many years after menopause is associated with increased risk of breast cancer. Clearly, data from the WHI clinical trials could contribute substantially to addressing several of these questions. It is also critical to increase understanding of the physiologic mechanisms by which HRT reduces vasomotor symptoms and mood disturbances to develop alternative, safer therapies.

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REFERENCES