Impact of cyclooxygenase inhibitors in the women's health initiative hormone trials: secondary analysis of a randomized trial

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1371/journal.pctr.0010026</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:4885969">http://nrs.harvard.edu/urn-3:HUL.InstRepos:4885969</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Impact of Cyclooxygenase Inhibitors in the Women’s Health Initiative Hormone Trials: Secondary Analysis of a Randomized Trial

Judith Hsia1*, JoAnn E. Manson2, Lewis Kuller3, Mary Pettinger4, John H. Choe5, Robert D. Langer6, Marian Limacher7, Albert Oberman8, Judith Ockene9, Mary Jo O’Sullivan10, Jennifer G. Robinson11, for the Women’s Health Initiative Research Group

1 Department of Medicine, George Washington University, Washington, D. C., United States of America, 2 Division of Preventive Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, 3 Department of Epidemiology, University of Pittsburgh School of Public Health, Pittsburgh, Pennsylvania, United States of America, 4 Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America, 5 Department of Medicine, University of Washington, Seattle, Washington, United States of America, 6 Department of Family Medicine, University of California San Diego, La Jolla, California, United States of America, 7 Department of Medicine, University of Florida, Gainesville, Florida, United States of America, 8 Department of Medicine, University of Alabama Birmingham, Birmingham, Alabama, United States of America, 9 Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, United States of America, 10 Department of Obstetrics and Gynecology, University of Miami, Miami, Florida, United States of America, 11 Department of Medicine, University of Iowa, Iowa City, Iowa, United States of America

Trial Registration: ClinicalTrials.gov: NCT00000611

Funding: The Women’s Health Initiative was funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, United States. The sponsor contributed to the study design, but had no role in data collection. For this paper, data analysis and interpretation, manuscript preparation, and the decision to submit for publication were independent of the sponsor.

Competing Interests: JGR has received grants from Abbott, Andrx Labs, Astra-Zeneca, Atherogenics, Bristol-Myers Squibb, GlaxoSmithKline, Hoffman La Roche, Merck, Pfizer, Procter and Gamble, Sanofi-Aventis, Schering-Plough, Sankyo. Takeda, and Wyeth Ayerst; has received speaker honoraria from Bristol-Myers Squibb, Merck, and Pfizer; and is consultant for Bristol-Myers Squibb, Merck, Pfizer, and Proliant. JH, JEM, LK, MF, JHC, RDL, ML, AO, JD, and MJO have declared that no competing interests exist.

Citation: Hsia J, Manson JE, Kuller L, Pettinger M, Chopra ML, AO, JO, and MJO have declared that no competing interests exist.


Received: June 3, 2006
Accepted: August 10, 2006
Published: September 29, 2006

Objectives: We evaluated the hypothesis that cyclooxygenase (COX) inhibitor use might have counteracted a beneficial effect of postmenopausal hormone therapy, and accounted for the absence of cardioprotection in the Women’s Health Initiative hormone trials. Estrogen increases COX expression, and inhibitors of COX such as nonsteroidal anti-inflammatory agents appear to increase coronary risk, raising the possibility of a clinically important interaction in the trials.

Design: The hormone trials were randomized, double-blind, and placebo-controlled. Use of nonsteroidal anti-inflammatory drugs was assessed at baseline and at years 1, 3, and 6.

Setting: The Women’s Health Initiative hormone trials were conducted at 40 clinical sites in the United States.

Participants: The trials enrolled 27,347 postmenopausal women, aged 50–79 y.

Interventions: We randomized 16,608 women with intact uterus to conjugated estrogens 0.625 mg with medroxyprogesterone acetate 2.5 mg daily or to placebo, and 10,739 women with prior hysterectomy to conjugated estrogens 0.625 mg daily or placebo.

Outcome Measures: Myocardial infarction, coronary death, and coronary revascularization were ascertained during 5.6 y of follow-up in the estrogen plus progestin trial and 6.8 y of follow-up in the estrogen alone trial.

Results: Hazard ratios with 95% confidence intervals were calculated from Cox proportional hazard models stratified by COX inhibitor use. The hazard ratio for myocardial infarction/coronary death with estrogen plus progestin was 1.13 (95% confidence interval 0.68–1.89) among non-users of COX inhibitors, and 1.35 (95% confidence interval 0.86–2.10) among continuous users. The hazard ratio with estrogen alone was 0.92 (95% confidence interval 0.57–1.48) among non-users of COX inhibitors, and 1.08 (95% confidence interval 0.69–1.70) among continuous users. In a second analytic approach, hazard ratios were calculated from Cox models that included hormone trial assignment as well as a time-dependent covariate for medication use, and an interaction term. No significant interaction was identified.

Conclusions: Use of COX inhibitors did not significantly affect the Women’s Health Initiative hormone trial results.
ESTROGEN, CHD RISK, AND COX INHIBITORS

INTRODUCTION

The relationship between cyclooxygenase (COX) inhibition and coronary heart disease (CHD) risk is currently the focus of intense scrutiny [1, 2]. The putative increase in CHD risk with selective COX-2 inhibitors has been attributed to reduction in atheroprotective prostacyclin levels [3]. Estrogen activates COX-2 in female mice through an estrogen-receptor-mediated mechanism, thereby increasing levels of prostacyclin [4]. This observation has raised concern that COX inhibition might counteract a beneficial effect of estrogen on prostacyclin levels and, in fact, account for the absence of cardioprotection with estrogen in recent randomized trials [5].

Mammals have two isoforms of COX. COX-1 is expressed in most tissues and mediates activities such as vascular homeostasis and gastroprotection [6]. COX-2 is induced at sites of inflammation and mediates inflammatory responses [7], making its blockade a target for treatment of arthritis and postoperative pain. Low-dose aspirin inhibits COX-1 [8], traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX-1 and COX-2 [9], and selective COX-2 inhibitors such as rofecoxib, celecoxib, and valdecoxib selectively inhibit COX-2 [10].

The Women’s Health Initiative hormone trials unexpectedly demonstrated no overall reduction in coronary risk [11], and a suggestion of harm with combination estrogen with progestin [12]. This analysis evaluates the hypothesis that COX inhibition with NSAIDs modulated the effect of postmenopausal hormone therapy on coronary risk in the Women’s Health Initiative randomized hormone trials.

METHODS

The design, recruitment, randomization, data collection, intervention, and outcomes ascertainment procedures for the Women’s Health Initiative hormone trials, including CONSORT diagrams, have been described in detail elsewhere [13–16]. Also see Figure 1.

Participants and Interventions

Between November 1993 and October 1998, 16,608 postmenopausal women, aged 50–79 y with intact uterus, were randomized to conjugated estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily (Premarin; Wyeth Pharmaceuticals, Madison, New Jersey, United States) or placebo in the estrogen plus progestin trial, and 10,739 women with prior hysterectomy were randomized to conjugated estrogens 0.625 mg daily (Premarin; Wyeth Pharmaceuticals) or placebo in the estrogen alone trial (Figure 1). The estrogen plus progestin trial was stopped ahead of schedule after 5.6 y of follow-up upon recommendation of the Data and Safety Monitoring Board because of increased breast cancer risk [16]; the estrogen alone trial was stopped ahead of schedule after 6.8 y of follow-up by the National Institutes of Health because of increased stroke risk and lack of cardioprotection [17].

CONTRIBUTIONS TO THE EVIDENCE

The investigators did not set out specifically to evaluate the cardiovascular safety of particular medications in this study. Rather, they wanted to see if these NSAIDs could have modified the effects of the hormone therapy. The secondary analysis done here shows that the main findings from the Women’s Health Initiative hormone trials were not significantly affected by use of NSAIDs outside the trial.
Adherence, follow-up, and clinical outcomes in the randomized trials have been previously reported [11,12,16,17].

Baseline Data

For the individual hormone trials, baseline characteristics were balanced between the active intervention and placebo groups [16,17]. Women with intact uterus in the estrogen plus progestin trial had generally lower prevalence of CHD risk factors than women with prior hysterectomy in the estrogen alone trial (Table 1). For example, the average body mass index of women in the estrogen plus progestin trial was 28.5 ± 5.9 kg/m² compared with 30.1 ± 6.2 kg/m² in the estrogen alone trial. Prevalent hypertension was identified in 36.1% versus 47.7% participants in the two trials, respectively, at baseline, and self-reported diabetes mellitus requiring medication was reported by 4.4% versus 7.7% of participants in the two trials, respectively. The annualized rate percent of myocardial infarction/CHD death was 0.56% for the placebo group in the estrogen alone trial [11], compared with 0.33% for the placebo group of the estrogen plus progestin trial [12].

Outcomes

Medication use. Participants were asked to bring all medications, including prescription medications, over-the-counter medications, vitamins, minerals, and bulk fiber supplements to clinic for inventory at baseline and at years 1, 3, and 6. Over-the-counter medications taken at least twice a week for the preceding 2 wk, supplements taken at least once a week, and all prescription medications were recorded. Aspirin use indicates a dose of at least 80 mg taken at least twice weekly. NSAIDs and selective COX-2 inhibitors were recorded regardless of dose if they met the frequency of use criteria. Continuous use indicates reported use at baseline and at each follow-up inventory; some use indicates use at some, but not all, medication inventories.

Clinical outcomes. Clinical outcomes were identified from semiannual medical update questionnaires and confirmed by medical record review. CHD death and hospitalized myocardial infarction were confirmed by central adjudicators, the latter using an algorithm that included symptoms, cardiac enzymes, and electrocardiograms [18]. Coronary revascularization was confirmed by centrally trained local adjudicators.

Statistical Methods

Cox proportional hazard models were stratified by age, prevalent CHD, and randomization in the dietary modification trial [13], and adjusted for coronary revascularization at baseline. The first set of Cox models stratified participants by NSAID use at baseline. The second set of models included a main effect for randomization assignment in the hormone trial and use of aspirin ≥80 mg daily, other NSAIDs, and selective COX-2 inhibitors as time-dependent covariates, and an interaction term. All reported p-values are two-sided. Analyses were carried out by the coordinating center statistics unit using the SAS system for Windows version 9 (SAS Institute, Cary, North Carolina, United States).

RESULTS

Adherence, follow-up, and clinical outcomes in the randomized trials have been previously reported [11,12,16,17].
Randomized hormone assignment and COX inhibitor use. Hazard ratios and 95% confidence intervals are shown for coronary risk with randomized hormone assignment, stratified by NSAID use (Table 3). Among women reporting no NSAID use, the hazard ratio for myocardial infarction/coronary death was 1.13 (95% confidence interval 0.68–1.89) with estrogen plus progestin, and 0.92 (95% confidence interval 0.57–1.48) with unopposed estrogen. Among women taking aspirin and/or other NSAIDs, confidence intervals for CHD risk were similar and spanned unity for both hormone trials. For three strata (none, some, and continuous NSAID use), the p-value for interaction with hormone assignment was 0.92 for estrogen with progestin and 0.82 for estrogen alone.

Similarly, for the composite outcome of myocardial infarction/coronary death/coronary revascularization, the hazard ratio among women reporting no NSAID use was 1.21 (95% confidence interval 0.80–1.84) with estrogen plus progestin, and 0.88 (95% confidence interval 0.57–1.34) with unopposed estrogen. For women taking NSAIDs, hazard ratios were similar and 95% confidence intervals for the composite coronary outcome also spanned unity. For three strata of NSAID use (none, some, and continuous), the p-value for interaction with hormone assignment was 0.63 for estrogen with progestin and 0.30 for estrogen alone.

A separate set of Cox models evaluating the risk of myocardial infarction/coronary death or myocardial infarction/coronary death/coronary revascularization with NSAID use included a main effect for randomization assignment in the hormone trials, along with NSAID use as a time-dependent covariate and an interaction term (Table 4). No significant interaction was identified between randomization assignment and use of aspirin only, other NSAID only, NSAID with aspirin, or NSAID without aspirin for either CHD outcome.

**DISCUSSION**

**Interpretation**

COX inhibitor use did not significantly modulate the effect of either unopposed conjugated estrogens or combined conjugated estrogens with medroxyprogesterone acetate on coronary risk in the Women's Health Initiative randomized hormone trials. The effects of hormone therapy on risk of coronary events were generally similar among users and non-users of COX inhibitors, and no significant interactions were observed.

The strengths of our study include the systematic ascertainment of clinical coronary outcomes, the large number of CHD events, the randomized, placebo-controlled design, and the periodic re-inventory of medications, permitting inclusion of COX inhibitor use as a time-dependent covariate (Table 4). Limitations include the fact that use of aspirin <80 mg/d at least twice weekly was not recorded, that only about 20% of women were using NSAIDs, and that only a few percent used selective COX-2 inhibitors. Thus, we were unable to adequately test the possibilities that concurrent use of very low dose aspirin or exclusive use of selective COX-2 inhibitors might modulate CHD risk among women taking postmenopausal hormone therapy. Further, the numbers of clinical events were small for some categories of COX inhibitor use.

**Generalizability**

Characteristics of the Women's Health Initiative hormone trials include the large, diverse cohort and wide geographic distribution of clinical sites. Each trial tested a single regimen: when they were designed, the unopposed estrogen regimen: when they were designed, the unopposed estrogen or exclusive use of selective COX-2 inhibitors might modulate CHD risk among women taking postmenopausal hormone therapy. Further, the numbers of clinical events were small for some categories of COX inhibitor use.

**Table 2. Use of Aspirin, NSAIDs, and Selective COX-2 Inhibitors at Baseline and at Year 3**

<table>
<thead>
<tr>
<th>Drugs Used*</th>
<th>Time Point</th>
<th>Estrogen Plus Progestin</th>
<th>Estrogen Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Active Drug (n = 8,506)</td>
<td>Placebo (n = 8,102)</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>Baseline</td>
<td>1,411 (17)</td>
<td>1,365 (17)</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>1,452 (19)</td>
<td>1,473 (20)</td>
</tr>
<tr>
<td>NSAID only</td>
<td>Baseline</td>
<td>1,222 (14)</td>
<td>1,196 (15)</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>768 (10)</td>
<td>785 (11)</td>
</tr>
<tr>
<td>COX-2 only</td>
<td>Baseline</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>119 (2)</td>
<td>143 (2)</td>
</tr>
<tr>
<td>NSAID and aspirin</td>
<td>Baseline</td>
<td>292 (3)</td>
<td>312 (4)</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>244 (3)</td>
<td>222 (3)</td>
</tr>
<tr>
<td>NSAID or aspirin</td>
<td>Baseline</td>
<td>2,930 (34)</td>
<td>2,875 (35)</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>2,518 (33)</td>
<td>2,531 (35)</td>
</tr>
<tr>
<td>NSAID, COX-2, or aspirin</td>
<td>Baseline</td>
<td>2,930 (34)</td>
<td>2,875 (35)</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>2,637 (34)</td>
<td>2,674 (36)</td>
</tr>
<tr>
<td>Aspirin with or without NSAID/COX-2</td>
<td>Baseline</td>
<td>1,703 (20)</td>
<td>1,677 (21)</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>1,741 (23)</td>
<td>1,739 (24)</td>
</tr>
</tbody>
</table>

Values are n (percent). Use at year 3 indicates medication use was reported at year 3, regardless of prior use.

*Aspirin indicates ≥80 mg/d at least twice weekly. COX-2 indicates a selective COX-2 inhibitor.

DOI: 10.1371/journal.pctr.0010026.t002
Table 3. CHD Risk with Postmenopausal Hormone Therapy, Stratified by COX Inhibitor Use

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug Usea</th>
<th>Estrogen Plus Progestin</th>
<th>Estrogen Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Number of Events</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Active Drug Group</td>
<td>Placebo Group</td>
<td></td>
</tr>
<tr>
<td>MI/CHD death</td>
<td>No aspirin, NSAID, COX-2 use</td>
<td>6,100</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Some or continuous aspirin use, no NSAID or COX-2</td>
<td>3,740</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Continuous aspirin use, no NSAID or COX-2</td>
<td>953</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Some or continuous NSAID use, no aspirin</td>
<td>2,855</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Continuous NSAID or COX-2 use, no aspirin</td>
<td>523</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Continuous aspirin or NSAID use</td>
<td>2,367</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>No aspirin, with or without NSAID or COX-2</td>
<td>6,100</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Some or continuous aspirin use, with or without NSAID or COX-2</td>
<td>3,740</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Continuous aspirin use, with or without NSAID or COX-2</td>
<td>953</td>
<td>33</td>
</tr>
<tr>
<td>MI/CHD death/coronary revascularization</td>
<td>No aspirin, NSAID, COX-2 use</td>
<td>6,100</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Some or continuous aspirin use, no NSAID or COX-2</td>
<td>3,740</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Continuous aspirin use, no NSAID or COX-2</td>
<td>953</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Some or continuous NSAID use, no aspirin</td>
<td>2,855</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Continuous NSAID or COX-2 use, no aspirin</td>
<td>523</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Continuous aspirin or NSAID use</td>
<td>2,367</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Some or continuous aspirin use, with or without NSAID or COX-2</td>
<td>5,694</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>Continuous aspirin use, with or without NSAID or COX-2</td>
<td>1,323</td>
<td>49</td>
</tr>
</tbody>
</table>

Cox models are shown for subgroups of women who did or did not use COX inhibitors. Continuous use indicates reported use at baseline and at each follow-up inventory. Some use indicates reported use at some, but not all, medication inventories. Duration of follow-up was 5.2 y in the estrogen plus progestin trial and 6.8 y in the estrogen alone trial.

aAspirin indicates > 80 mg/d at least twice weekly. COX-2 indicates selective COX-2 inhibitor.

CI, confidence interval; MI, myocardial infarction.

DOI: 10.1371/journal.pctr.0010026.t003

Overall Evidence

This analysis is not intended to assess the coronary risk associated with COX inhibitor use. Although we have more complete information about over-the-counter NSAID use and CHD risk characteristics, including physical activity and diet, than some other epidemiologic analyses, this issue is best examined in randomized trials [21–25] because of intrinsic biases in COX inhibitor use related to patient selection and treatment indications.

Iatrogenic imbalance between COX-1 and COX-2 activities has been proposed as a mechanism underlying both favorable and unfavorable cardiovascular effects of drugs [5,26]. COXs synthesize prostacyclin I2 and thromboxane A2 from arachidonic acid. Prostacyclin I2, predominantly a product of COX-2, is a vasodilator that inhibits platelet aggregation and smooth muscle proliferation, effects that might be expected to reduce acute coronary syndromes and stroke. Thromboxane A2, produced by COX-1 in platelets, is a vasoconstrictor that stimulates platelet aggregation, an effect that might be expected to increase cardiovascular risk. Selective COX-2 inhibitors reduce prostacyclin without inhibiting production of platelet-COX-1-derived thromboxane A2, a pharmacologic effect that has been hypothesized to underlie the putative adverse cardiovascular effects of these agents [24]. In contrast, NSAIDs reduce formation of both prostacyclin and thromboxane A2, with individual drugs differing in their relative blockade of COX-1 and COX-2 activities. Naproxen and aspirin predominantly inhibit COX-1, whereas diclofenac, etodolac, and meloxicam predominantly inhibit COX-2 [27]. Participants in the Women’s Health Initiative hormone trials consumed a variety of NSAIDs, encompassing a range of ratios of COX-1:COX-2 inhibition.

Estrogen increases expression of COX-2 and production of prostacyclin I2 effects that have been proposed to underlie its apparent cardioprotective effects in animal models [28]. Female low-density lipoprotein cholesterol receptor knockout mice developed more aortic plaque if they also lacked the prostacyclin receptor; this phenomenon was not observed in male mice. The prostacyclin-receptor-deficient female mice also demonstrated increased oxidative stress and platelet...
In cultured mouse aortic smooth muscle cells, estrogen exposure increased COX-2 expression and prostacyclin formation [4].

In view of these new findings and of the public health impact of the Women’s Health Initiative hormone trials, we felt it was important to assess any possible impact of COX inhibitor use on the hormone trial results. Although this analysis cannot conclusively determine whether exogenous estrogen could ever modulate CHD risk with COX inhibition, it does confirm that use of COX inhibitors did not significantly affect the Women’s Health Initiative hormone trial results.

**SUPPORTING INFORMATION**

**CONSORT Checklist**

Found at DOI: 10.1371/journal.pctr.0010026.sd002 (147 KB PDF).

**ACKNOWLEDGMENTS**

The following persons are investigators in the Women’s Health Initiative.

In the program office at the National Heart, Lung, and Blood Institute, Bethesda, Maryland, United States: Barbara Alving, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller.

In the clinical coordinating center at Fred Hutchinson Cancer Research Center, Seattle, Washington, United States: Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, and Anne McTiernan.

In the clinical coordinating center at Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States: Sally Shumaker.

In the clinical coordinating center at Medical Research Labs, Highland Heights, Kentucky, United States: Evan Stein.

In the clinical coordinating center at the University of California San Francisco, San Francisco, California, United States: Steven Cummings.

At clinical centers: Sylvia Wassertheil-Smoller (Albert Einstein College of Medicine, Bronx, New York, United States); Jennifer Hays (Baylor College of Medicine, Houston, Texas, United States); JoAnn Manson (Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States); Anmol R. Assaf (Brown University, Providence, Rhode Island, United States); Lawrence Phillips (Emory University, Atlanta, Georgia, United States); Shirley Beresford (Fred Hutchinson Cancer Research Center, Seattle, Washington, United States); Judith Hsia (George Washington University Medical Center, Washington, District of Columbia, United States); Rowan Chlebowski (Harbor-UCLA Research and Education Institute, Torrance, California, United States); Evelyn Whitlock (Kaiser Permanente Center for Health Research, Portland, Oregon, United States); Bette Caan (Kaiser Permanente Division of Research, Oakland, California, United States); Jane Morley Kotchen (Medical College of Wisconsin, Milwaukee, Wisconsin, United States); Barbara V. Howard (MedStar Research Institute/Howard University, Washington, District of Columbia, United States); Linda Van Horn (Northwestern University, Evanston, Illinois, United States); Henry Black (Rush Medical Center, Chicago, Illinois, United States); Marcia L. Stefanick (Stanford Prevention Research Center, Stanford, California, United States); Dorothy Lane (State University of New York at Stony Brook, Stony Brook, New York, United States); Rebecca Jackson (Ohio State University, Columbus, Ohio, United States); Cora E. Lewis (University of Alabama Birmingham, Birmingham, Alabama, United States); Tamsen Baxfield (University of Arizona, Tucson, Arizona, United States); Jean Wactawski-Wende (University at Buffalo, Buffalo, New York, United States); John Robbins (University of California Davis, Davis, California, United States); F. Allan Hubbell (University of California Irvine, Irvine, California, United States); Howard Judd (University of California Los Angeles, Los Angeles, California, United States); Robert D. Langer (University of California San Diego, La Jolla, California, United States); Margery Gass (University of Cincinnati, Cincinnati, Ohio, United States); Marian Limacher (University of Florida, Gainesville, Florida, United States); David Carrub (University of Hawaii, Honolulu, Hawaii, United States); Robert Wallace (University of Iowa, Iowa City, Iowa, United States); Judith Ockene (University of Massachusetts/Fallon Clinic, Worcester, Massachusetts, United States); Norman Lasser (University of Medicine and Dentistry of New Jersey, Newark, New Jersey, United States); Mary Jo O’Sullivan (University of Miami, Miami, Florida, United States); Karen Margolis (University of Minnesota, Minneapolis, Minnesota, United States); Robert Brunner (University of Nevada, Reno, Nevada, United States); Gerardo Heiss (University of North
References


