Estrogen affects post-menopausal women differently than estrogen plus progestin replacement therapy

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BACKGROUND: In the Women’s Health Initiative Randomized Controlled Trial (WHI RCT), estrogen-only treatment compared with combined estrogen–progestin treatment resulted in less coronary artery disease, no increase in breast cancer and no reduction in colorectal cancer. Since we previously reasonably replicated the combined estrogen–progestin WHI RCT using the UK General Practice Research Database (GPRD), estrogen-only treatment was investigated using a similar methodology. METHODS: This GPRD study simulated the estrogen-only WHI RCT of women who had undergone a hysterectomy except for randomization. The primary analysis examined 11,572 unexposed and 6,890 Exposed women (aged 55–79) treated with conjugated equine estrogen and was compared with the combined estrogen–progestin GPRD study. RESULTS: At baseline, women with a hysterectomy exhibited more cardiovascular disease than those with an intact uterus. In the estrogen-only GPRD study, adjusted hazard ratios (HRs) were 0.50 (0.38–0.67) for myocardial infarction (MI), 1.13 (0.91–1.41) for breast cancer, and 1.18 (0.72–1.92) for colorectal cancer. Compared to the HRs in the estrogen–progestin GPRD study, the estrogen-only results are significantly lower for MI and breast cancer and higher for colon cancer, a pattern similar to the WHI RCT study comparisons. CONCLUSIONS: This study confirms that post-menopausal women in the overall population respond differently to estrogen-only treatment compared with estrogen–progestin treatment, due to different hormone regimens and/or increased cardiovascular disease in hysterectomized women.

Keywords: cohort studies/coronary heart disease/hormone replacement therapy/hysterectomy/menopause

Introduction

Controversy exists about the discrepancy between the results of observational studies that found that hormone replacement therapy (HRT) in post-menopausal women protected against coronary artery disease and the results of the Women’s Health Initiative Randomized Controlled Trial (WHI RCT) that reported no protection and a potential increase in cardiac risk (Tannen et al., 2007, Writing Group for Women’s Health Initiative Investigators, 2002). In contrast, our observational study, which simulated the RCT using data from a large primary care medical record database reflective of the entire population of the United Kingdom, reasonably replicated most of the findings in the RCT and did not find a protective effect of combined estrogen–progestin therapy on coronary artery disease (Tannen et al., 2007). Furthermore, younger women in a second General Practice Research Database (GPRD) study also behaved similarly to the older post-menopausal women in the WHI RCT (Weiner MG et al., submitted). In addition to women treated with a combination of estrogen and progestin, the WHI RCT studied women with a prior hysterectomy treated solely with conjugated equine estrogen (CEE) (The Women’s Health Initiative Steering Committee, 2004). The response to treatment with estrogen-alone differed from treatment with both estrogen and progestin in several important ways: (i) the hazard ratio (HR) for coronary artery disease was <1.0 in contrast to the significant increase found with estrogen–progestin; (ii) breast cancer showed a slight decrease rather than a significant increase in HR and (iii) in contrast to combined human replacement therapy, colon cancer was not reduced in women with a hysterectomy treated with estrogen only.

Given the relative comparability between our GPRD study and the WHI trial of women treated with estrogen and progestin, we employed the GPRD methodology to simulate the estrogen-only arm of the WHI RCT. Our goal was to determine whether the differences between the estrogen-only and combined estrogen–progestin arms of the WHI RCT could be verified in the overall population contained in the GPRD database.
Materials and Methods

UK GPRD

The UK GPRD, described in detail previously, contains virtually complete electronic medical records of primary care practices, encompassing a representative sample of 5.6% of the UK population (Gelfand et al., 2005; Tannen et al., 2006). In addition to primary care medical encounters, it contains detailed data on medications prescribed and information from all consultant encounters and hospitalizations.

The database preserves confidentiality by central data compilation with removal of personal identifiers. This project was approved by GPRD Scientific and Ethical Advisory Group and by the University of Pennsylvania Institutional Review Board for Research Involving Human Beings.

GPRD study protocol

The GPRD study was designed to simulate the WHI RCT, except for randomization. To the extent possible, the study time frame, inclusion and exclusion criteria and the treatment protocol used in the GPRD study were similar to the WHI RCT (Table 1).

Selection of subjects for the GPRD study is summarized in Figure 1. First, the Exposed group was selected from all women aged 50–79 who underwent a hysterectomy prior to 31 December 1994, post-hysterectomy had received CEE (0.625 mg daily) at any time during the recruitment interval from 1 January 1990 through 31 December 1994 and did not meet any exclusion criteria. The Unexposed group was selected from all women aged 50–79 who underwent a hysterectomy and did not receive any estrogen-containing preparation during the study recruitment interval. These subjects were age-matched to the exposed group using a random matching technique with a goal of two matches per exposed subject, and their study start date was considered identical to the matched exposed women. After definition of the start date, those meeting exclusion criteria were eliminated from the cohort.

Participants in our initial GPRD study were restricted to aged 55–79 years to more closely simulate the age profile in the WHI RCT, and a separate analysis was done in women aged 50–55 (Tannen et al., 2007; Weiner MG et al., submitted). These same ages were replicated in the GPRD study of women taking estrogen only. The primary analysis was performed on the 55–79-year-old age group.

Outcome stop points replicated those in the WHI RCT and included breast cancer, pulmonary embolus, deep venous thrombosis (DVT) and malignant melanoma. Patients were considered lost to follow-up if they left the practice prior to a stop point or the study end date or if the practice was dropped from the GPRD.

Data analysis

Outcomes ascertained in the WHI estrogen-only RCT were similar to those in the previous GPRD Study of combined estrogen–progestin therapy (Tannen et al., 2007). The primary analysis included women aged 55–79 and a secondary analysis of women aged 50–55, was performed. Both sets of analyses were done as follows:

(i) A simulated ‘Intention to Treat’ analysis, in which regardless of subsequent use of estrogen-containing preparations in either group, the study continued until attainment of a stop point, a lost to follow-up event (vide supra), or the study end date.

(ii) An ‘As-Treated’ analysis, in which the study ended if an unexposed women was treated with any estrogen-containing preparation and if an Exposed subject discontinued estrogen treatment.

Two cohort subsets also were analysed:

(i) a ‘Without Missing Data’ subset, restricted to all subjects not missing baseline data for systolic blood pressure (SBP), body mass index (BMI) or smoking and

(ii) a ‘Without Prior Estrogen-containing Preparation’ subset, restricted to subjects who did not take any estrogen-containing preparation within the year preceding study Start date.

Statistical analysis

Unadjusted and adjusted Cox proportional hazard analyses were performed using multiple imputations for any missing data on SBP, BMI or smoking and using the same baseline confounders (age, blood pressure (BP), BMI smoking, previous myocardial infarction (MI) or stroke and evidence for angina or other ischaemic cardiovascular disease, transient ischaemic attack or other ischaemic cerebrovascular disease, heart failure or diabetes mellitus) as the prior estrogen–progestin GPRD study (Rubin, 1987; Raghunathan et al., 1998, 2001; Tannen et al., 2007).

Outcomes also were analysed using propensity score methodology (Rosenbaum and Rubin, 1983, 1984; D’Agostino and Rubin, 2000; Tannen et al., 2007). Since the adjusted (HRs) were similar to the propensity score analysis and the Cox analysis with multiple imputations, only the Cox adjusted HRs are reported.

HR differences between studies were analysed statistically using a standard normal z-test (Tannen et al., 2007).

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### Table 1. The effect of estrogen-only replacement therapy: comparison of Women’s Health Initiative Randomized Controlled Trial (WHI RCT) and General Practice Research Database (GPRD) >55-year-old

<table>
<thead>
<tr>
<th>Study protocol</th>
<th>WHI RCT</th>
<th>GPRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollments</td>
<td>Until 1998</td>
<td>Until 1995</td>
</tr>
<tr>
<td>Participant age</td>
<td>50–79</td>
<td>55–79</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Assumed, based on age and prior hysterectomy</td>
<td>Assumed, based on age and prior hysterectomy</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Acute MI, CVA, or TIA within 6 months entry</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>H/O breast or endometrial cancer</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>H/O malignant melanoma</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>H/O other malignancies in past 10 years</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Abnormal PAP smear, pelvic exam</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>H/O nontraumatic pulmonary embolus or DVT</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>severe hypertension</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>chronic hepatitis or cirrhosis</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>corticosteroid, tamoxifen or anticoagulant Rx at entry</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Medical condition with predicted survival &lt;3 years</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Condition inconsistent with study adherence</td>
<td>Same</td>
</tr>
<tr>
<td>Exposure</td>
<td>Conjugated estrogen 0.625 mg, PO, daily</td>
<td>Same</td>
</tr>
</tbody>
</table>

*Exclusive of non-melanotic skin cancers.

*bConditions included in GPRD study were: AIDS, chronic pulmonary disease, heart failure, renal impairment.

*cConditions included in GPRD study were: alcoholism, drug dependency, dementia, mental illness.

Abbreviations: H/O, history of; MI, myocardial infarction; CVA, cerebrovascular accident; TIA, transient ischaemic attack; DVT, deep venous thrombosis.
Results

Primary GPRD study of women with a hysterectomy treated with estrogen only: aged 55–79

Baseline characteristics: comparison of WHI RCT estrogen-only and GPRD estrogen-only cohorts

In comparison to the estrogen-only WHI RCT, women in the estrogen-only GPRD study were younger, weighed less and had fewer cardiovascular risk factors except for smoking and a lower prevalence of identified cardiovascular disease (Table 2). Hypertension was less frequent but SBP was higher because fewer women received anti-hypertensive medications. Current estrogen use was higher in the exposed and lower in the unexposed GPRD groups than in the WHI RCT, and fewer women in the GPRD study had undergone bilateral oophorectomy. Hysterectomy was performed at a younger age in the WHI RCT than in the GPRD study.

Baseline characteristics: comparison of GPRD estrogen-only exposed and unexposed groups (Table 2)

The exposed compared to the unexposed group of the GPRD estrogen-only study weighed less and had less identified cardiovascular disease and risk factors. Use of estrogen-containing preparations prior to study entry was more prevalent in the exposed group. The exposed also had less missing data on BMI, SBP or smoking than the unexposed group (29.3 versus 37.9%).

Outcomes

Simulated intention to treat analysis: GPRD estrogen-only versus WHI RCT estrogen-only studies (Table 3)

Compared with the placebo arm of the WHI RCT, the Unexposed Group of the GPRD estrogen-only study had similar
event rates for MI, stroke, breast cancer and death, but differed strikingly for venous thromboembolic events (VTEs), colorectal cancer and hip fracture (Table 3).

### GPRD estrogen-only HRs (Table 3)

The only significant differences in outcomes between the GPRD exposed and unexposed groups were decreased adjusted HRs for MI, death and hip fracture. Angina (not shown) was unchanged [adjusted HR 0.98 (0.85–1.13)].

The GPRD adjusted HR’s for MI, stroke, DVT and death were all significantly lower than in the WHI RCT, and the HR for breast cancer was significantly higher.

### GPRD estrogen-only subset analyses

The subset without any missing data on confounders did not differ meaningfully from the total cohort, except that the HR for death was not decreased significantly [adjusted HR 0.82 (0.66–1.02), nor did it differ significantly from the WHI RCT. The subset not exposed to prior estrogen-containing preparations had results largely similar to the total cohort. Furthermore, analysis of a subset, which consisted of subjects who had not had a prior oophorectomy, had results essentially similar to the total cohort.

### As-Treated Analysis: GPRD estrogen-only primary analysis

The results of the ‘As-Treated’ analysis (Fig. 2) were largely similar to the simulated ‘Intention to Treat’ analysis.

### Secondary GPRD estrogen-only study: women aged 50–55 (Fig. 2)

The outcomes in the GPRD estrogen-only study of younger women (aged 50–55) were generally more similar to the WHI RCT estrogen-only arm than the primary GPRD study of older women (age > 55). Angina (not shown) was increased in the exposed younger women [adjusted HR 1.28 (1.06–1.54)].
Comparison of GPRD and RCT studies of women treated with combined hormone therapy (estrogen and progestin) to those treated with estrogen only

Baseline characteristics

The unexposed older women (>55) with a hysterectomy in the GPRD study compared to those without a hysterectomy in the prior GPRD study with older women (Table 4) were slightly older and weighed more, but fewer were current smokers. Otherwise, women with a hysterectomy had more cardiovascular risk factors and existing cardiovascular disease than those without a hysterectomy.

Comparisons between the WHI RCT placebo groups of estrogen-only and the combined hormone replacement studies had a pattern of cardiovascular risk factors and established cardiovascular disease similar to the comparison between the unexposed cohorts of the GPRD studies (Writing

Figure 2. Comparison of hazard ratios (HRs). The HRs and confidence limits for the Women’s Health Initiative Randomized Controlled Trial (WHI RCT) are taken from the WHI publication (The Women’s Health Initiative Steering Committee, 2004). MI, nupcardial infarction; VIE, venous thromboembolic events.

Comparison of GPRD and RCT studies of women treated with combined hormone therapy (estrogen and progestin) to those treated with estrogen only

Baseline characteristics

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Table 4. Baseline characteristic—estrogen plus progestin versus estrogen only

<table>
<thead>
<tr>
<th></th>
<th>WHI RCT—Placebo</th>
<th></th>
<th>GPRD—unexposed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estrogen plus</td>
<td>Estrogen only</td>
<td></td>
<td>Estrogen plus</td>
</tr>
<tr>
<td></td>
<td>progestin</td>
<td></td>
<td></td>
<td>progestin</td>
</tr>
<tr>
<td></td>
<td><em>P</em>-value</td>
<td></td>
<td></td>
<td><em>P</em>-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.3</td>
<td>63.6</td>
<td>0.017</td>
<td>59.8</td>
</tr>
<tr>
<td>BMI kg m(^{-2})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 (%)</td>
<td>28.5</td>
<td>30.1</td>
<td>0.001</td>
<td>26.4</td>
</tr>
<tr>
<td>smoker—current (%)</td>
<td>10.5</td>
<td>10.6</td>
<td>0.76</td>
<td>19.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
<td></td>
<td></td>
<td>24.1</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td></td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td>15.5</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>12.9</td>
<td>15.9</td>
<td>0.001</td>
<td>140.4</td>
</tr>
<tr>
<td>Prior MI (%)(^b)</td>
<td>1.9</td>
<td>3.2</td>
<td>0.001</td>
<td>8.6</td>
</tr>
<tr>
<td>Prior CVA (%)(^b)</td>
<td>0.7</td>
<td>1.7</td>
<td>0.001</td>
<td>1.06</td>
</tr>
<tr>
<td>Fracture (%)(^c)</td>
<td>13.6</td>
<td>13.2</td>
<td>0.55</td>
<td>2.7</td>
</tr>
<tr>
<td>Angina (%)</td>
<td></td>
<td>2.9</td>
<td>0.001</td>
<td>2.5</td>
</tr>
</tbody>
</table>

\(^a\)Some subjects in the GPRD studies were missing data on BMI, SBP or smoking. The data shown for these three parameters exclude these subjects.

\(^b\)Prior MI or CVA refers to events >6 months prior to study start.

\(^c\)Fracture refers to fractures occurring at age 55 or older.
Outcomes in the unexposed/placebo groups
Compared with the prior GPRD study of older women without a hysterectomy, the unexposed women with a hysterectomy had significantly increased event rates for MI, stroke and VTE (Table 5). Angina (not shown) also was higher (1.45 vs. 0.74 events/100 patient years, \( P < 0.01 \)). An increase in breast cancer was also observed.

Similarly, when the WHI placebo group of women with a hysterectomy is compared with those without, the event rates for MI and stroke were significantly higher; however, the increases in VTE and breast cancer were not significant... 

Outcome comparisons between the exposed/HRT and unexposed/placebo cohorts (Table 5 and Fig. 3)
Comparison of the GPRD study of older women with a hysterectomy (exposed to estrogen only) with women in the prior study without a hysterectomy (exposed to combined estrogen–progestin) showed significantly lower adjusted HRs for MI, VTE and breast cancer, a higher HR for colorectal cancer and no differences for stroke or death.

In the WHI RCT, the HRs in the estrogen-only study when compared with the study of women taking combined estrogen–progestin were significantly lower for MI, VTE and breast cancer, higher for colorectal cancer and similar for stroke and death.

Discussion
The response to HRT differs in women with and without a hysterectomy. In the WHI RCT, women with a prior hysterectomy treated with estrogen replacement therapy exhibit a significantly lower HR for MI and VTEs than women without a hysterectomy treated with combined estrogen–progestin. In addition, the HR for breast cancer is decreased and for colorectal cancer is increased in comparison to women taking estrogen and progestin. No significant differences were noted between the estrogen–only and combined estrogen–progestin therapy WHI RCTs in the other outcomes reported including stroke, cancer, hip fracture and death.

The comparison between the hysterectomy and non-hysterectomy components of the GPRD study is virtually identical, as shown in Table 5 and Figure 3. The HRs for MI and VTEs were decreased. In addition, the HRs for breast cancer were decreased and for colorectal cancer were increased in comparison to women taking estrogen and progestin. No significant differences were noted between the estrogen–only and combined estrogen–progestin therapy WHI RCTs in the other outcomes reported including stroke, cancer, hip fracture and death.

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Thus, the differences in outcomes between the estrogen plus progestin arm of the WHI studies and those treated with estrogen only are confirmed by the GPRD studies. These differences may be accounted for by the different hormone replacement...
regimens, i.e. estrogen alone or combined estrogen and proges-
tin. Alternatively, the results may be influenced by the in-
creased cardiovascular risk profile of the women with, as
contrasted to those without, a hysterectomy, found in both
the WHI and GPRD studies (Stefanick et al., 2003).

Several studies suggest that combined estrogen–progestin
imparts a greater risk for development of breast cancer than
estrogen alone (Ross et al., 2000; Schairer et al., 2000; Li
et al., 2003; Million Women Study Collaborators, 2003; Four-
nier et al., 2005; Yager and Davidson, 2006), which would be
consistent with both the WHI RCT and GPRD studies. Al-
though an increase in breast cancer with estrogen-only
therapy was not detected in either the WHI RCT or GPRD
studies, a duration of estrogen therapy exceeding 5 years has
been reported to increase breast cancer (Lyytinen et al., 2006).

Experiments suggesting that progestins might increase the
risk for coronary artery disease exist; however, there are no
definitive clinical studies that address this issue (Kim et al.,
1996; Register et al., 1998; Bladhi et al., 2002). Finally,
some data suggest that combined estrogen–progestin increases
the risk of VTE when compared with estrogen alone (Smith
et al., 2004).

As shown in Table 4, despite similar selection criteria for
entry into both the WHI trials, when the placebo group of
women with a hysterectomy in the estrogen-only trial is com-
pared to the placebo group without a hysterectomy in the
estrogen–progestin trial, women in the estrogen-only trial had a
higher incidence of existing cardiovascular disease and also a
greater likelihood for developing future cardiovascular
disease (Stefanick et al., 2003; The Women’s Health Initiative
Steering Committee 2004; Tannen et al., 2007). Similarly, in
the GPRD studies, women with a hysterectomy in the estrogen-
only study who were unexposed had a higher risk profile for
cardiovascular disease than unexposed women in the estrogen–
progestin trial. Furthermore, the increased likelihood for
cardiovascular disease in women with a prior hysterectomy,
both in the placebo Arm of the WHI and the unexposed
cohort of the GPRD study, was accompanied by higher rates
of MI, stroke and VTEs than in women with an intact uterus
(Table 5).

Increased cardiovascular disease in women who have had a
hysterectomy has been noted previously (Rosenberg et al.,
1981; Falkeborn et al., 2000; Brett, 2005; Howard et al.,
2005; Hsia et al., 2003; Nozaki et al., 2004). Our GPRD
study, which represents a non-selected sample of the overall
population, indicates that this finding generalizes to the popu-
lation at large. It has been suggested that bilateral oophorec-
томy may contribute to the increase in cardiovascular disease,
but the recent analysis of the data from the WHI Trial could
not verify this assumption (Brett, 2005; Howard et al.; 2005).
Whether underlying cardiovascular disease increases the like-
lihood of requiring a hysterectomy or whether undergoing a
hysterectomy increases the predisposition for developing cardi-
vascular disease is unresolved. Furthermore, whether this
difference in health profile contributes to the different out-
comes between the estrogen-only and combined estrogen–
progestin studies is unresolved.

In our prior investigation of women treated with combined
estrogen and progestin, the results of a simulated study using
the GPRD were largely similar to those of the WHI RCT. How-
ever, when the simulated GPRD and WHI RCT of the
estrogen-only studies are compared directly, the GPRD study
of women treated solely with CEE appeared to replicate only
some of the RCT findings. Similar to the findings in the WHI
RCT, hip fracture was decreased and the GPRD study did not
show an increase in breast cancer or a decrease in colon
cancer. However, the GPRD study in older women differed
by finding that estrogen treatment decreased MI and did not
increase either stroke or VTEs.

The difference in the response of MI between the RCT and
GPRD study is not entirely clear. Overall, the estrogen-only
WHI RCT did not show a significant decline in coronary
artery disease, but did suggest a possible protective effect by
finding a significant trend for a decline in coronary heart
disease over time and also a possible reduction in treated
younger women (The Women’s Health Initiative Steering
Committee, 2004; Hsia et al., 2006). In the GPRD study, MI
was decreased in older women, but the secondary analysis of
younger women did not show a significant decrease. In
addition, angina was unchanged in the older women but
increased significantly in the exposed group of younger women. Thus, both the WHI RCT and the GPRD studies of estrogen-only treatment provide hints that are not concordant regarding the possibility of a protective effect against coronary artery disease, but neither study provides a definitive answer. However, both studies clearly show that estrogen-only therapy results in less coronary artery disease than estrogen and progestin treatment.

There are several important limitations to the GPRD study. As in our prior study (Tannen et al., 2007), the difference in estrogen use prior to starting the study could influence the results; although the lack of difference between the results of the total cohort and the subset that did not take estrogen in the year preceding study suggests this was not an important factor. Missing data on certain key baseline confounders may also introduce a bias to our GPRD studies (Tannen et al., 2007). Comparability of the adjusted HRs analysed either by multiple imputations or by propensity score; most important comparability between the total cohort and the subset that did not have any missing data suggests the results were valid despite this problem. The exception is the finding with death, a result that mimicked our prior study of women without a hysterectomy treated with combined estrogen–progestin, wherein the apparent decrease in death appears to be spurious and does not occur in subjects without missing data (Tannen et al., 2007).

The dropout rate in the GPRD study, shown in Figure 1, was high but similar in both arms of the study. Since dropout only occurs when a subject leaves a practice or the practice no longer participates in the GPRD database, there is no reason to expect that it biases the study results.

Another potentially important difference between the RCT and GPRD Study was the younger age of hysterectomy and higher percentage of women with a prior oophorectomy in the RCT. However neither the age of hysterectomy nor the presence of an oophorectomy imparted any substantive difference on the results of the GPRD study.

The dosage and formulation of estrogen used in the WHI and GPRD studies of women with and without a hysterectomy was identical. However, the progestin therapy differed between the WHI and GPRD studies of combined estrogen–progestin therapy in women without a hysterectomy. In the WHI trial, daily medroxyprogesterone was administered, whereas in the GPRD study, norgestrel was taken on the last 12 days of the cycle. Despite this difference, the outcomes of the WHI and GPRD studies of combined HRT were reasonably similar. Because the WHI and GPRD studies of estrogen-only therapy both compared similarly to their respective studies of combined estrogen–progestin, use of a progestin rather than its specific formulation or administration regimen appears to account for the different outcomes in contrast to therapy with estrogen only.

In summary, this GPRD study, using a representative sample of the overall population, confirms the WHI RCT findings of important differences between the response to estrogen replacement in women with a hysterectomy when compared with estrogen plus progestin replacement in women with an intact uterus. However, the disparity in some outcomes with direct comparison of the WHI RCT and GPRD studies of women with a prior hysterectomy raises a note of caution about the interpretation of observational studies. What accounts for less concordance with the RCT between the results of this observational study and the prior study of women treated with combination HRT is not clear. Of interest, the recent report of the WHI observational study of estrogen treated women with a hysterectomy compared with the WHI RCT in a fashion similar to our GPRD study [Prentice et al., (2006)].

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